Ambident Reactivity

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Farewell to the HSAB Treatment of Ambident Reactivity

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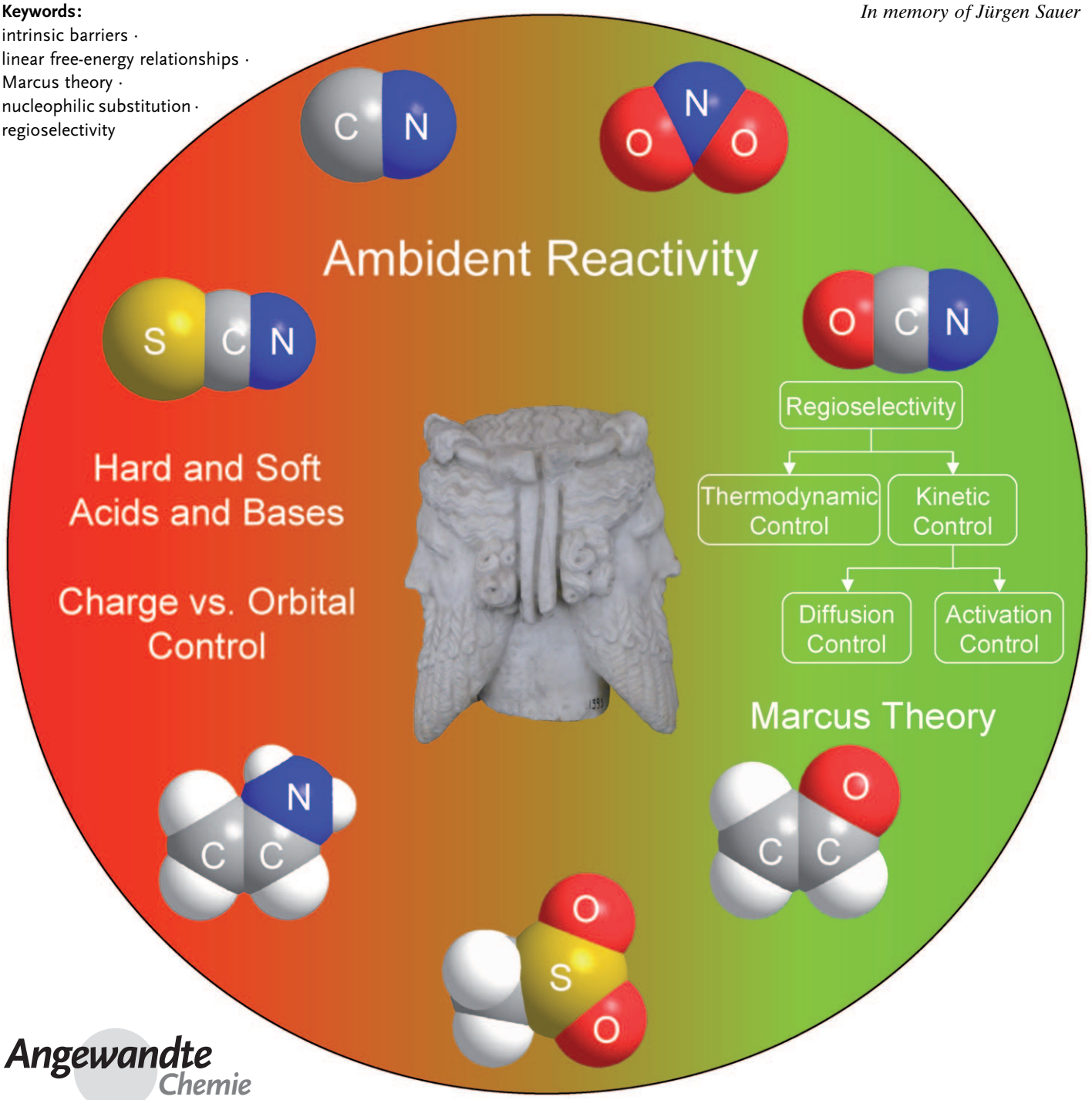
Marcus theory ·
nucleophilic substitution ·
regioselectivity

In memory of Jürgen Sauer



The concept of hard and soft acids and bases (HSAB) proved to be useful for rationalizing stability constants of metal complexes. Its application to organic reactions, particularly ambident reactivity, has led to exotic blossoms. By attempting to rationalize all the observed regioselectivities by favorable soft–soft and hard–hard as well as unfavorable hard–soft interactions, older treatments of ambident reactivity, which correctly differentiated between thermodynamic and kinetic control as well as between different coordination states of ionic substrates, have been replaced. By ignoring conflicting experimental results and even referring to untraceable experimental data, the HSAB treatment of ambident reactivity has gained undeserved popularity. In this Review we demonstrate that the HSAB as well as the related Klopman–Salem model do not even correctly predict the behavior of the prototypes of ambident nucleophiles and, therefore, are rather misleading instead of useful guides. An alternative treatment of ambident reactivity based on Marcus theory will be presented.

From the Contents

> *"Mache die Dinge so einfach wie möglich—aber nicht einfacher."*
> *Albert Einstein*

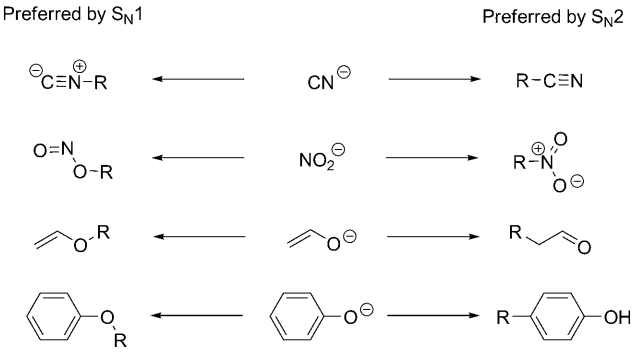
1. Introduction

Understanding and controlling ambident[+] reactivity is of eminent importance for a rational design of organic syntheses.[1] Kornblum et al. summarized their systematic investigations on the alkylations of ambident anions[2] by the statement "*The greater the S_N1 character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity and, conversely, the greater the S_N2 contribution to the transition state the greater the preference for bond formation to the atom of lower electronegativity*".[2e]

These ideas were generalized within Pearson's concept of hard and soft acids and bases (HSAB),[3] which still represents the most popular rationalization of ambident reactivity, as illustrated by a quotation from the latest edition of *March's Advanced Organic Chemistry* (Scheme 1):[4a]

"*The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (…). In an S_N1 mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from S_N1- to S_N2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom. Therefore, changing from S_N1 to S_N2 conditions should favor C attack by CN^-, N attack by NO_2^-, C attack by enolate or phenoxide ions, etc.*"

The Klopman–Salem concept of charge and orbital control of organic reactions uses similar ideas: Hard–hard interactions are charge-controlled and soft–soft interactions



Scheme 1. Preferred reaction pathways of ambident nucleophiles according to March's Advanced Organic Chemistry textbook.[4b]

are orbital-controlled.[5] Although these concepts have widely been accepted, they have also been criticized. Gompper and Wagner[6] pointed out that the HSAB concept does not differentiate between kinetic and thermodynamic control, although in many cases different conditions give rise to different products.[7] Numerous reactions of ambident electrophiles, which yield different products under conditions of kinetic and thermodynamic control, have been reviewed by Hünig.[8] Gompper and Wagner furthermore noted that the

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[+] According to IUPAC[1] an ambident system possesses two alternative and strongly interacting distinguishable reactive centers, both of which can undergo a certain reaction, but the reaction at either site stops or greatly retards subsequent attack at the second site.

decision as to whether a certain reaction is dominated by charge or orbital control is often made a posteriori, that is, after knowing the experimental facts, with the consequence that it has little predictive value. Drago summarized his criticism of the HSAB principle as follows: "*This can't miss approach sweeps a lot of interesting chemistry under the rug and leads one to believe he has understanding when in reality he may not*".[9a] Attemps to predict the reactivity of ambident nucleophiles and electrophiles using a single, general-purpose reactivity indicator[9b] were later shown not to be appropriate.[9c]

During recent years, we have extensively studied the kinetics of the reactions of benzhydrylium ions and structurally related quinone methides with a large variety of nucleophiles,[10] including hard and soft ones. While the hardness of the electrophiles shown in Figure 1 increases significantly from left to right,[11] one does not find that the correlation lines for hard nucleophiles are generally steeper than those for soft nucleophiles, which should be the case if hard nucleophiles had a particular preference to react with hard electrophiles.

Furthermore, it has been shown that the reactivity order of nucleophiles towards tritylium ions (Ritchie N_+) and benzhydrylium ions (Patz–Mayr N) is roughly the same as towards CH_3I or CH_3Br (Swain–Scott n),[12] which indicates that the order of nucleophilicities does not depend on the hardness of the electrophilic reaction partner when the electrophilic reaction center is carbon.

These observations prompted us to reexamine the applicability of the HSAB principle on the alkylations of ambident nucleophiles.[13] During this study we have found that the HSAB principle does not even correctly predict the site of alkylation of NCS^-,[13a] NC^-,[13b] NO_2^-,[13c] NCO^-,[13d] $RCHNO_2^-$,[13e] benzene sulfinate,[13f] and amide anions,[13g,h] that is, of the prototypical ambident nucleophiles, which have been used to demonstrate the applicability of the principle. Misinterpretations of experimental results, references to untraceable experiments, and neglecting the role of the diffusion limit (k ca. 10^9–$10^{10}\,M^{-1}s^{-1}$) were identified as origins of the confusion.[13]

Sensitized by these observations, we have analyzed literature reports on the regioselectivities of these and other ambident nucleophiles and electrophiles, and we have realized that the number of cases where the HSAB principle and the concept of charge- and orbital-controlled reactions give correct predictions approximate the number of cases where they fail. For that reason, we suggest abandoning these concepts as guides for predicting ambident reactivity. In the following we present an alternative approach to rationalize the behavior of ambident nucleophiles.

2. Systematic Analysis of Ambident Reactivity

2.1. General Procedure

As illustrated in Scheme 2, the first step of a systematic analysis is to clarify whether the isolated products are the results of thermodynamic or kinetic control. Methods to differentiate between kinetic and thermodynamic control are well-known and need not be discussed in this context.[4c,7] An overview of relative product stabilities obtained from important ambident nucleophiles is given in Table 1.

If the product ratio is kinetically controlled, one should analyze whether the product-determining step is diffusion-controlled ($k_2 = 10^9$–$10^{10}\,M^{-1}s^{-1}$) or activation-controlled ($k_2 < 10^9\,M^{-1}s^{-1}$). This differentiation can be based on the correlation Equation (1) introduced in Section 2.3.

If the product-determining step is activation-controlled, Marcus theory can

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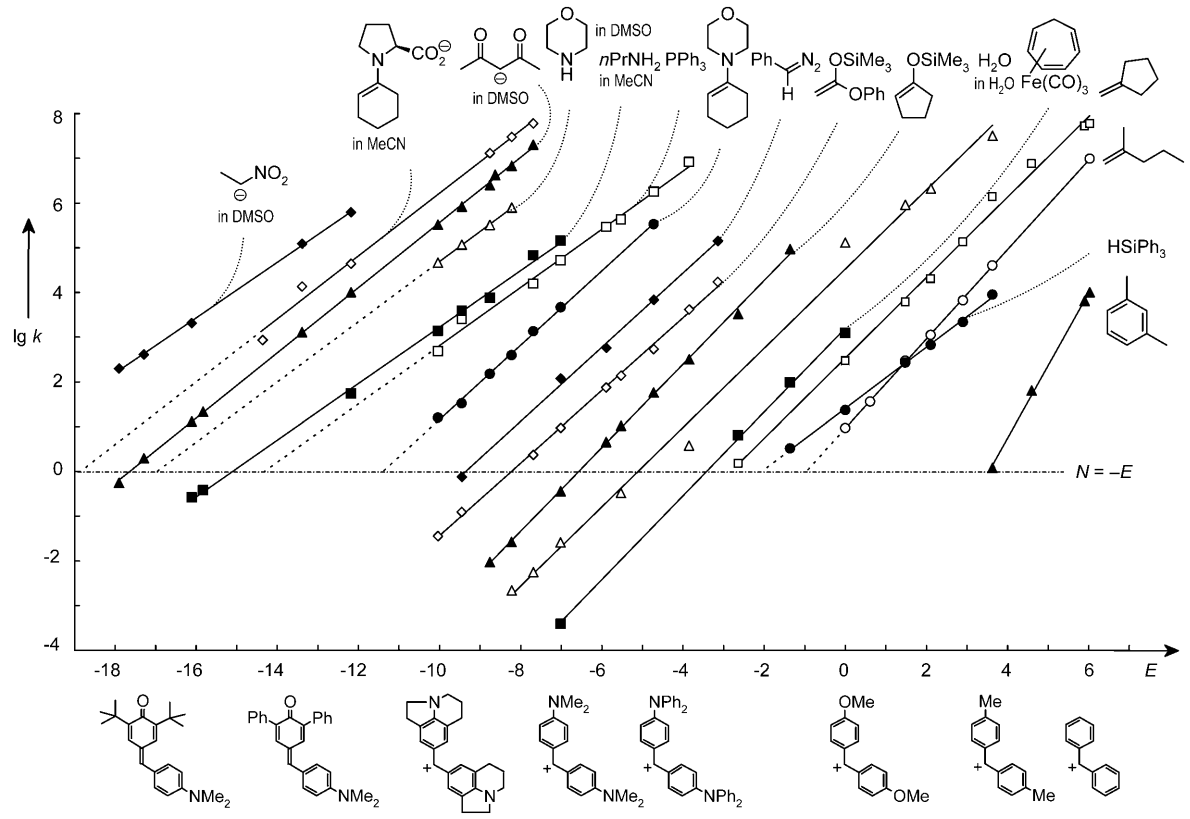
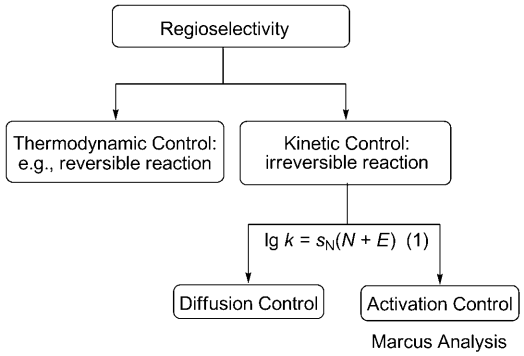


Figure 1. Comparison of the reactivities of different classes of nucleophiles (in CH_2Cl_2, 20 °C). Plots of lg *k* versus the empirical electrophilicity parameter *E*.[10]



Scheme 2. A systematic approach to ambident reactivity.

be employed to predict relative activation energies, as described in Sections 2.4–2.6.

2.2. Product Stabilities

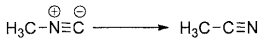
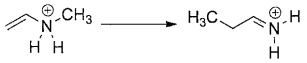
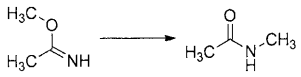
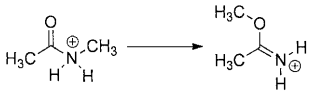
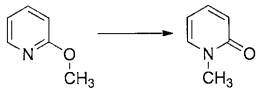
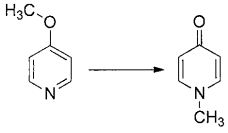
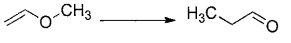
Relative thermodynamic stabilities are usually determined by calorimetric measurements, equilibrium studies, or by quantum chemical calculations. To use the same basis for comparing the thermodynamic stabilities of products which may be generated by alkylation of ambident nucleophiles, we have calculated the Gibbs energy of methyl shifts at the MP2/6-311 + G(2d,p) level of theory (Table 1). A detailed discussion of the thermodynamic stabilities will be presented in Section 3 for the individual substrates.

2.3. Differentiation between Activation- and Diffusion-Controlled Reactions

The rates of bimolecular reactions in solution are limited by diffusion, in other words, the time needed for two molecules to meet in an encounter complex. Sophisticated theories have been developed to calculate diffusion rate constants, which consider the size of the molecules, the viscosity of the reaction medium, and the temperature.[14] Since knowledge of the precise values of diffusion-controlled rate constants is not needed for our analysis, we derive the approximate magnitude of diffusion-controlled rate constants empirically from the upper limits of directly measured rate constants in various reaction series. Thus, the second-order rate constants for the reactions of benzhydrylium and tritylium ions generated by laser-flash photolysis with neutral nucleophiles in common organic solvents (CH_2Cl_2, CH_3CN) or water never exceeded $4 \times 10^9\,M^{-1}s^{-1}$.[15a] The upper limit for cation–anion combinations was $2 \times 10^{10}\,M^{-1}s^{-1}$ in acetonitrile and about $5 \times 10^9\,M^{-1}s^{-1}$ in water.[15b] Intermolecular selectivities, which were derived from competition experiments, are consistent with these numbers.[16]

As reactions which proceed with such high rates do not have activation energies, the corresponding regioselectivities

Table 1: Relative stabilities of the products obtained by methylation of ambident nucleophiles [MP2/6-311 + G(2d,p)].

Entry	Isomerization	ΔG^0 [kJ mol^{-1}]
1		−115[a]
2		−19.7[b]
3		−60.7[b]
4		−17.1[a]
5		−117[a]
6		−28.3[a]
7		−80.1[b]
8		−20.1[b]
9		−32.9[c]
10		−13.7[c]
11		−120[b]
12		−93.9[a]
13		−28.9[b]
14		−50.4[b]

[a] From Ref. [19]. [b] See the Supporting Information. [c] From Ref. [13h].

(as well as stereoselectivities) cannot be derived from transition-state models.

In numerous publications we have shown that the second-order rate constants for the reactions of carbocations and Michael acceptors with n nucleophiles (alcohols, amines, etc.), π nucleophiles (alkenes, arenes, etc.), and σ nucleophiles (hydrides) can be calculated by Equation (1), where nucleophiles are characterized by two parameters (nucleophilicity N, slope s_N, previously termed s), while electrophiles are characterized by one parameter (electrophilicity E).[10] For the inclusion of S_N2-type reactions, an additional electrophile-specific parameter s_E is needed.[12c]

$$\lg k(20\,^{\circ}\mathrm{C}) = s_N(N + E) \quad (1)$$

As discussed elsewhere,[10a,g] Equation (1) is mathematically equivalent to a conventional linear free-energy relationship. However, unlike in ordinary linear free-energy relationships, where the intercepts with the ordinate are considered, Equation (1) defines the nucleophilicity parameter N as the intercept with the abscissa ($N = -E$ for $\lg k = 0$; see Figure 1); in this way it is possible to arrange nucleophiles of widely varying reactivity in a single scale without the need for long-ranging extrapolations. As Equation (1) holds only for rate constants up to 10^8 M^{-1} s^{-1}, calculated rate constants $\lg k > 9$ are not real, but indicate diffusion control.

With reactivity parameters published for 620 nucleophiles and 182 electrophiles,[17] one can already predict the boundary between activation and diffusion control for a considerable number of reactions. Reactions which proceed without a barrier at both sites of an ambident system are generally unselective, although exceptions have been observed.[18] The selectivity of activation-controlled reactions can be rationalized by Marcus theory.

2.4. Marcus Theory

Marcus theory[20] considers reactants and products nestling in a parabolic bowl, and the transition state is approximated as the point of intersection of the two bowls. For electron-transfer reactions between metal ions, that is, the types of reactions first analyzed by the Marcus Equation, the parabolic curves refer to the movement of solvent molecules around the reactants and products. In the case of group-transfer reactions [Eq. (2)], which are depicted in Figure 2, a major contribution to the parabolic term comes from the A–X and B–X vibrations.[20e]

$$\mathrm{A{-}X + B \rightarrow A + X{-}B} \quad (2)$$

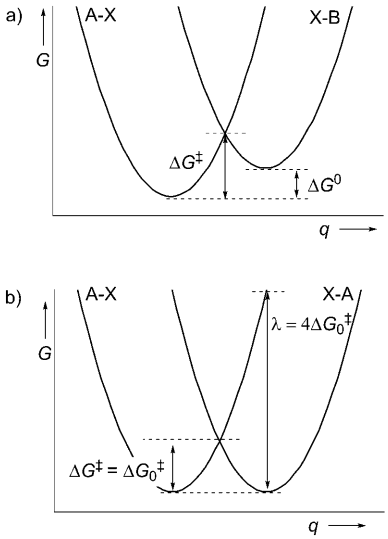


Figure 2. Intersecting parabolas in a) non-identity reactions and b) identity reactions. q refers to the nuclear configuration.

The point of intersection of the two parabolas in Figure 2a can be expressed by the Marcus Equation [Eq. (3)].

$$\Delta G^{+} = \Delta G_0{}^{+} + 0.5\Delta G^0 + (\Delta G^0)^2/(16\Delta G_0{}^{+}) \quad (3)$$

Equation (3) ignores the work term *w*, which includes the Gibbs energy for bringing the separate reactants together and separating the products. This neglect is fully justified when considering intramolecular selectivity, because *w* refers to the formation of the common encounter complex.

In Equation (3), the Gibbs energy of activation $\Delta G^{\neq}$ is expressed by a combination of the Gibbs energy of reaction ΔG^0 and the intrinsic barrier $\Delta G_0^{\neq}$, which corresponds to $\Delta G^{\neq}$ of an identity reaction, where $\Delta G^0 = 0$ (Figure 2b). The intrinsic barrier $\Delta G_0^{\neq}$ can thus be considered as the fraction of $\Delta G^{\neq}$ which is left after eliminating the thermodynamic component.

Marcus suggested calculating the intrinsic barrier of a non-identity reaction as the average of the two corresponding identity reactions.[20c,d,21] Application of this so-called additivity principle to methyl transfer reactions yields Equation (7), wherein the intrinsic barrier $\Delta G_0^{\neq}$ for the S_N2 reaction in Equation (4) is calculated as the average of the activation energies of the identity reactions in Equations (5) and (6).

$$X^- + H_3C{-}Y \rightarrow X{-}CH_3 + Y^- \quad (4)$$

$$X^- + H_3C{-}X \rightarrow X{-}CH_3 + X^- \quad (5)$$

$$Y^- + H_3C{-}Y \rightarrow Y{-}CH_3 + Y^- \quad (6)$$

$$\Delta G_0^{\neq}[\text{Eq. (4)}] = 0.5\,(\Delta G^{\neq}[\text{Eq. (5)}] + \Delta G^{\neq}[\text{Eq. (6)}]) \quad (7)$$

The validity of this approach has been confirmed computationally and experimentally by several research groups.[22,23] The excellent agreement of directly calculated activation energies with those obtained by the Marcus approach (Figure 3)[22h] already implies that there are no variable hard–hard or soft–soft interactions between the different groups X and Y in Equations (4)–(6). Thus, the intrinsic barrier for the reaction of $HS^- + H_3CF$ equals the average of the barriers for $F^- + CH_3F$ and $HS^- + H_3CSH$.

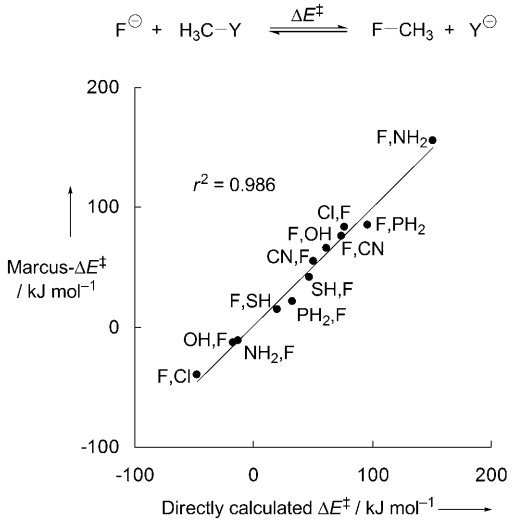


Figure 3. Correlation of the directly calculated activation energies with those derived from the Marcus Equation; (F,X) values refer to the forward reactions while (X,F) refer to the reverse reaction [from Ref. [22h], CCSD(T)/TZ2PF + dif data].

Application of the Marcus equation [Eq. (3)] to ambident reactivity thus requires knowledge of relative product stabilities ($\Delta\Delta G^0$) and relative magnitudes of the intrinsic barriers ($\Delta\Delta G_0^{\neq}$). As relative product stabilities ($\Delta\Delta G^0$) are usually known or can be derived experimentally or computationally by standard methods (Section 2.2), we will now focus on intrinsic barriers.

2.5. How Can Relative Magnitudes of Intrinsic Barriers Be Predicted?

2.5.1. Hoz Approach

By using the G2(+) method, Hoz and co-workers were the first to recognize a continuous decrease in the intrinsic barriers, namely, the Gibbs energies of activation for the identity reactions [Eq. (5)], as X changes from $MeCH_2$ to MeNH, MeO, and F (Table 2).[23] Uggerud correlated this trend with the ionization energy of the nucleophile X^-, and rationalized that those nucleophiles that form bonds to carbon atoms with stronger electrostatic character give rise to lower barriers because of decreased electron repulsion in the transition state.[24] Furthermore, Hoz et al. noticed that the intrinsic barriers $\Delta G_0^{\neq}$ change only slightly as one moves from top to bottom within one group in the periodic table.[23] The almost constant values of the intrinsic barriers within a group have been rationalized by Arnaut and Formosinho by two opposing effects:[25] When moving from the top to the bottom within the periodic table, the C–X bond length increases, thereby leading to increasing separation of the parabolas and a rise in the energy of the transition state. At the same time, the force constants decrease and cause a flattening of the parabola and a lowering of the transition-state energy. Both effects clearly compensate each other and result in almost constant values of $\Delta G_0^{\neq}$ within one group. While we usually employ SI units, the energies in Table 2 are given in kcal mol^{-1}, because the series 10→20→30→40 kcal mol^{-1} when moving from Group 17 to Group 14 can more easily be memorized.

Table 2: G2(+) Intrinsic barriers for the identity reactions (all in kcal mol^{-1}, data from Ref. [23]).

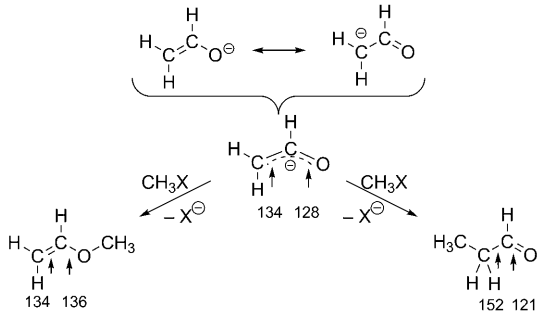
$X^- + H_3C{-}X \rightarrow X{-}CH_3 + X^-$			
Me**C**H$_2^-$	Me**N**H$^-$	Me**O**$^-$	**F**$^-$
44.7	29.3	19.5	11.6
Me**Si**H$_2^-$	Me**P**H$^-$	Me**S**$^-$	**Cl**$^-$
45.8	29.8	21.9	13.2
Me**Ge**H$_2^-$	Me**As**H$^-$	Me**Se**$^-$	**Br**$^-$
38.1	24.5	17.8	10.8
Me**Sn**H$_2^-$	Me**Sb**H$^-$	Me**Te**$^-$	**I**$^-$
30.6	19.7	15.3	9.6

Organic chemists may associate the results of Table 2 with the well-known fact that halide exchange reactions in S_N2

processes proceed smoothly (Finkelstein reaction), whereas transetherifications (alkoxide exchange reactions) or transaminations cannot be performed under basic conditions.

2.5.2. Principle of Least Nuclear Motion (PLNM)

An alternative access to relative intrinsic barriers employs the reorganization energy λ that is required for the deformation of the reactants to the geometry of the products. According to Figure 2b, the intrinsic barrier $\Delta G_0^{\neq}$ equals $^1/_4$ of the reorganization energy λ. Thus, relative intrinsic barriers can be derived from the principle of least nuclear motion,[26] which claims that "*those elementary reactions will be favored that involve the least change in atomic position and electronic configuration*".[26d] Despite an excellent review by Hine[26d] in 1977, the PLNM has become unfashionable in recent years. We think that this disrespect is unjustified because the principle of least nuclear motion, as described by Hine, provides useful estimates of the relative magnitudes of intrinsic barriers. Let us consider the enolate anion, for example. From the bond lengths listed in Scheme 3, one can derive that the geometry of the enolate anion resembles that of the enol ether more closely than that of the aldehyde. In addition, O-alkylation avoids rehybridization of the $H_2C_{sp^2}$ group and thus requires less reorganization energy λ ($= 4\Delta G_0^{\neq}$) than C-alkylation. As a consequence, the PLNM predicts that the intrinsically favored site of attack is at the oxygen atom, where the negative charge is located in the most important resonance structure of the enolate ion (Scheme 3, top left).

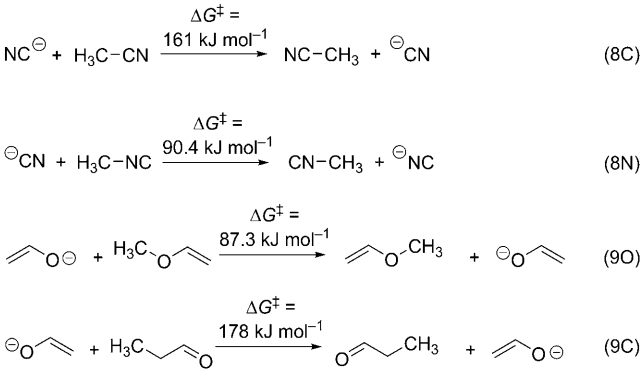


Scheme 3. Ambident reactivity of an enolate anion (bond lengths in pm).[27]

The situation discussed for the enolate anions is typical for π-delocalized systems: The intrinsically preferred site can usually be derived from the electron distribution in the most important resonance structure.

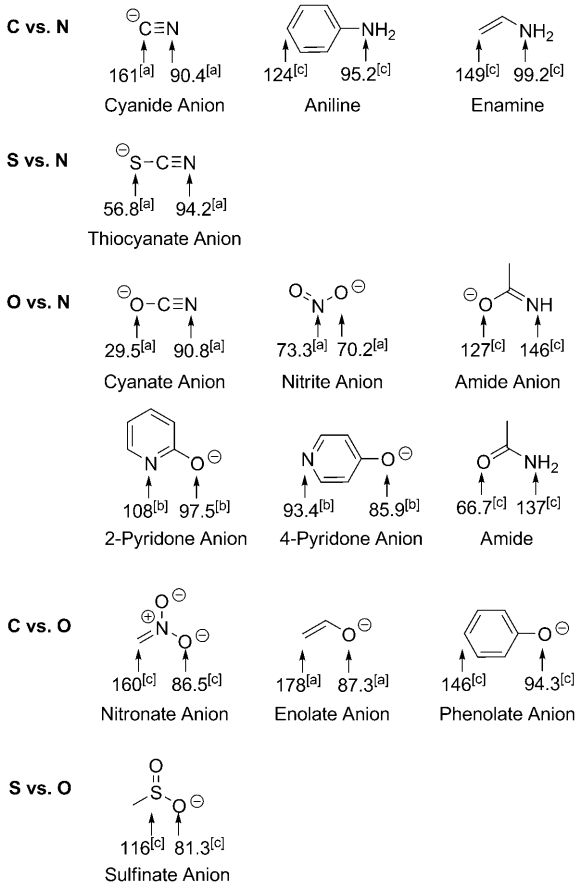
2.5.3. Calculated Barriers for Identity Reactions of Ambident Nucleophiles

As formulated in Equations (8C/8N) and (9O/9C), we have calculated the barriers for the identity methyl transfer reactions of ambident systems at the MP2/6-311 + G(2d,p) level of theory; details of these calculations have previously been reported.[19]



In analogy to the observations by Hoz, the intrinsic barrier is lower for N attack at CN^- ions [Eqs. (8C/8N)] and for O attack at enolate ions [Eqs. (9O/9C)]. The same trend—smaller intrinsic barriers for attack at the atom which is further right in the periodic table—has been observed for many other ambident nucleophiles, as summarized in Scheme 4.

It should be noted that the same ordering of intrinsic barriers can also be derived for π-delocalized systems from the PLNM: less reorganization is needed for O attack at



Scheme 4. Energy barriers [$\Delta G^{\neq}$, kJ mol^{-1}, MP2/6-311 + G(2d,p)] for identity methyl transfer reactions as exemplified in Equations (8C/8N) and (9O/9C) ([a] from Ref. [19], [b] from Ref. [13h], [c] see the Supporting Information of this Review).

enolates and phenolates and for N attack at enamines and anilines.

2.6. A Qualitative Marcus Approach to Ambident Reactivity

As recently reported, one can substitute the calculated values of the intrinsic barriers $\Delta G_0^{\neq}$ and Gibbs energies ΔG^0 into the Marcus equation [Eq. (3)] to calculate $\Delta G^{\neq}$ and thus arrive at complete Gibbs energy diagrams for the reactions of cyanide, cyanate, thiocyanate, nitrite, and enolate anions with alkyl halides in the gas phase.[19] Solvation models would be needed for a quantitative analysis in solution, particularly when reactions are considered, where ionic products are generated from neutral reactants.[28] Although this approach appears feasible, a qualitative analysis of the thermodynamic data in Table 1 and of the intrinsic reactivities in Scheme 4 may be more practical.

Figure 4 represents a qualitative description of the reactions of an ambident nucleophile $A{-}B^-$ with alkyl halides RX of different reactivity. For the sake of simplicity, all

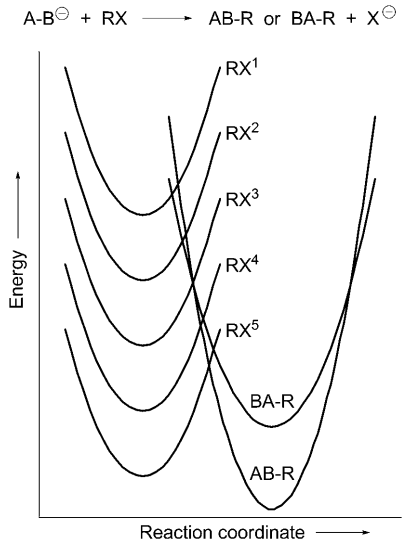


Figure 4. Influence of the Gibbs energy of reaction on the Gibbs energy of activation and thus on the regioselectivity of the attack at an ambident nucleophile with reactive sites A and B.

parabolas for RX^1 to RX^5 are assumed to have the same opening and just differ in their relative positions. The two parabolas for the products on the right differ in their position and opening. The product obtained by alkylation at atom B is thermodynamically favored (more negative ΔG^0) and intrinsically disfavored (steeper parabola) than the product obtained by alkylation at atom A.

Figure 4 shows that the highly exergonic reactions with RX^1 and RX^2 follow the intrinsically favored pathway leading to alkylation at A ($\rightarrow$ BA–R). The reaction with RX^3 yields both products with equal rates, and the transition state for the reaction with RX^4 is already dominated by the $\Delta\Delta G^0$ term, which favors attack at B ($\rightarrow$ AB–R). A frequently encountered situation is shown for the reaction of RX^5: As attack at site A yields a product which is thermodynamically less stable than the reactants, only the products AB–R can be generated.

As the Marcus-inverse region, that is, a decrease in the rate constant with increasing exergonicity, has only been observed for highly exergonic intramolecular electron-transfer reactions,[29] the relative magnitudes of the Gibbs energy of activation ($\Delta\Delta G^{\neq}$) of the group-transfer reactions under consideration can be derived from the first two terms of Equation (3). The following discussion of the individual ambident systems, which is based on the thermodynamic data in Table 1 and the intrinsic barriers in Scheme 4, furthermore assumes that the relative product stabilities are not significantly altered when the methyl group is replaced by another alkyl or aryl group; exceptions can be expected when two isomers differ only slightly in energy. According to the second term of Equation (3) the ΔG^0 values given in Table 1 have to be divided by 2 to estimate their contribution to the Gibbs energies of activation. On the other hand, application of the additivity postulate [Eq. (7)] to calculate the contribution of the intrinsic barriers also implies division of $\Delta G^{\neq}$ for the identity reactions given in Scheme 4 by a factor of 2. As a result, one can directly compare the absolute values given in Table 1 and Scheme 4.

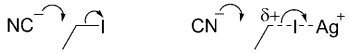
The algebraic form of Equation (3) implies that the quadratic term only becomes significant for highly exergonic reactions with small intrinsic barriers, which are not encountered in group-transfer processes. We can, therefore, conclude that whenever a thermodynamically less stable product is formed preferentially under conditions of kinetic control, it must be generated via the lower intrinsic barrier. On the other hand, kinetically controlled reaction products are not necessarily formed via the lower intrinsic barrier.

3. Ambident Nucleophiles

3.1. Carbon versus Nitrogen Attack

3.1.1. Cyanide Anion

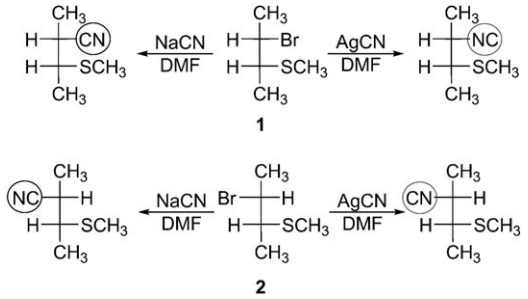
The cyanide ion CN^- used to be one of the classical examples for illustrating the application of the Klopman–Salem Equation and the HSAB principle. As described in Scheme 5, the formation of nitriles by the reaction of alkali



Scheme 5. Common description of the ambident reactivity of cyanide, which should be revised.

cyanides with alkyl halides was explained by the preferred attack of the "soft" carbon terminus of the cyanide ion at the "soft" alkyl halides. A change from an S_N2 to S_N1 mechanism was postulated to rationalize the formation of isonitriles in the reactions of alkyl halides with silver cyanide; in this case, the favorable hard–hard interaction between the carbocation and the nitrogen atom of the cyanide was considered to be responsible for the change in regioselectivity.

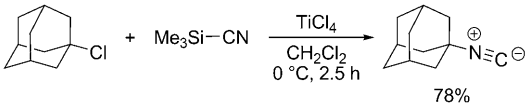
This rationalization is contradicted by several experimental findings. More than two decades ago, Carretero and Garcia Ruano reported that *erythro*- and *threo*-2-bromo-3-(methylthio)butane (**1** and **2**) react with sodium cyanide and silver cyanide with retention of configuration and with > 96 % regioselectivity to give cyanides and isocyanides, respectively (Scheme 6).[30]



Scheme 6. Reactions of *erythro*- and *threo*-2-bromo-3-(methylthio)-butanes **1** and **2** with metal cyanides.[30]

Their conclusion that the reactions with NaCN and AgCN follow the same mechanism and that "*the observed regioselectivity with both metal cyanides (…) cannot be explained as variations in the hardness of the electrophilic carbon induced by the interactions between the metal cation and the halogen*" found little attention.[31] In agreement with "*older hypotheses*", the formation of isonitriles with AgCN (Scheme 6) was explained by the "*participation of a species (non-free CN^-) in which the Ag^+ ion is bonded to the carbon atom.*"[30]

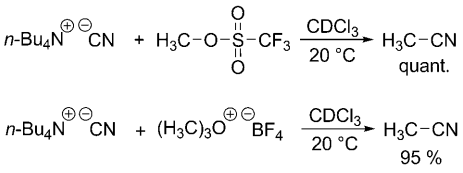
The formation of 1-isocyanoadamantane from 1-chloroadamantane and trimethylsilyl cyanide in the presence of $TiCl_4$ (Scheme 7) demonstrates that blocking of the carbon atom of cyanide is not restricted to Ag^+.[32]



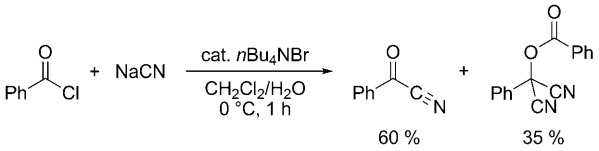
Scheme 7. Formation of 1-isocyanoadamantane.[32a]

Exclusive formation of nitriles, which is well known for reactions of primary alkyl bromides and alkyl iodides with NaCN and KCN, has also been observed for the methylation of $[Bu_4N]^+[CN]^-$ with methyl triflate and trimethyloxonium tetrafluoroborate, two of the hardest methylating agents available (Scheme 8). Attack at the hard nitrogen atom, as predicted by the HSAB principle, has not been observed.[13b]

Only benzoyl cyanide and follow-up products were formed when benzoyl chloride was combined with $[(Ph_3P)_2N]CN$,[33] guanidinium cyanide,[34] or NaCN under conditions of phase-transfer catalysis[35] (Scheme 9). This observation also contrasts the expectations based on the HSAB principle, which predicts the formation of isonitriles by attack of the "hard" nitrogen end of the cyanide at the "hard" acyl center of acyl chlorides.

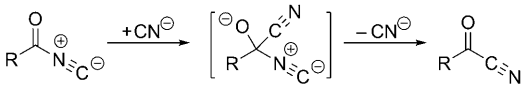


Scheme 8. Exclusive formation of acetonitrile in the reactions of $Bu_4N^+CN^-$ with the hard methylation agents methyl triflate and trimethyloxonium tetrafluoroborate.[13b]



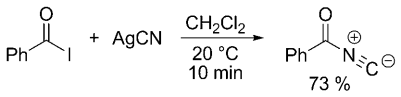
Scheme 9. Synthesis of benzoyl cyanide from NaCN and benzoyl chloride by phase-transfer catalysis.[35]

As rearrangements of isocyanides into cyanides are well-known,[36] one cannot a priori exclude that the acyl cyanides described in Scheme 9 are formed from intermediate acyl isocyanides, which may isomerize via acylium ions or the mechanism shown in Scheme 10.



Scheme 10. Rearrangement of acyl isocyanides to acyl cyanides.

On the other hand, acyl isocyanides, which were generated by treatment of acyl iodides with silver cyanide, were shown to be stable in dilute solution after removal of Ag^+ salts (Scheme 11).[37]



Scheme 11. Formation of benzoyl isonitrile through reaction of benzoyl iodide with silver cyanide.[37]

From the cited experiments one can derive that free cyanide ions generally react at the carbon atom with "hard" and "soft" electrophiles and that nitrogen attack only occurs when the attack at carbon is blocked by another group (e.g. by Ag^+ or Me_3Si^+).[38]

For a systematic analysis of the behavior of the cyanide ion we have studied the rates of its reactions with benzhydrylium ions (Figure 5), which have been used as reference electrophiles for the determination of nucleophilicity parameters. Exclusive formation of benzhydryl cyanides was observed in all reactions with stabilized benzhydrylium ions, and from the plot of $\lg k$ versus the electrophilicity parameter E of the benzhydrylium ions one can extrapolate that the diffusion limit is reached when the electrophilicity E of the

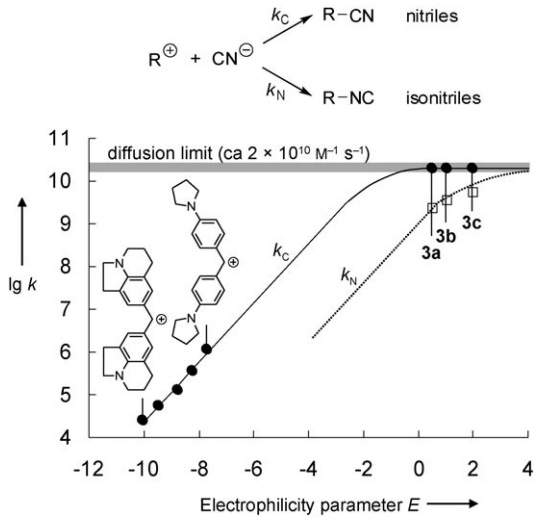
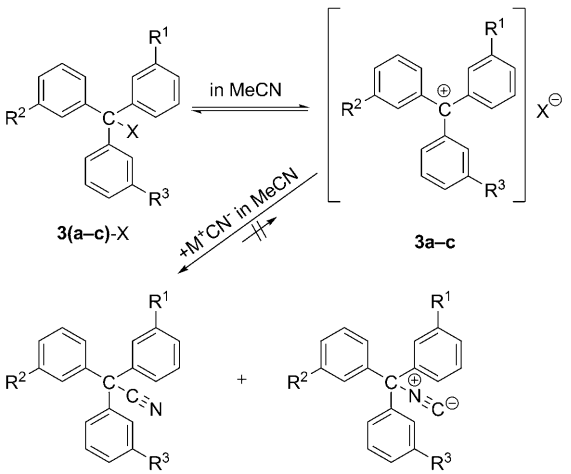


Figure 5. Plot of lg k for the reactions of benzhydrylium ions Ar_2CH^+ and tritylium ions Ar_3C^+ with the cyanide ion versus the electrophilicity parameters E (in MeCN at 20 °C). The structures of the tritylium ions **3a–c** are shown in Scheme 12.[13b]

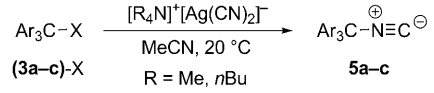
carbocations exceeds values of approximately −2 to 0 (Figure 5).[13b]

As illustrated in Figure 5, the observation by Songstad et al.[39] of 10% trityl isocyanide (**5a**) along with 88% trityl cyanide (**4a**) from the reactions of trityl halides with free CN^- can be explained by barrierless attack at the carbon atom ($k_C \approx 2\times10^{10}\,M^{-1}s^{-1}$) and a ninefold lower rate of attack at the N atom. When the more electrophilic *m*-chloro-substituted tritylium ions **3b** and **3c** were employed, the nitrile/isonitrile ratio decreased because the rate of attack at the carbon atom remained constant while the rate of attack at the nitrogen atom increased (Scheme 12).



	R^1	R^2	R^3	X	Reagent	[4] / [5]
3a	H	H	H	Cl	$(Ph_4As)CN$	8.8 : 1
3b	Cl	H	H	Cl	$(Bu_4N)CN$	5.7 : 1
3c	Cl	Cl	Cl	Br	$(Bu_4N)CN$	3.6 : 1

Scheme 12. Product distribution in the reactions of the trityl halides (**3a–c**)-X with cyanide ions.[13b,39]



Scheme 13. Selective formation of isonitriles **5a–c** in reactions of trityl derivatives (**3a–c**)-Cl/Br with tetraalkylammonium dicyanoargentate.[13b]

All the trityl halides (**3a–c**)-X gave trityl isocyanides exclusively when treated with tetraalkylammonium dicyanoargentates (Scheme 13).[13b]

From Figure 5 one can extrapolate that the unsubstituted benzhydrylium ion ($E = 5.9$), α-alkyl benzyl cations (E ca. 3 to 9),[40] and tertiary alkyl cations (E ca. 8)[41] will undergo barrierless reactions with both termini of the free CN^- ion in acetonitrile. Therefore, attempts to explain C/N ratios by classical transition-state models are obsolete.

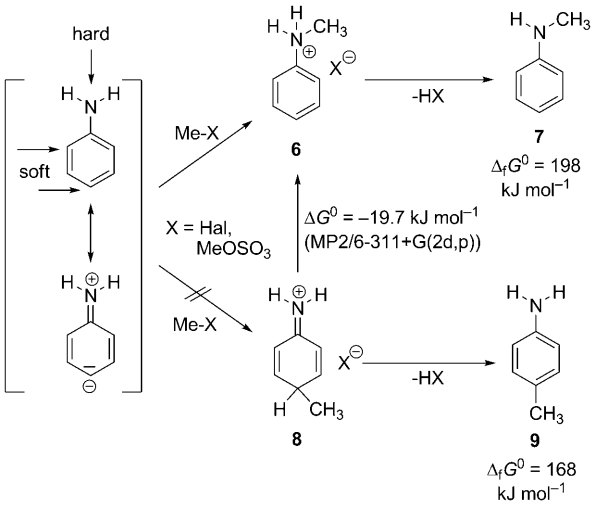
Furthermore, it has to be considered that S_N1 reactions with cyanide ions rarely occur in protic solvents. Since the nucleophilicity of CN^- decreases significantly from $N = 16.27$ ($s_N = 0.70$) in CH_3CN[13b] to $N = 9.19$ ($s_N = 0.60$) in water,[42] most carbocations generated as S_N1 intermediates in alcoholic or aqueous solution react faster with the solvent (which is present in large excess) than with CN^-.[43] Thus, the reaction of 1-chloro-1-(4-methoxyphenyl)ethane with KCN in an ethanolic solution yields the corresponding ethyl ether in almost quantitative yield.[44] Reactions of *tert*-haloalkanes with alkali-metal cyanides in alcohols give particularly low yields of substitution products because of the high Brønsted basicity of CN^-. Depending on the reaction conditions, only small amounts of *tert*-alkyl cyanides are formed along with tertiary ethers and elimination products.[45]

In summary, all the experimental investigations indicate that free cyanide ions are attacked at the carbon atom by C electrophiles. Attack at the C atom accompanied by attack at the N atom is observed in diffusion-controlled reactions, and predominant attack at the nitrogen atom was only found when the carbon terminus was blocked by coordination with silver ions or other Lewis acids. The large thermodynamic preference for C-alkylation (Table 1, entry 1), which is also reflected by Rüchardt's work on the isocyanide–cyanide rearrangement,[36b] overrules the intrinsically favored attack at the nitrogen atom, which is quantified in Scheme 4.

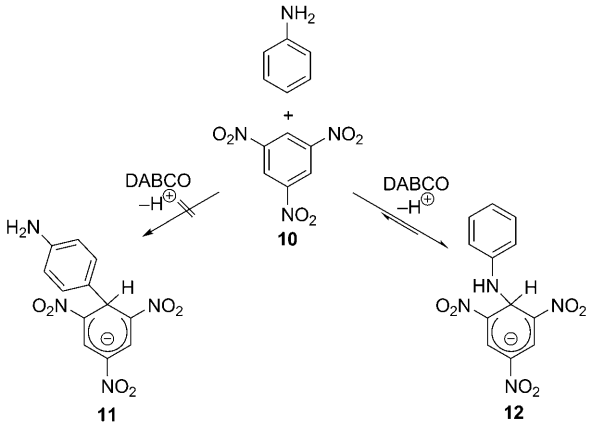
3.1.2. *Anilines*

Following the HSAB principle, one would expect hard electrophiles to attack at the nitrogen atom of aniline and soft electrophiles to attack at the carbon atom. However, as shown in Scheme 14, soft alkyl halides as well as hard dialkyl sulfates react selectively at the nitrogen atom of aniline.[46] From the known Gibbs energies of formation, we can derive that 4-methylaniline (**9**) is thermodynamically favored over *N*-methylaniline (**7**) by 30 kJ mol^{-1}.[47] On the other hand, the anilinium ion **6**, the precursor of **7**, was calculated to be 19.7 kJ mol^{-1} more stable than the benzenium ion **8** (entry 2 in Table 1).

In line with the facts that nitrogen is located further right in the periodic table than carbon and less reorganization is



Scheme 14. Methylation of aniline (attack at the *ortho* position is not shown; $\Delta_f G^0$ from Ref. [47]).



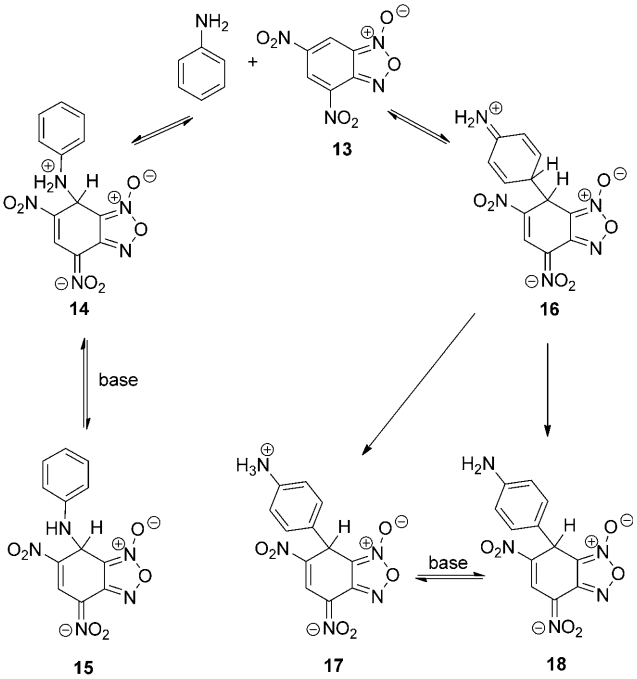
Scheme 15. Reaction of aniline with trinitrobenzene (**10**) to yield only the product of N attack **12** (in DMSO at 25 °C).[50] DABCO = 1,4-diazabicyclo[2.2.2]octane.

needed for attack at the nitrogen atom than at the carbon atom, a lower intrinsic barrier was calculated for N attack (Scheme 4). As both terms ($\Delta\Delta G^0$ and $\Delta\Delta G_0^{\neq}$) in Equation (3) indicate a preference for N attack, one can rationalize that aniline is alkylated at nitrogen by hard and soft methylating agents.

The kinetically preferred attack of carbon electrophiles at the nitrogen atom can also be calculated by using the correlation Equation (1). While $N = 12.64$ ($s_N = 0.68$)[48] has been derived from the reactions of the amino group of aniline (in acetonitrile) with electrophiles, $N \approx 4$ has been extrapolated for the *para* position of aniline from the correlation of the N values of monosubstituted benzenes with σ^+ of the corresponding substituents.[49]

Nitrogen is also the preferred site of attack of trinitrobenzene at aniline.[50] From $E = -13.2$[51] for trinitrobenzene (**10**) and $N \approx 4$, $s_N = 0.8$–1.0 for the *para* position of aniline, one can estimate rate constants in the range of 4×10^{-8} to $7 \times 10^{-10}\,\text{M}^{-1}\text{s}^{-1}$ for the attack of trinitrobenzene at the aromatic ring of aniline. From these rate constants one can derive that the attack of trinitrobenzene at the *para* position of aniline (electrophilic aromatic substitution) would have half-reaction times of 1 to 50 years in 1 M solutions of the reactants at 20 °C. As a consequence, rearrangement of the σ adduct **12** to the biphenyl derivative **11** was not observed (Scheme 15).

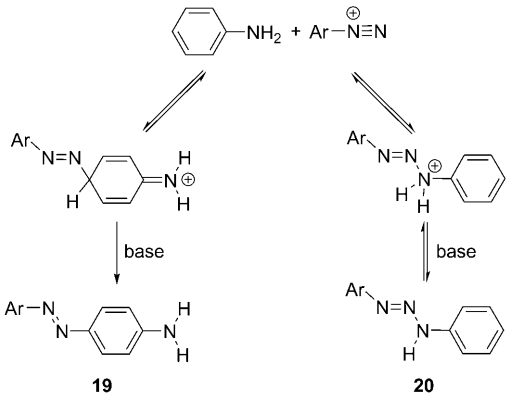
When 4,6-dinitrobenzofuroxan (**13**) was treated with one equivalent of aniline, C attack with rapid formation of **17** was observed (Scheme 16).[52] A 1:1 mixture of **15** and **18** was found, however, when **13** was treated with two equivalents of aniline. These results are consistent with the assumption that, for the same reasons as discussed above, N attack at aniline is kinetically preferred. When aniline is not used in excess, **14** cannot be deprotonated to give **15** and, therefore, undergoes dissociation with formation of the reactants, which eventually yield the thermodynamically preferred product **17**. In contrast to the situation described for trinitrobenzene (Scheme 15), the higher electrophilicity of **13** now enables the attack at the



Scheme 16. Ambident reactivity of aniline towards 4,6-dinitrobenzofuroxan (**13**; in DMSO at 20 °C).[52b]

para position of aniline (→**16**), for which a rate constant of $0.1\,\text{M}^{-1}\text{s}^{-1}$ (at 20 °C) can be calculated by Equation (1) from $E(\mathbf{13}) = -5.1$[53] and N(*p* position of aniline) ≈ 4.

Similar regioselectivities are found in azo coupling reactions. It has long been known that anilines as well as *N*-alkyl anilines initially form triazenes in coupling reactions with benzenediazonium salts (N coupling), whereas C coupling takes place with tertiary aromatic amines.[54] Different behavior was only observed when the nucleophilicity of the aromatic ring of the aniline was raised by additional substituents; however, an initial attack at nitrogen has to be

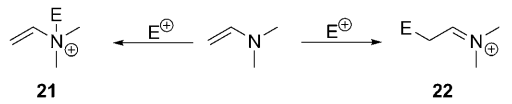


Scheme 17. Ambident reactivity of aniline in reactions with arene diazonium ions.[55]

considered even in such cases.[55] It was reported that the reversible attack at the nitrogen atom is generally 20–25 times faster than the attack at the carbon atom. The mechanism depicted in Scheme 17 is consistent with the experimental findings[55] and shows that even diazonium ions prefer N attack under conditions of kinetic control. In the absence of base, the formation of the triazene **20** is reversible and one observes the azo compound **19** as the only reaction product.

3.1.3. Enamines

Enamines can be attacked by electrophiles either at the nitrogen atom to yield enammonium ions **21** or at the carbon atom to yield iminium ions **22** (Scheme 18).[56]

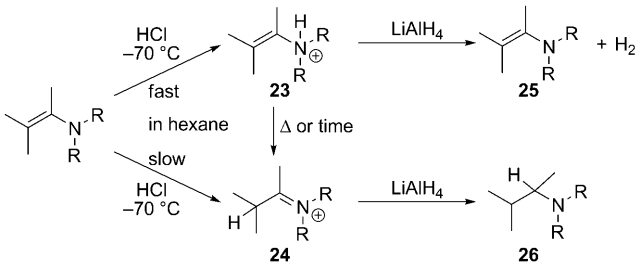


Scheme 18. Ambident reactivity of enamines.

A large variety of enamines derived from aldehydes and ketones was protonated exclusively at the nitrogen atom by gaseous HCl in hexane at −70 °C.[57] The resulting enammonium ions **23** rearranged to the thermodynamically more stable iminium ions **24** upon warming to room temperature. Spectroscopic methods as well as reactions of the protonated enamines have been employed to elucidate the site of protonation (Scheme 19).

Freshly prepared hydrochlorides of 1-morpholino-2-ethylhexa-1,3-diene at −70 °C consist mainly of the N-protonated species; after several hours C2- and C4-protonated species were identified exclusively.[57d,e]

The reactions with weaker acids such as acetic or benzoic acid in diethyl ether yielded only iminium ions, while products of N protonation were not detectable.[57e] These and related[58] observations led to the conclusion that protonation at the nitrogen atom is fast and reversible, while protonation at the carbon atom is slow but yields the thermodynamically favored



Scheme 19. Protonation of enamines and subsequent reaction with $LiAlH_4$.[57f]

iminium ions (Figure 6). Enammonium ions are more readily deprotonated by the more basic counterion acetate than by the less basic chloride ion. Hence, only protonation of the carbon atom can be observed in protonation experiments with carboxylic acids.

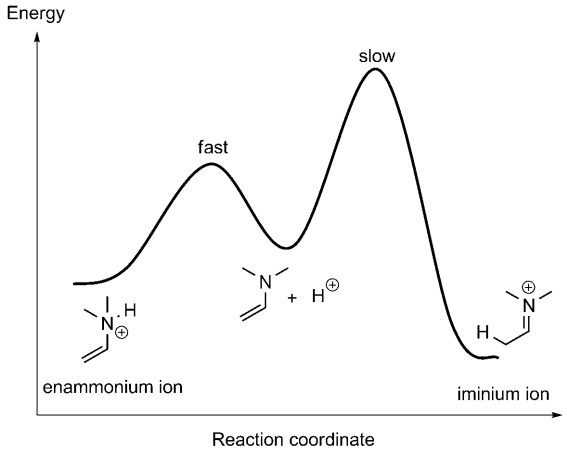
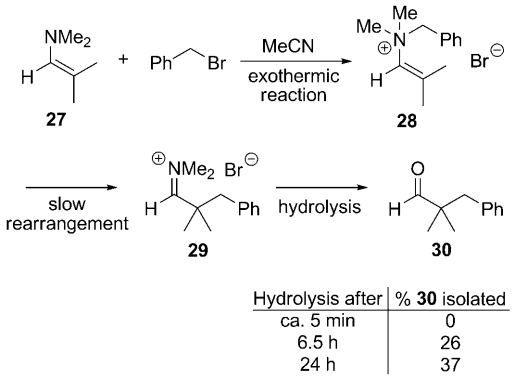


Figure 6. Energy profile for the protonation of enamines.

Although this behavior has been explained by hard–hard interactions between H^+ and the enamine, the following examples show that soft alkylating reagents show a similar pattern.

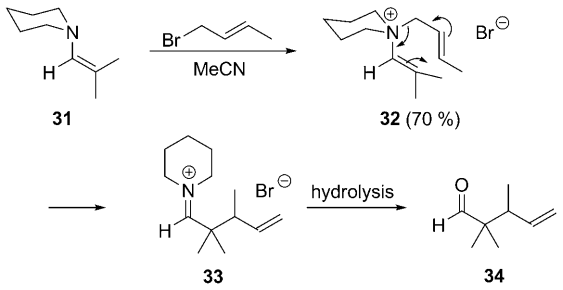
While Stork et al. reported that enamines of ketones generally give C-alkylated products when treated with alkylating agents under reflux,[59a–c] Elkik observed N alkylation with methyl iodide and ethyl bromide of some enamines derived from aliphatic aldehydes.[60] The selective C allylation of these enamines by allyl bromide prompted Elkik to suggest that enamines are also initially attacked by alkyl halides at the nitrogen atom followed by a subsequent rearrangement to yield the product of C attack. Further support for this hypothesis comes from results of Brannock and Burpitt[61] who observed a fast exothermic reaction when benzyl bromide was added to the enamine **27** in acetonitrile (Scheme 20). The variable yield of aldehyde **30** after hydrolysis of the reaction mixture at different time intervals also suggests that enamines are initially attacked at the nitrogen atom (yielding the enammonium ion **28**). The thermodynami-



Scheme 20. Alkylation of enamine **27** with benzyl bromide.[61]

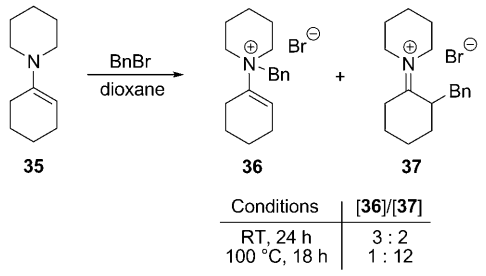
cally more stable product of C-alkylation **29** is then formed in a subsequent slow rearrangement reaction.

Consistent with these findings, Opitz isolated the N-allylated enammonium bromide **32** and showed that it isomerized through an aza-Claisen rearrangement to the corresponding iminium salt **33** (Scheme 21).[62]



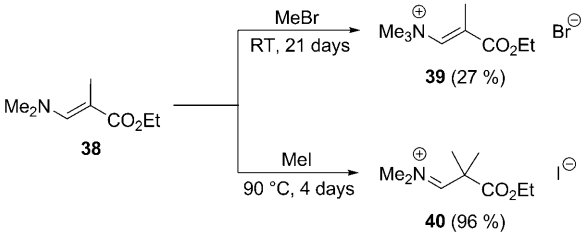
Scheme 21. Reaction of enamine **31** with crotyl bromide.[62]

A systematic study by Kuehne and Grabacik revealed that a significant percentage of N-alkylated products is detectable when ketone-derived enamines are treated with benzyl bromide or methyl iodide at room temperature (Scheme 22).[63] The percentage of C-alkylated products increased in all cases when the reactions were performed at 100 °C, thus indicating that, also in these cases, thermodynamic product control with formation of iminium ions is feasible. From the observation of C- and N-alkylated products at room temperature, one can derive that also in alkylations N attack is also intrinsically favored over C attack.



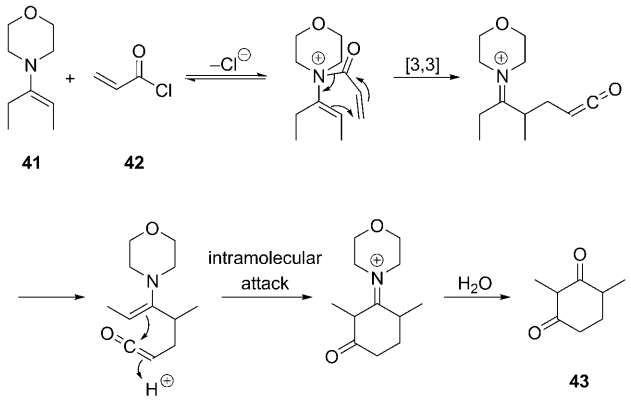
Scheme 22. Benzylation of enamine **35** at different temperatures.[63]

In line with these observations, Böhme isolated exclusively the product of N-methylation **39** when **38** was treated with methyl bromide at room temperature (kinetic control). In contrast, treatment with methyl iodide at 90 °C resulted in C-methylation (→**40**), probably because of thermodynamic control (Scheme 23).[64]



Scheme 23. Methylation of enamine **38** by methyl halides.[64]

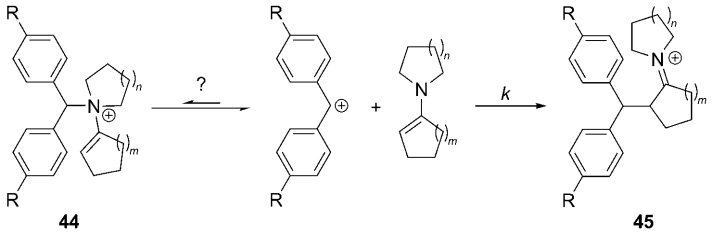
Probably because of the high reversibility of the formation of N-acylated enamines, enamines generally react with acyl chlorides with formation of C-acylated enamines, which yield 1,3-dicarbonyl compounds by hydrolysis.[65] The isolation of cyclohexane-1,3-diones (e.g. **43**) in reactions of enamines with α,β-unsaturated acyl chlorides has been explained by N-acylation followed by a fast [3,3] sigmatropic rearrangement (Scheme 24).[66] Although the formation of **43** can also be rationalized by C-alkylation and intramolecular Michael addition of an intermediate enamine, further observations have been reported which support the mechanism depicted in scheme 24.



Scheme 24. N-Acylation of enamines (in benzene under reflux).[66]

Monoexponential decays of the absorbances of stabilized benzhydrylium ions were observed when they were treated with an excess of various enamines. While this observation does not rigorously exclude that products **45** are formed after initial N attack, the concentration of N-alkylated enamines **44** must remain so low that their intermediacy is irrelevant for the observed kinetics (Scheme 25).[67]

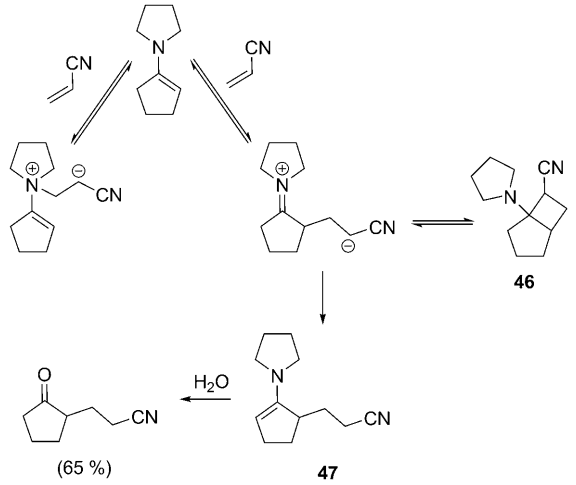
The exclusive carbon–carbon bond formation in reactions of enamines with Michael acceptors had been rationalized by the more favorable frontier orbital interactions. In our view, it



44 **45**

Scheme 25. Reactions of enamines with benzhydrylium ions to yield iminium ions **45** (in dichloromethane at 20 °C).[67]

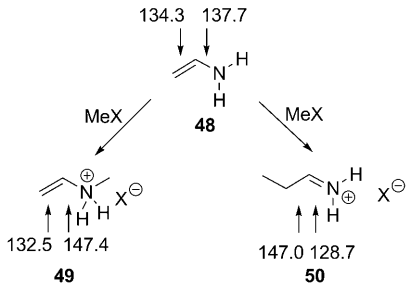
is better explained by thermodynamic product control, because N attack of Michael acceptors can be assumed to be reversible, as previously suggested by Stork et al. (Scheme 26).[59c] Later investigations by Fleming et al. provided evidence for the initial formation of the [2 + 2] cycloadduct **46**, which can be isolated.[59d,e] Heating the cyclobutane **46** gave rise to the formation of the enamine **47**.



46 **47**

Scheme 26. Reaction of an enamine with a Michael acceptor.[59c–e]

The calculated bond lengths of vinylamine and its N- and C-methylated derivatives show that less deformation is required for N attack than for C attack (Scheme 27). In combination with the "Hoz effect", which predicts lower intrinsic barriers for attack at the atom further right in the periodic table, one can qualitatively derive that N attack is intrinsically preferred. A quantitative confirmation of this analysis has been obtained by MP2/6-311 + G(2d,p) calculations of the identity reactions [Eq. (5)], which showed that the barriers are 50 kJ mol^{-1} lower when methyl is transferred from N to N instead of from C to C (Scheme 4).



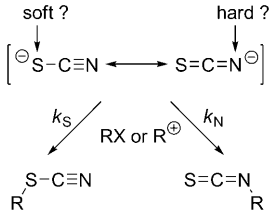
48 **49** **50**

Scheme 27. Calculated bond lengths (in pm) for vinylamine (**48**) and the products **49**/**50** obtained by N- and C-methylation [MP2/6-311 + G-(2d,p), see the Supporting Information].

3.2. Nitrogen versus Sulfur Attack: Thiocyanate Anion

3.2.1. Alkylation Reactions

More than 100 years ago, Kaufler and Pomeranz[68] as well as Walden[69] synthesized alkyl thiocyanates by treatment of potassium thiocyanate with dimethyl sulfate. Later, systematic studies on alkylations of thiocyanate ions (Scheme 28) had shown that attack at the sulfur atom is approximately 10^2 to 10^3 times faster than at the nitrogen atom in S_N2-type reactions, while the S/N ratio decreased to 2:1–9:1 in S_N1-type reactions (Table 3).[70]



Scheme 28. Ambident reactivity of the thiocyanate anion.

Table 3: Ambident reactivity of the thiocyanate anion towards different electrophiles.

S_N2-type reactions			S_N1-type reactions		
electrophile	k_S/k_N	Ref.	electrophile	k_S/k_N	Ref.
$(CH_3)_2CHI$	85	[70h]	$(4\text{-}CH_3\text{-}C_6H_4)_2CH^+$	5	[70e]
$C_6H_5CH_2Cl$	430	[70h]	$(4\text{-}CH_3\text{-}C_6H_4)_2CH^+$	8.3	[70i]
$C_6H_5CH_2Br$	850	[70h]	$(C_6H_5)_2CH^+$	9.0	[70a]
$C_6H_5CH_2I$	1300	[70h]	$(4\text{-}Cl\text{-}C_6H_4)PhCH^+$	3.8	[70g]
$C_6H_5CH_2SCN$	725	[70f]	$C_6H_5CH_2^+$	4.4	[70j]
$4\text{-}MeO\text{-}C_6H_4CH_2Br$	220	[70h]	$(CH_3)_3C^+$	ca. 2	[70a]
$4\text{-}O_2N\text{-}C_6H_4CH_2Br$	730	[70h]	$CH_3CH_2CH^+CH_3$	5	[70a]

Although preferential attack at the nitrogen atom of SCN^- has never been observed with carbocations (hard electrophiles), the small S/N ratio in S_N1 reactions had been rationalized on the basis of the HSAB concept: "*As the electrophilic character of the reaction center increases, the reactivity of the more basic nitrogen atom, which forms the stronger bond to carbon, increases with respect to that of the more polarizable sulfur atom*".[70e]

This interpretation has recently been revised (Figure 7).[13a] Benzhydrylium ions with electrophilicity parameters $-6 < E < -4$ generated by laser-flash photolysis showed bisexponential decays in solutions of $[Bu_4N]^+$ $[SCN]^-$ in acetonitrile. Depending on the concentration of SCN^-, up to 40 % of the benzhydrylium ions were consumed by a fast

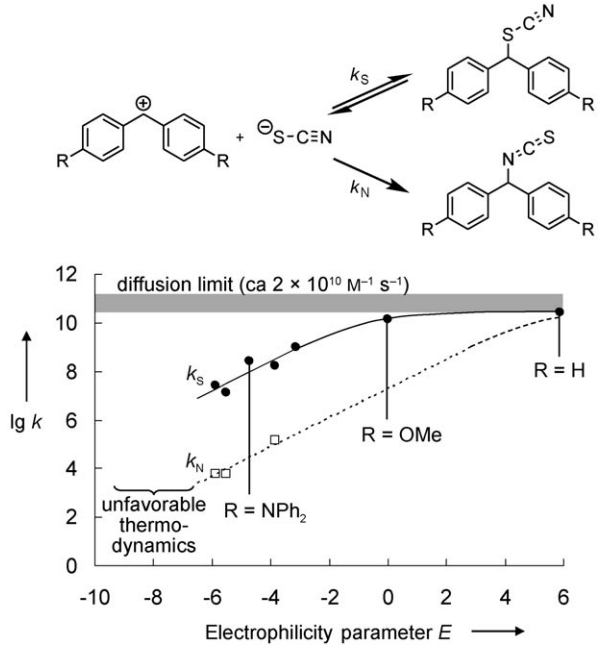
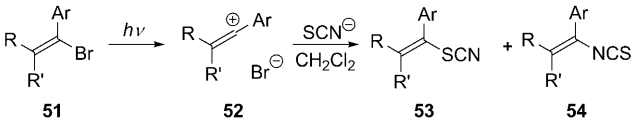


Figure 7. Rate constants (lg*k*) for the reactions of benzhydrylium ions at the S and N terminus of the thiocyanate ion (in MeCN at 20 °C).[13a]

reversible reaction ($10^7 < k_S < 3 \times 10^8\,M^{-1}s^{-1}$), and the remaining benzhydrylium ions reacted by a "slow" process ($5 \times 10^3 < k_N < 10^5\,M^{-1}s^{-1}$). While benzhydrylium ions with $E < -6$ did not react at all with SCN^- in acetonitrile, more electrophilic benzhydrylium ions ($E > -3.5$) were consumed almost quantitatively by a fast process ($k_S \approx 10^9$–$10^{10}\,M^{-1}s^{-1}$), and the rates of their reactions with the N terminus of SCN^- could not be measured directly.

Figure 7 shows that S attack is diffusion-controlled for all carbocations with $E > 0$. If one assumes that the $\lg k_N$ versus E correlation has a similar slope as the corresponding plots for other anionic n nucleophiles ($s_N \approx 0.6$), one can draw the dashed correlation line shown in Figure 7. Thus, the k_S/k_N ratio, which is approximately 2000:1 for carbocations of $-6 < E < -4$, can be expected to decrease as the electrophilicity E of the carbocations increases. Accordingly, small k_S/k_N ratios have been reported for $(4\text{-}CH_3\text{-}C_6H_4)_2CH^+$ ($E = 3.63$), Ph_2CH^+ ($E = 5.90$), and $(4\text{-}Cl\text{-}C_6H_4)_2CH^+$ ($E = 6.02$), as quoted in Table 3. For the benzyl and alkyl cations listed in Table 3, barrierless N attack is expected, and the slightly higher k_S/k_N ratios for $PhCH_2^+$ and *sec*-butyl cations may indicate nucleophilic assistance of ionization by the sulfur atom (change to S_N2). Product ratios obtained from SCN^- and stabilized carbocations ($E < 3$) have not been reported because it was realized that thiocyanates R-SCN obtained from such carbocations would reionize and eventually give isothiocyanates R-NCS, the thermodynamically favored products.

In agreement with this interpretation, photochemically generated vinyl cations **52** (E ca. 3.3–5.4)[71] underwent diffusion-controlled reactions with thiocyanate anions at both termini of SCN^- (see Figure 7), with the S attack slightly dominating (Scheme 29).[72] Since the ionization of vinyl derivatives is generally very slow, isomerizations of the

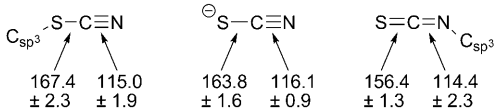


Scheme 29. Reaction of photochemically generated vinyl cations **52** with thiocyanate (at 10 to 15 °C).[72]

initially formed vinyl thiocyanates to vinyl isothiocyanates through ionization and subsequent ion recombination was not observed.

For some reactions of benzhydrylium ions with SCN^-, rate and equilibrium constants could be measured in acetonitrile at 20 °C.[13a] Substitution of these data into the Marcus equation yielded intrinsic barriers of approximately 61 kJ mol^{-1} for the attack of benzhydrylium ions at the nitrogen atom, and of 35–38 kJ mol^{-1} for attack at the sulfur atom.

In line with these findings, lower intrinsic barriers for S attack have been derived computationally [MP2/6-311 + G(2d,p)] by comparing the Gibbs energies of activation of the identity reactions in the gas phase [Eq. (5), Scheme 4]. Qualitatively, the ordering of the intrinsic barriers thus follows the Hoz rule, since sulfur is further right in the periodic table than nitrogen. The smaller intrinsic barrier for sulfur attack can also be explained in terms of Hine's PLNM model: Less reorganization energy is required for the formation of thiocyanates than of isothiocyanates because of the closer structural resemblance of thiocyanate anions with alkyl thiocyanates than with alkyl isothiocyanates (Scheme 30).



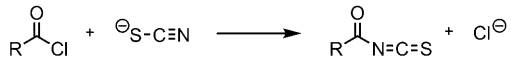
Scheme 30. Average bond lengths (in pm) of organic thiocyanates, "free" thiocyanate anions, and organic isothiocyanates derived from crystal structures (see Ref. [13a], and references therein).

As the thermodynamic preference of alkyl isothiocyanates over alkyl thiocyanates is relatively small ($\Delta\Delta G^0 = 17.1$ kJ mol^{-1} for H_3CNCS and H_3CSCN), kinetically controlled alkylations of SCN^- occur generally at the intrinsically preferred site (sulfur) to give alkyl thiocyanates that may rearrange to isothiocyanates under thermodynamically controlled conditions.

3.2.2. Acylation Reactions

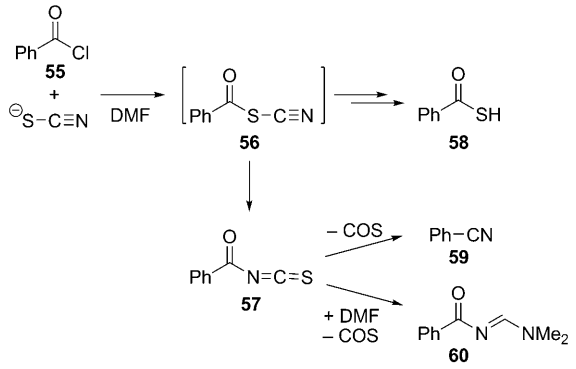
The reaction of acyl chlorides with thiocyanate ions (Scheme 31), first published by Miquel in 1877,[73] is still the most common method for preparing acyl isothiocyanates.[74] This regioselectivity was one of the experimental facts, Klopman set out to rationalize by the concept of charge- and frontier-orbital-controlled reactions.[5a]

When trying to answer the question why acyl chlorides attack at the nitrogen terminus of SCN^- while methyl iodide



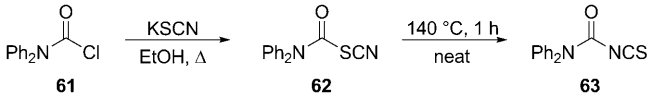
Scheme 31. Synthesis of acyl isothiocyanates from acyl chlorides and thiocyanate.

attacks at the sulfur atom, Klopman overlooked that in 1961 Ruske and Keilert had already provided evidence for kinetically controlled S attack of benzoyl chloride at SCN^-. Thiobenzoic acid (**58**), benzonitrile (**59**), and *N*,*N*-dimethyl-*N*′-benzoylformamidine (**60**) were isolated when benzoyl chloride (**55**) was combined with KSCN or $Pb(SCN)_2$ in DMF. As shown in Scheme 32, the formation of these products was interpreted by the initial formation of benzoyl thiocyanate (**56**), which is partially hydrolyzed before it rearranges to the thermodynamically more stable benzoyl isothiocyanate (**57**).[75]



Scheme 32. Reaction of benzoyl chloride (**55**) with thiocyanate in DMF.[75]

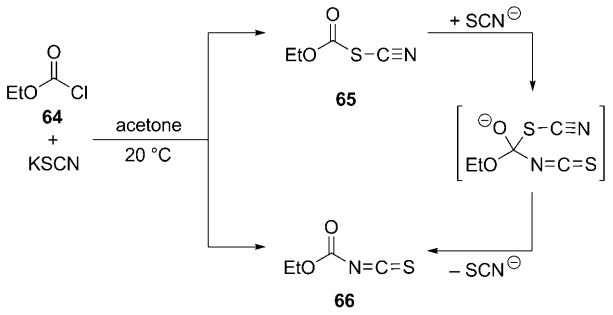
Analogously, SCN^- was exclusively attacked at the sulfur atom when diphenylcarbamoyl chloride (**61**) was heated with KSCN in ethanol; the resulting carbamoyl thiocyanate **62** rearranged to the corresponding isothiocyanate **63** at 140 °C (Scheme 33).[76]



Scheme 33. Synthesis of diphenylcarbamoyl thiocyanate (**62**) and its rearrangement to the isothiocyanate **63**.[76]

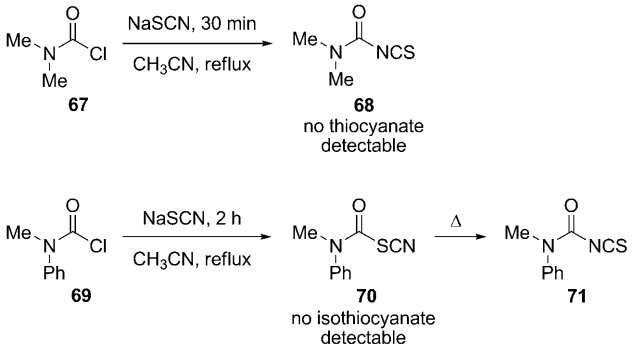
Takamizawa, Hirai, and Matsui obtained a 1:1 mixture of thiocyanate **65** and isothiocyanate **66** in the reaction of ethyl chloroformiate (**64**) with potassium thiocyanate in acetone.[77] The isolated ethoxycarbonyl thiocyanate **65** is thermally stable when refluxed in ethanol; however, an isomerization of the thiocyanate **65** to the isothiocyanate **66** occurs in the presence of catalytic amounts of KSCN in acetone at 20 °C (Scheme 34).

Goerdeler and Wobig studied the reactions of differently substituted carbamoyl chlorides with NaSCN[78] and found a



Scheme 34. Reaction of ethyl chloroformiate (**64**) with potassium thiocyanate in acetone.[77]

"dualism" in selectivity (Scheme 35). In another publication, Goerdeler stated that "*earlier investigators had sometimes failed to observe that these reactions are not unambiguous*".[74] According to Goerdeler and Wobig, aliphatic carbamoyl chlorides, such as *N*,*N*-dimethylcarbamoyl chloride (**67**) reacted with NaSCN in refluxing acetonitrile to give the



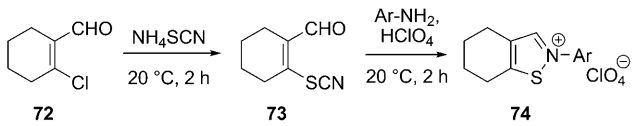
Scheme 35. Reactions of thiocyanate anions with different carbamoyl chlorides.[78]

isothiocyanate **68** without the intermediate formation of thiocyanates. However, in liquid SO_2, mixtures of thiocyanates and isothiocyanates were formed, as shown by IR spectroscopy. The analogous reaction of *N*-methyl-*N*-phenylcarbamoyl chloride (**69**) with NaSCN in acetonitrile gave the thiocyanate **70** selectively which rearranged to the corresponding isothiocyanate **71** upon warming.

3.2.3. ***Nucleophilic Vinylic and Aromatic Substitution***

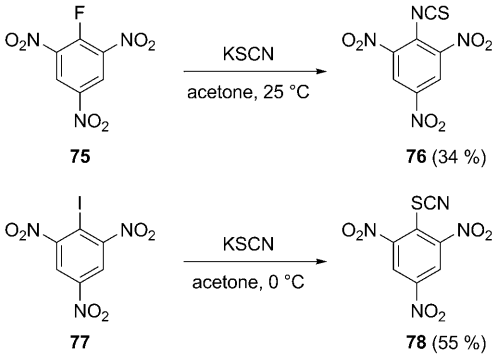
Preferred S attack was also reported in nucleophilic vinylic substitutions. Treatment of the chlorinated cyclohexene carbaldehyde **72** with NH_4SCN gave the vinyl thiocyanate **73**, which was combined with aniline to yield the isothiazolium ion **74** (Scheme 36).[79]

Giles and Parker studied the nucleophilic aromatic substitutions of dinitro- and trinitrohalobenzenes with potassium thiocyanate and isolated different products depending on the nature of the leaving group. Under comparable conditions, fluoroarene **75** gave the isothiocyanate **76**, while



Scheme 36. Reaction of ammonium thiocyanate with the vinyl chloride **72**.[79b]

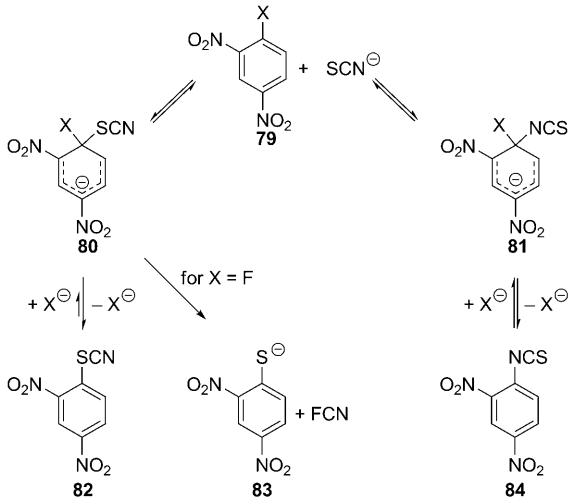
the iodo derivative **77** furnished the thiocyanate **78** (Scheme 37).[80a] These regioselectivities seemed to agree with the expectations based on the HSAB model: The harder fluoro compound reacts preferentially with the harder nitrogen atom of SCN^-, whereas the softer iodo arene is attacked by the softer sulfur terminus.



Scheme 37. Reactivity of thiocyanate anions towards 1-halo-2,4,6-trinitrobenzenes.[80a]

As already noted by Parker and co-workers, the individual rate constants for the reactions of 2,4-dinitrohalobenzenes **79** with SCN^- indicate, however, that S attack with formation of the σ adduct **80** is also always faster than the formation of **81** in these reactions, irrespective of the nature of X (Scheme 38).[80a,b] Since Cl^-, Br^-, and I^- are good leaving groups, the corresponding σ adducts **80** (X = Cl, Br, I) yield the aryl thiocyanates **82**, which are thus formed by fast reactions. As F^- is a poor leaving group, the σ adduct **80** (X = F) expels F^- only slowly and either decomposes to **83**, which can undergo subsequent reactions, or reverts to the starting materials **79** and SCN^-. In this way, the slow formation of σ adduct **81**, which is thermodynamically more favorable than **80**, becomes possible. Elimination of F^- can now occur, which affords the isothiocyanate **84**. Although the attack of nucleophiles at 2,4-dinitrohalobenzenes initially occurs at C3 or C5,[80c–e] the resulting intermediates are neglected in Scheme 38 because they are not relevant for the final products.

One can summarize that thermodynamically controlled reactions of SCN^- generally yield isothiocyanates, while kinetically controlled reactions yield thiocyanates. It is the lower intrinsic barrier for S attack which controls the regioselectivity of kinetically controlled reactions because the thermodynamic preference for N attack is too small to overrule the intrinsic preference for S attack.



X	Products arising from S attack lg k_S	Products arising from N attack lg k_N
F	– 2.7	–3.00
Cl	–2.00	–4.7
Br	–1.55	—
I	–1.60	–4.85

Scheme 38. Nucleophilic aromatic substitution of 2,4-dinitrohalobenzenes **79** with thiocyanate (in DMF at 75 °C).[80a,b]

3.3. Nitrogen versus Oxygen Attack

3.3.1. Cyanate Anion

The most common method to synthesize alkyl isocyanates is the reaction of alkyl or dialkyl sulfates with alkali metal cyanates [Eq. (10)], as reported by Wurtz[81] and later modified by Slotta and Lorenz.[82]

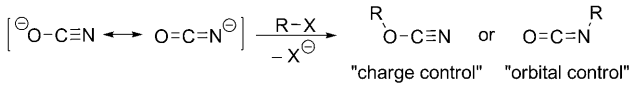
$$KOCN + (RO)_2SO_2 \rightarrow R{-}NCO + ROSO_3K \quad (10)$$

It cannot be excluded that the selective formation of alkyl isocyanates in these reactions is due to a catalyzed isomerization of an initially formed alkyl cyanate to the thermodynamically more stable isocyanate [Eq. (11)], since ethyl cyanate has been reported to rearrange to ethyl isocyanate in polar and nonpolar solvents.[83]

$$R{-}OCN + NCO^- \rightarrow R{-}NCO + NCO^- \quad (11)$$

According to semiempirical calculations, the charge density in cyanate ions is highest at the oxygen atom, while the largest HOMO coefficient is at the nitrogen atom.[84] By employing the concept of charge and orbital control, Schädler and Köhler rationalized the preferred formation of isocyanates by the dominance of orbital control (Scheme 39).

Product studies showed the exclusive formation of benzhydryl isocyanates in the reactions of OCN^- with benzhydrylium ions (Figure 8).[13d] However, because of the low thermodynamic stability of benzhydryl cyanates, we cannot exclude that low concentrations of benzhydryl cyan-



Scheme 39. Common rationalization of the ambident reactivity of the cyanate anion.

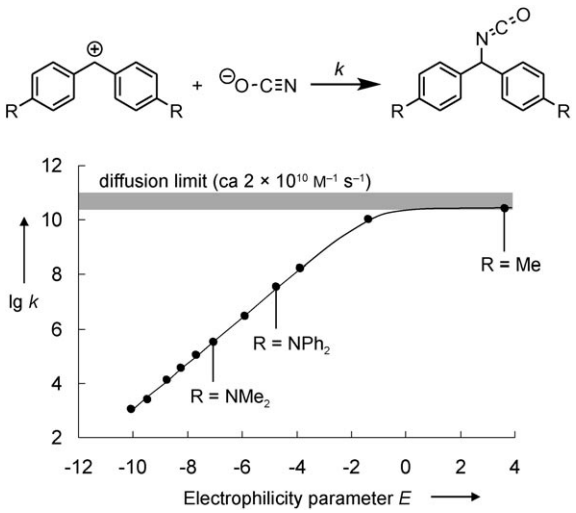


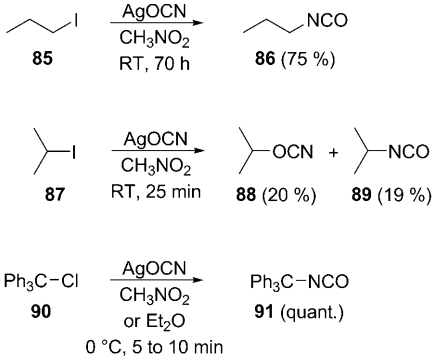
Figure 8. Plot of $\lg k_2$ for the reactions of the cyanate ion with benzhydrylium ions versus their electrophilicity parameters E (in MeCN at 20 °C).[13d]

ates are formed in a fast preequilibrium which is irrelevant for the observed kinetics.

Figure 8 shows that all carbocations with $E > -1$ (carbocations that are less stabilized than the dianisylcarbenium or the tritylium ion, that is, typical S_N1 substrates) will undergo diffusion-controlled reactions with cyanate. These reactions proceed without passing through a transition state and, therefore, cannot be rationalized by transition-state models.

According to Table 1, alkyl isocyanates are considerably more stable than alkyl cyanates. On the other hand, O attack—attack at the atom further right in the periodic table—is preferred intrinsically, as derived from the identity reactions summarized in Scheme 4. As the $\Delta\Delta G^0$ term (Table 1) is much larger than the $\Delta\Delta G_0^{\neq}$ term (Scheme 4), the experimentally observed N-alkylations are in line with the predictions of Marcus theory.

With the nucleophilicity parameters $N = 13.60$ and $s_N = 0.84$,[13d] which can be derived from the left linear part of Figure 8, one can now rationalize the change of regioselectivity in the reactions of alkyl halides with AgOCN described by Holm and Wentrup (Scheme 40).[83c] As primary alkyl cations do not exist in the condensed phase, the exclusive formation of propyl isocyanate (**86**) from propyl iodide (**85**) can be explained by an S_N2 reaction, where the product stability term outweighs the intrinsic term in the transition state. The mixture of isopropyl cyanate (**88**) and isopropyl isocyanate (**89**) described in the second reaction in Scheme 40 reflects the result of diffusion-controlled reactions of the cyanate anion with the isopropyl cation, which can be derived from Equation (1) by using N and s_N for NCO^- and an estimated electrophilicity parameter of $E \gg 8$ for $i\mathrm{Pr}^+$.[40]

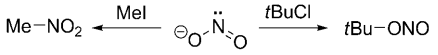


Scheme 40. Experimentally observed regioselectivities for the reactions of silver cyanate with different alkyl halides.[83c]

From the low thermodynamic stability of alkyl cyanates (Table 1) and the low intrinsic barriers for O attack at NCO^-, one can derive that a potentially generated trityl cyanate (last reaction in Scheme 40) would rapidly re-ionize and generate the more stable trityl isocyanate **91** (thermodynamic product control).

3.3.2. *Nitrite Anion*

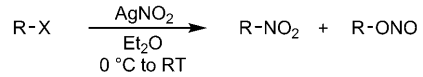
Extensive investigations[2] on the reactions of the nitrite ion with alkylating agents led Kornblum to the conclusion "*The greater the carbonium contribution to the transition state the greater is the yield of nitrite ester and the smaller is the yield of nitroparaffin*".[2e] However, Pearson's specification of this rule, "*t-C_4H_9Cl reacts with the hard oxygen atom of NO_2^-, while the softer CH_3I reacts with the softer nitrogen atom,*"[3c] which was expressed in later theoretical treatments of ambident reactivity by Scheme 41,[5a,85] is not consistent with experimental findings; methyl iodide and other primary haloalkanes actually yield mixtures of alkyl nitrites and nitroalkanes with either $NaNO_2$ or $AgNO_2$.[2b–g,86]



Scheme 41. Partially incorrect specification of the ambident reactivity of the nitrite anion.[5a]

Previous statements such as "*Although silver nitrite does react with alkyl halides to give nitrites, sodium nitrite gives more nitroalkane than alkyl nitrite*"[5d] were contradicted by Streitwieser, Heathcock, and Kosower, who refer to Kornblum's studies on the reactions of iodo- and bromoalkanes with $NaNO_2$ and $AgNO_2$ and concluded "*Yields of nitroalkane are higher when silver nitrite is used, but this added economy is tempered by the cost of silver salt*" (Scheme 42).[87]

The HSAB model and the concept of charge and orbital control thus correctly predict that the reaction of *tert*-butyl chloride with silver nitrite yields *tert*-butyl nitrite preferentially (64 % *t*Bu–ONO and 4–6 % *t*Bu–NO_2),[2c] but mislead the chemist intending to synthesize primary nitroalkanes. These concepts would advise not to combine alkyl halides



RX = *n*-C_4H_9Br	73 %	13 %
n-$C_6H_{13}Br$	76 %	10 %
n-$C_8H_{17}Br$	80 %	14 %
n-C_4H_9I	74 %	12 %
n-$C_6H_{13}I$	78 %	13 %
n-$C_8H_{17}I$	83 %	11 %

Scheme 42. Reactions of silver nitrite with alkyl halides.[2a]

with silver nitrite, the method which provides the highest yields of nitroalkanes (Scheme 42).

Our investigations on the rates of the reactions of benzhydrylium ions with nitrite ions in acetonitrile[13c] showed (Figure 9) that carbocations with electrophilicity parameters $E > 0$, that is, the bis(4-methoxyphenyl)carbenium ion ($E = 0$) and all less-stabilized carbocations, undergo diffusion-controlled reactions with the nitrite ion. For that reason, the reactions of *tert*-alkyl cations ($E \approx 7$–8) with nitrite ions do not proceed through classical transition states, and attempts to employ frontier orbital models for deriving relative activation energies for O and N attack are inappropriate.

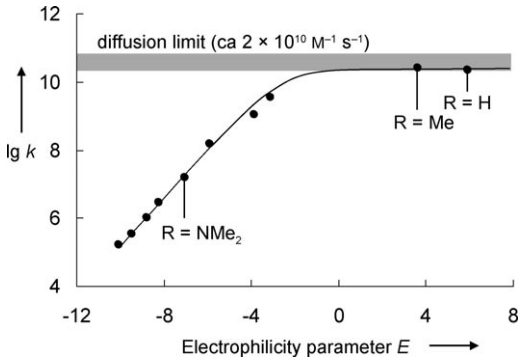


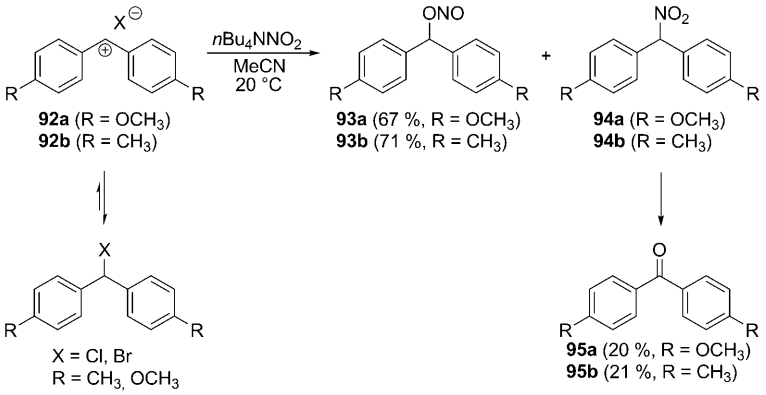
Figure 9. Plot of $\lg k_2$ for the reactions of the nitrite ion with benzhydrylium ions (for structures, see Scheme 43) versus their electrophilicity parameters E (in MeCN at 20 °C).[13c]

Carbocations with electrophilicities $E < -3$ have been found to react reversibly with NO_2^- in acetonitrile, and the exclusive formation of nitro compounds from amino-substituted benzhydrylium ions was explained by thermodynamic control, since nitro compounds are thermodynamically more stable than the isomeric alkyl nitrites.[88]

The bis(*p*-methoxy)- and the less stabilized bis(*p*-methyl)-substituted benzhydrylium ions **92** undergo diffusion-controlled, irreversible reactions with nitrite anions to give approximately 70 % of the benzhydryl nitrites **93** and 20 % of the benzophenones **95** (Scheme 43), which are formed from the corresponding diaryl nitromethanes as described by Wagner, Mioskowski, and co-workers.[89]

The exclusive formation of nitroalkanes under conditions of thermodynamic product control is in accord with our calculations [MP2/6-311 + G(2d,p)], which showed that nitromethane is 28.3 kJ mol^{-1} more stable than methyl nitrite (Table 1).

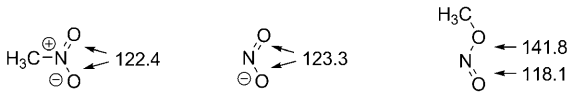
Calculated activation energies for the identity reactions [Eq. (5)] show similar intrinsic barriers for O and N attack (Scheme 4). In this case, the Hoz effect, which favors attack at the oxygen atom because of its position in the periodic table, is compensated by the higher reorganization energy for O attack, which can be derived from the greater change of



Scheme 43. Reactions of less stabilized benzhydrylium ions with nitrite anions.[13c]

bond lengths when generating methyl nitrite from nitrite anions (Scheme 44).[90]

From the almost identical intrinsic barriers for O and N attack reported in Scheme 4 and a thermodynamic term which favors N attack, one would derive that nitroalkane formation is also generally preferred over alkyl nitrite formation in kinetically controlled reactions. As mixtures of methyl nitrite and nitromethane are obtained when nitrite anions are treated with different methylating agents (Table 4) we have to conclude, that in contrast to the data shown in Scheme 4, there must be a weak intrinsic preference for O-alkylation, which compensates the $\Delta\Delta G^0$ term in the Marcus



Scheme 44. Bond lengths (in pm) in the nitrite anion, nitromethane, and methyl nitrite.[90]

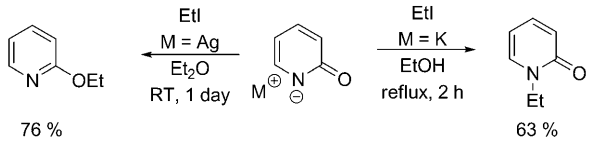
Table 4: N/O Selectivities for methylation reactions of nitrite ions (at room temperature).

Nitrite	Electrophile	Solvent	$MeNO_2$/MeONO	Ref.
$NaNO_2$	MeI	DMSO	54:46	[86]
$AgNO_2$	MeI	DMSO	46:54	[86]
$NaNO_2$	MeI	DMF	54:46	[86]
$AgNO_2$	MeI	DMF	54:46	[86]
(nBu$_4$N)NO_2	MeI	$CDCl_3$	70:30	[13c]
(nBu$_4$N)NO_2	$MeOSO_2Me$	$CDCl_3$	67:32	[13c]
(nBu$_4$N)NO_2	Me_3OBF_4	$CDCl_3$	50:50	[13c]
(nBu$_4$N)NO_2	$MeOSO_2CF_3$	$CDCl_3$	41:59	[13c]

Equation. It should be noted, however, that the selectivities shown in Table 4 are also not related to the hardness of the electrophiles.

3.3.3. Amides and Amide Anions

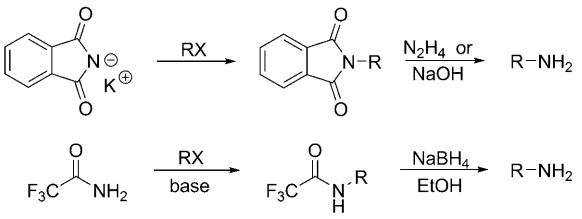
The observation that the potassium salt of 2-pyridone reacted with ethyl iodide at nitrogen[91] while the corresponding silver salt was alkylated at the oxygen atom[92] (Scheme 45) was one of the examples which prompted Kornblum to formulate his rule, which later became integrated into the HSAB principle of ambident reactivity and the Klopman–Salem concept of charge- and orbital-controlled reactions.[2e]



Scheme 45. Regioselective alkylation of potassium and silver salts of 2-pyridone.[91,92]

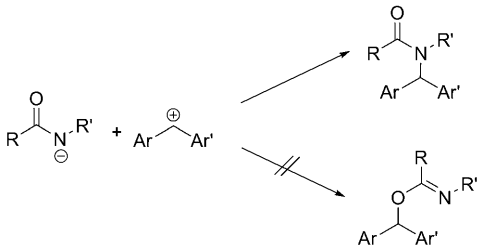
Systematic investigations of the alkylation of 2-pyridone salts led Tieckelmann and co-workers[93] to conclude that "*these results are completely consistent with Kornblum's proposal that the silver ion enhances unimolecular character in the silver salt reactions, thereby favoring alkylation at the more electronegative oxygen atom*".[93a] However, at the end of their thorough investigation, Tieckelmann and co-workers stated: "*The mechanism which leads to oxygen alkylation of the silver salts of 2-pyridones also needs further examination and may be more related to heterogeneous reaction than to the ability of the silver ion to promote unimolecular reaction as previously suggested*".[93a]

Selective N attack has also been observed with alkali salts of other amide and imide anions.[94] This selectivity is synthetically used in Gabriel syntheses and related reactions (Scheme 46).[95,96]



Scheme 46. Gabriel synthesis and related methods for the preparation of primary amines and amino acids.[95a,96]

Alkylation of the oxygen atoms of imide anions has only been observed when silver salts were employed.[97] However, this selectivity cannot be explained by a change from an S_N2 to S_N1 mechanism because systematic investigations of the reactions of amide and imide anions with benzhydrylium ions showed that nitrogen attack is also preferred with carbocations (Scheme 47).[13g,h] X-ray investigations have shown that Ag^+ is coordinated to the nitrogen atom of imide anions[98] and thus blocks the attack of electrophiles at this position.



Scheme 47. Reactions of amide anions with benzhydrylium ions in DMSO.[13g]

According to entry 7 of Table 1, amides are 80 kJ mol^{-1} more stable than the isomeric imidates. The resulting large $\Delta\Delta G^0$ term in the Marcus equation favors N attack and cannot be compensated by the small intrinsic preference for O attack, which is shown in Scheme 4. The selective N-alkylation of amide anions under conditions of kinetic and thermodynamic control can thus be explained.

The large thermodynamic preference of the amide over the imidate structure (80 kJ mol^{-1}) is greatly reduced when the C=N bond becomes part of an aromatic ring during O-methylation. As shown in Table 1 (entries 9 and 10) and Figure 10, *N*-methyl-2-pyridone and *N*-methyl-4-pyridone are

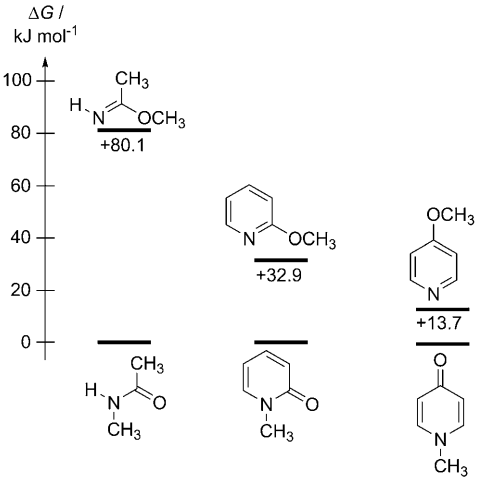


Figure 10. Comparison of the thermodynamic stabilities of N- and O-methylated acetamide, 2-pyridone, and 4-pyridone (see also Table 1).

only 33 and 14 kJ mol^{-1} more stable, respectively, than the isomeric methoxypyridines. Since in both cases O attack is intrinsically only slightly favored over N attack (Scheme 4), N attack remains preferred, but O attack can compete (Table 5). Attack at the oxygen atom of the 2-pyridone anion becomes dominant with *i*Pr–I, which may be explained by a steric effect.

In kinetically controlled reactions of pyridone anions, N attack is mostly preferred, as the thermodynamic contri-

Table 5: Effect of alkylating agent and counterion on the N-/O-alkylation ratio for the alkylation of 2-pyridone anions in DMF at RT.[93]

Electrophile	Counterion	*N*/O ratio
MeI	Na^+	95:5
MeI	K^+	92:8
$PhCH_2Cl$	Na^+	94:6
$PhCH_2Br$	Na^+	97:3
$PhCH_2I$	Na^+	98:2
EtI	Na^+	69:31
*i*PrI	Na^+	30:61[a]

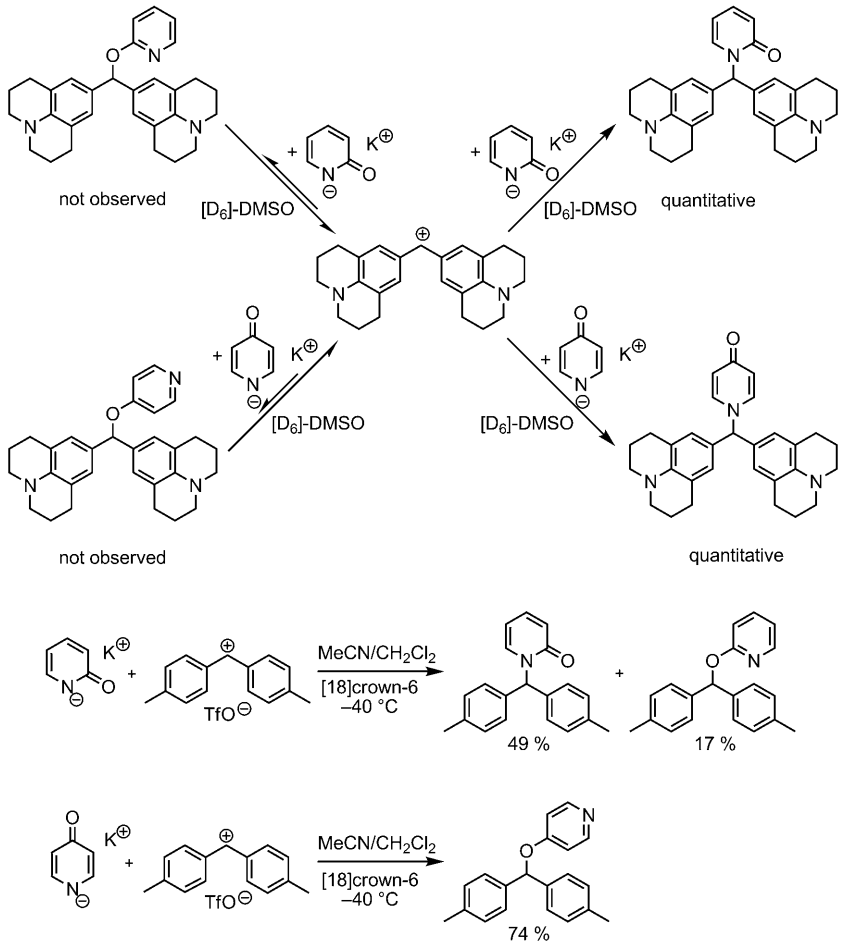
[a] 2-Pyridone was partially recovered.

bution to the Gibbs energy of activation (favoring N attack) outnumbers the contribution of the intrinsic barrier (favoring O attack). Only for bulky alkylating agents is the $\Delta\Delta G^0$ term, which favors N attack, so strongly diminished that O attack becomes more favorable. While diffusion-controlled reactions of the 2-pyridone anion give mixtures of O- and N-alkylated products,[93] exclusive O attack was observed in diffusion-controlled reactions with the 4-pyridone anion.[13h]

As expected from the relative stabilities depicted in Figure 10, the thermodynamically controlled reactions of the 2- and 4-pyridone anions with amino-substituted benzhydrylium ions gave *N*-benzhydrylpyridones exclusively. Attack at the oxygen atom was only found in the diffusion-controlled reactions of the pyridone anions with highly reactive carbocations, as shown in Scheme 48.

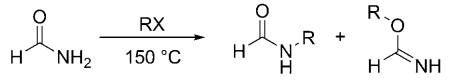
The situation changes dramatically when neutral amides are alkylated instead of their anions. Whereas N-methylation of the acetamide anion is 80 kJ mol^{-1} more favorable than O-methylation, N-methylation of the neutral amide is 20 kJ mol^{-1} less favorable than O-methylation (Table 1). Since O attack is also intrinsically highly favored over N attack (Scheme 4), kinetically controlled alkylations of neutral amides should generally yield O-alkylation products. However, as the relative thermodynamic stabilities of O- and N-alkylation products are reversed when the deprotonated products are considered (Scheme 49), N-alkylation takes place under conditions of thermodynamic control, as in alkylations of amide anions.[99]

As shown in Table 6, the alkylation of formamide with n-octyl bromide, a classical S_N2 substrate, yields the O-alkylated formamide selectively, whereas the tritylium cation leads to selective N-alkylation.[100] Gompper and Christmann concluded that S_N2 reactions as well as S_N1 reactions with "instable carbenium ions" occur preferentially at the oxygen atom, while S_N1 reactions with "stable carbenium ions" take place at the nitrogen terminus.[101] In the reactions with stable carbenium ions, the initial O attack at the neutral amide is reversible and subsequent rearrangement to the thermodynamically more stable amides takes place. As a consequence, they concluded that Kornblum's view "*The greater the S_N1 character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity*"[2e] requires extension for reactions of neutral carboxamides.[101] The model presented herein also allows a consistent explanation of these observations.

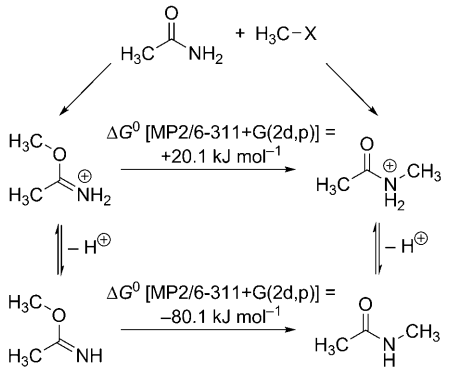


Scheme 48. Reactions of pyridone anions with benzhydrylium ions.[13h]

Table 6: Alkylations of formamide with different alkyl halides.[100]



R–X	*N*-Alkylformamide	Alkyl formimidate
n-$C_8H_{17}Br$	–	92%
$PhCH_2Cl$	5%	74%
Ph_2CHCl	95%	–
Ph_3CCl	94%	–



Scheme 49. Ambident reactivity of neutral amides. The bottom line of this scheme corresponds to the left column in Figure 10.

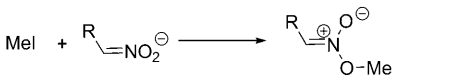
3.4. Oxygen versus Carbon Attack

3.4.1. Nitronate Anions

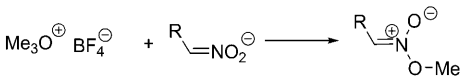
Deprotonated nitroalkanes are an important class of ambident anions which are widely used in organic synthesis.[102] According to the HSAB principle, nitronate anions are expected to react with soft electrophiles at the carbon atom to yield nitroalkanes and with hard electrophiles at the oxygen atom to yield nitronic esters.

In 1984 Katritzky and Musumarra[103a] contradicted this interpretation. Referring to a 1945 paper by Weisler and Helmkamp,[103b] they stated: "*It is well known that the alkylation of nitronate anions by halides or tosylates, which are ionic reactions, give exclusively O-alkylations*".

Preferred attack at the oxygen atoms of nitronate anions by soft alkyl halides such as methyl iodide [Eq. (12)] as well as with the hard methylating agent $Me_3O^+BF_4^-$ [Eq. (13)] has been confirmed by Severin et al.[104] as well as by Kornblum and Brown, respectively.[105] Whether the nitronic esters can be isolated depends on the reaction conditions.[103b]



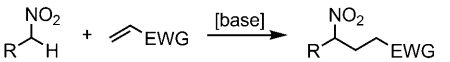
(12)



(13)

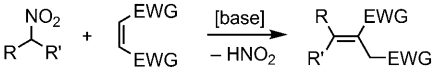
According to Table 1 (entry 11), nitroethane, the C-methylated product of the nitromethyl anion, is much more stable (120 kJ mol^{-1}) than methyl nitronate obtained by O-methylation of the nitromethyl anion. On the other hand, the intrinsic barrier for O attack is much smaller than the barrier for C attack (Scheme 4), in line with the Hoz rule, because oxygen is further right in the periodic table than carbon, and the PLNM, as C-alkylation requires a rehybridization from C_{sp^2} to C_{sp^3}.

We, therefore, explain the selective C attack by Michael acceptors (acrylonitrile, alkyl acrylates, vinyl sulfones, etc., [Eqs. (14) and (15)], and carbonyl groups [Eq. (16)] not by favorable soft–soft interactions but by the fact that a potential O attack would be reversible because of the low thermodynamic stability of the resulting products.[102]



(14)

EWG = CN, CO_2Et, SO_2R', CHO etc



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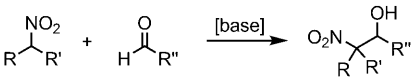
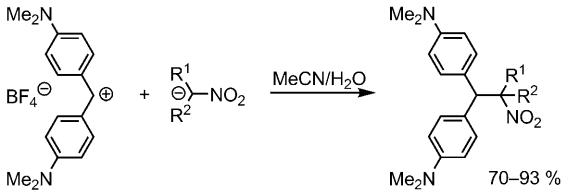


(16)

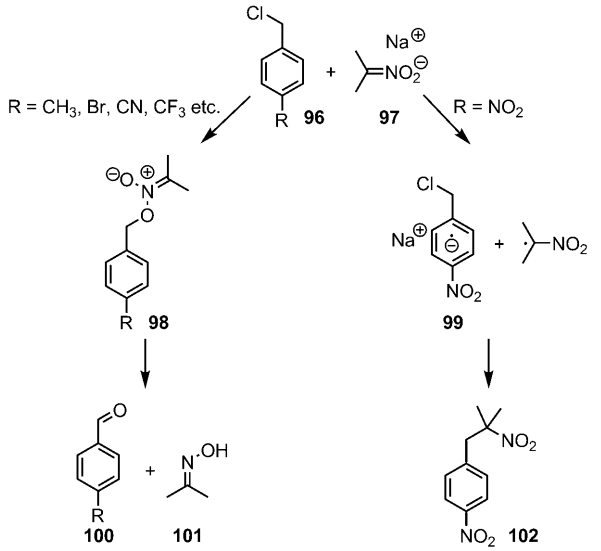
An analogous behavior was observed in the reactions with stabilized benzhydrylium ions. Although carbocations are generally regarded as hard electrophiles, the reactions of amino-substituted benzhydrylium ions with a large variety of nitronate ions gave the products of C attack exclusively (Scheme 50).[13e]



Scheme 50. Reactions of nitronate anions with benzhydrylium ions to yield nitro compounds exclusively.[13e]

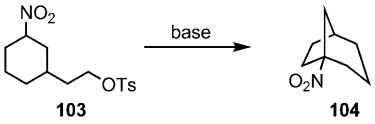
Possibly, these carbocations also react faster at the oxygen atom than at the carbon atom. However, oxygen-bound nitronate anions are good leaving groups, and the initially generated nitronic esters may undergo retroaddition and finally yield the thermodynamically more stable nitro compounds.[13e,106] From the monoexponential decay of the concentrations of the benzhydrylium ions in the presence of a large excess of nitronate anions, it has been derived that the concentration of nitronic esters—if they are formed at all—will always be very small when stabilized benzhydrylium ions are employed.

The intrinsic preference for O attack at nitronate anions is so large that irreversible S_N2 reactions with a variety of alkylating agents generally proceed at the oxygen atom. Thus, the sodium salt of 2-nitropropane (**97**) reacts with benzyl chlorides **96** at the oxygen atom to give nitronic esters **98**, which undergo subsequent cleavage with formation of the corresponding benzaldehydes **100** and the oxime of acetone (**101**). Only *p*-nitrobenzyl chloride reacts differently and yields the C-alkylation product **102** through a radical mechanism (Scheme 51).[107] An earlier proposal[108] that **102** is generated by rearrangement of an initially formed nitronic ester has been rejected by Boyd and Kelly.[109]



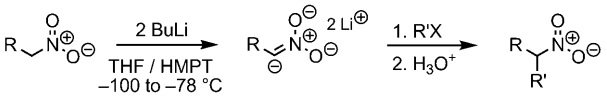
Scheme 51. Reactions of substituted benzyl chlorides **96** with the sodium salt of 2-nitropropane (**97**).[107]

The intramolecular cyclization [Eq. (17)] of **103** to give the bicyclic nitro compound **104**[110] is another of the rare cases where S_N2-type reactions of nitronate anions proceed through C-alkylation.[111]



(17)

As a consequence of the failure to achieve C-alkylation of nitronate anions by simple substitution reactions, Seebach et al. developed a method for the α-alkylation of nitroalkanes, which proceeds via doubly deprotonated nitroalkanes (Scheme 52).[112]

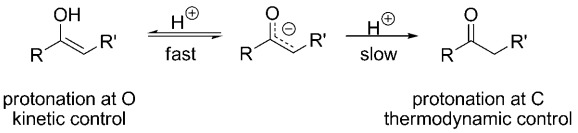


Scheme 52. C-alkylation of nitroalkanes via a dilithio derivative according to Seebach et al.[112] HMPT = hexamethylphosphoric triamide.

3.4.2. *Enolate Anions*

Enolate anions are probably the most widely used ambident anions in organic synthesis. Their C-alkylation is an important method for the construction of carbon–carbon bonds, whereas O-alkylation with formation of enol ethers is often used for the protection of carbonyl groups.[113] The site of attack in enolate anions depends on the structure of the enolate as well as the nature of the electrophile, the solvent, and the counterion.[114] The regioselectivities of the alkylation reactions were again mostly interpreted on the basis of the HSAB principle that predicts O-alkylation with hard and C-alkylation with soft electrophiles.

In line with this interpretation, Zimmerman[115] showed that protonation at the hard oxygen atom to yield the enols occurs in a fast and reversible reaction, whereas the protonation at the soft carbon atom leads in a slow reaction to the thermodynamically more stable ketones (Scheme 53).



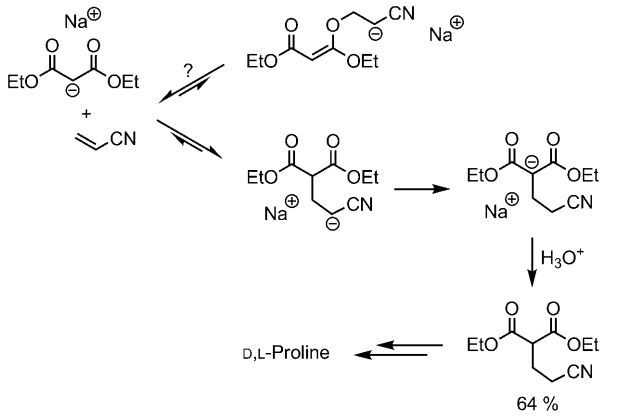
Scheme 53. Protonation of enolates.

However, in 1986 there were already numerous examples, particularly gas-phase studies which indicated that enolate anions may also react with the "soft" alkyl halides at their oxygen atom. For that reason, Houk and Paddon-Row[116] investigated the ambident reactivity of the acetaldehyde-derived enolate ion computationally (HF/3-21G and HF/6-31G(d) level of theory) and came to the conclusion that under kinetic control "[…] *O-alkylation of enolates is favored with all electrophiles. Changes in C/O alkylation ratios with the nature of the alkyl halide are probably not related to the 'hardness' or 'softness' of the alkyl halide but to the ability of the halide to influence the structures of metal enolate aggregates.*" These conclusions were later confirmed by calculations using basis sets including diffuse functions.[117]

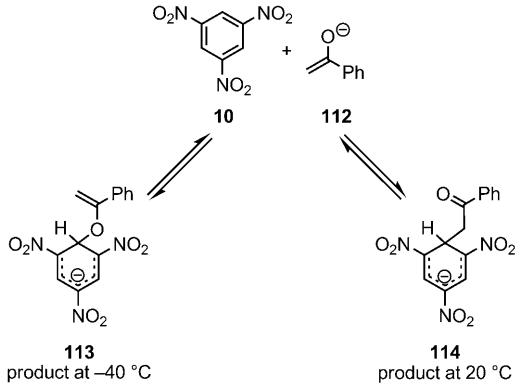
Computations at the MP2/6-31 + G(d)//MP2/6-31 + G(d) and QCISD/6-31 + G(d)//MP2/6-31 + G(d) level of theory by Lee et al.[118] showed that the transition state for the gas-phase O-methylation of the enolate H_2CCHO^- by methyl fluoride is favored by 15 kJ mol^{-1} over C-alkylation, which is thermodynamically preferred over O-methylation by 98 kJ mol^{-1}. A similar difference of product stabilities is given in Table 1.

The thermodynamic preference for C-alkylation is counteracted by the relative magnitudes of the intrinsic barriers. Scheme 4 shows that the intrinsic barrier for C-alkylation is significantly higher than that for O-alkylation, which was already rationalized by Lee et al. with the imbalanced transition structures of C-alkylation, where rehybridization of the enolate carbon atom is required.[118] The Hoz rule leads to the same ordering of intrinsic barriers, as oxygen is further right in the periodic table than carbon. As product stabilities and intrinsic barriers favor different sites of attack, it depends on the position of the transition state as to whether C- or O-alkylation takes place (Figure 4).

The synthetically important Michael additions of enolate anions to electron-deficient π systems generally proceed through C attack (Scheme 54). However, we do not interpret this regioselectivity by the favorable soft–soft interaction between the enolate carbon atom and the 4-position of the Michael acceptor in these reactions, but by the fact that the competing O attack is thermodynamically unfavorable and usually reversible.

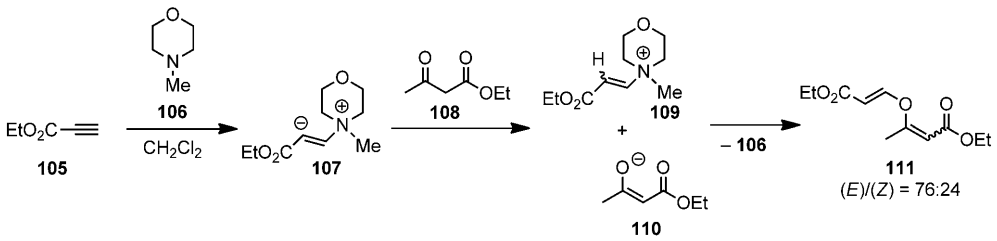


Scheme 54. Michael addition of the sodium salt of diethyl malonate to acrylonitrile (in ethanol at 35 °C).[119]



Scheme 56. Kinetically controlled O attack and thermodynamically controlled C attack of 1,3,5-trinitrobenzene (**10**) on the potassium enolate of acetophenone (**112**; in $CD_3CN/[D_{10}]$-dimethoxyethane 1:1 (v/v)).[122a]

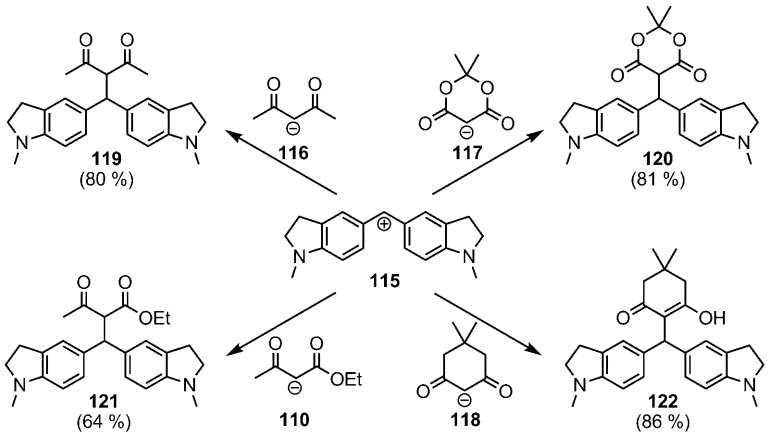
In line with this rationalization, products from O attack can be isolated when the initial adduct formed from an enolate and a Michael system can be stabilized. Thus, Tae and Kim observed the exclusive formation of divinyl ethers (such as **111**) by *N*-methylmorpholine-catalyzed reactions of β-ketoesters or 1,3-diketones with ethyl propiolate (**105**).[120] As illustrated in Scheme 55, this reaction was explained by initial attack of *N*-methylmorpholine (**106**) at the alkyne, followed by proton transfer, addition of the enolate anion to the Michael system, and elimination of the tertiary amine.[120] The last step of this reaction sequence appears to be irreversible and locks the O regioselectivity of the enolate anion. Exclusive C attack was observed when *N*-methylmorpholine was replaced by ethyldiisopropylamine.[121]



Scheme 55. Attack of ethyl acetoacetate (**108**) at the O atom of ethyl propiolate (**105**) according to Tae and Kim.[120]

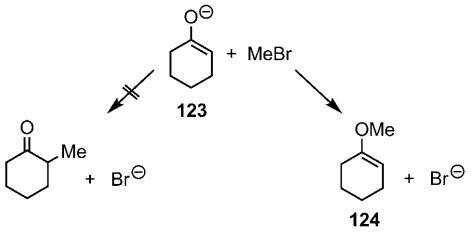
Attack at the oxygen atom of an enolate anion by an electron-deficient π system has also been observed in the reaction of trinitrobenzene with the potassium salt of acetophenone (**112**). Although 1,3,5-trinitrobenzene (**10**) is considered as a very soft electrophile, Buncel et al. reported that it attacks exclusively the hard site of the enolate of acetophenone at −40 °C.[122a] When the resulting solution of the Meisenheimer complex **113** in acetonitrile/dimethoxyethane was warmed up to 20 °C, rearrangement to the product of C attack **114** was detected by ^{1}H NMR spectroscopy (Scheme 56). Clearly, in both cases the intrinsic preference for O attack determines the regioselectivity of the kinetically controlled reactions.

On the other hand, stabilized benzhydrylium ions, commonly regarded as hard electrophiles, attack exclusively at the carbon center of various free enolates (Scheme 57), which we rationalize by thermodynamic product control, that is, reionization of any potentially generated benzhydryl vinyl ethers.[10c,122b] One can conclude from the monoexponential decays of the benzhydrylium absorbances under conditions of pseudo-first-order kinetics (high excess of the enolate anions) that the concentrations of potentially formed benzhydryl enol ethers remain so small that they are kinetically irrelevant.



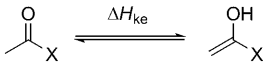
Scheme 57. Selective C-alkylation of different potassium enolates by the benzhydrylium ion **115** (in DMSO at RT for 10 min)[10c,122b]

Let us now analyze changes of the C/O ratios in gas-phase reactions, where counterion and solvent effects are eliminated. Exclusive attack at the oxygen atom was found in the reaction of the enolate derived from cyclohexanone (**123**) with methyl bromide in the gas phase (Scheme 58).[123] As methyl bromide is commonly considered a soft electrophile, this observation again contradicts the expectations derived from the HSAB principle.



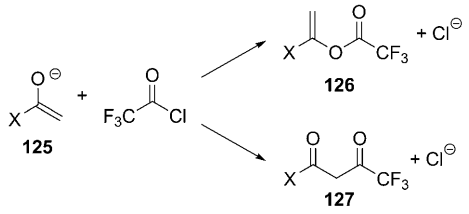
Scheme 58. Exclusive O-alkylation of the enolate anion **123** with methyl bromide in the gas phase.[123]

Brickhouse and Squires reported that the O/C selectivities of the reactions of enolate ions with hexafluoropropene in the gas phase were correlated with the keto–enol energy difference ΔH_{ke} of the parent carbonyl compounds [Eq. (18)],[124a] but some enolate ions deviated from this correlation.



(18)

Oxygen attack with formation of **126** dominated in the acylations of the enolate ions **125** with CF_3COCl in the gas phase (Scheme 59), which were studied by FT-ICR spectroscopy.[125] As shown in Figure 11, the O/C ratio decreased as the energy difference ΔH_{ke} increased.



Scheme 59. Acylation of enolate anions **125** by trifluoroacetyl chloride.[125a]

In contrast, the O/C ratio observed in reactions of enolate ions with hexafluorobenzene is only weakly correlated with ΔH_{ke}; these reactions appear to be predominantly controlled by HOMO–LUMO interactions.[124b]

Reactivities of enolates in solution are well-known to depend on the nature of the counterion and the solvent.[114] Le Noble et al. studied the reaction of ethyl acetoacetate salts **110** with different alkylation agents in HMPT (Scheme 60)

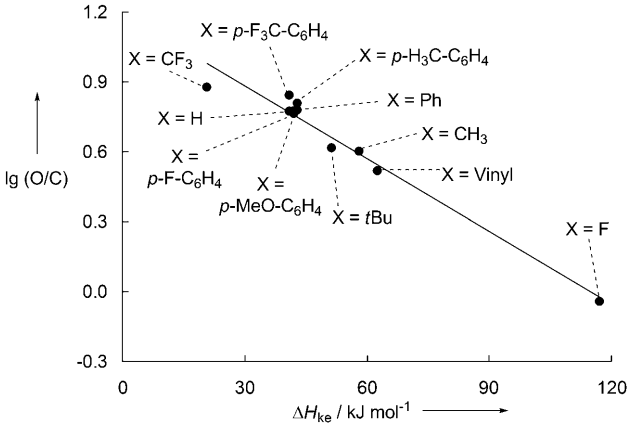
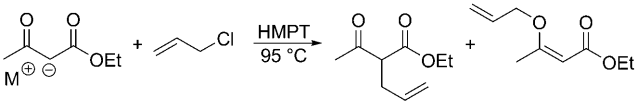


Figure 11. Correlation of the O/C ratio [lg(O/C)] with the keto–enol energy difference ΔH_{ke} of enolate anions.[125]



M	O/C ratio
Li	12 : 88
Na	17 : 83
K	17 : 83
NBu_4	17 : 83

Scheme 60. Dependence of the O/C ratios on counterions in allylations of ethyl acetoacetate salts (**110**) by allyl chloride (**128**).[126b]

and found that the O/C ratio did not change for Na^+, K^+, and NBu_4^+, thus indicating the reactivity of free carbanions.[126a,b] Only for lithium salts was a smaller O/C ratio observed.

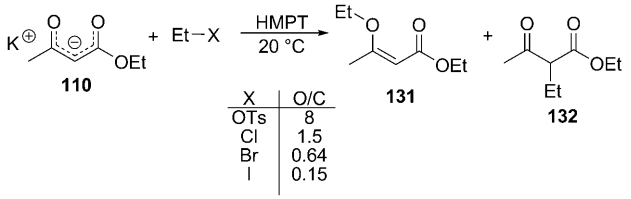
In line with these findings, Reutov and co-workers reported that the C/O ratios in the reactions of different alkali salts of ethyl acetoacetate with ethyl tosylate in HMPT are independent of the counterions, and also concluded that under these conditions only the free enolate ions were alkylated.[127]

A much larger effect of the counterions was found in the reaction of the anion of isobutyrophenone with methyl iodide in dimethoxyethane. While almost exclusive C attack (C/O ratio > 200:1) was observed for the lithium salt, the free anion obtained from the lithium salt and a [2.1.1]cryptand resulted in a C/O ratio of 8:1.[128]

Le Noble et al. showed that in the reactions of the anion of ethyl acetate with alkyl halides the O/C ratio increases as the solvent basicity increases in the series from acetone, acetonitrile, DMSO, DMF, to HMPT.[126a,b] The counterion will be less solvated in less basic solvents and will coordinate with the oxygen terminus of the enolate. The authors summarized their observations for ethyl acetoacetate concisely: "*The freer the anion, the larger the O/C ratio.*" They concluded that dissociated ions yield high O/C ratios, ion pairs yield intermediate O/C ratios, and higher aggregates lead to low O/C ratios.[126a,b]

The same rule applies for reactions of enolates with "hard" electrophiles. While the selective formation of O-acylated enols was observed by the reaction of "naked" enolates (obtained from silyl enol ethers and nBu$_4$NF) with acyl chlorides,[121b] Seebach et al. achieved selective C-alkylations when lithium enolates were treated with acyl chlorides in THF at −100 to −80 °C.[126c,d]

The change in the O/C ratio for the ethylation of the ethyl acetoacetate anion (**110**) with different ethylating agents (Scheme 61) has been rationalized by the decreasing hardness of the electrophile from top to bottom.[127] This trend cannot be explained by the qualitative Marcus analysis depicted in Figure 4, which neglects the different force constants in the reagents R–X and only considers the different exergonicities of the reactions.

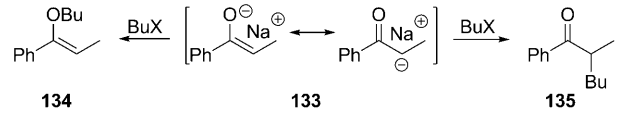


X	O/C
OTs	8
Cl	1.5
Br	0.64
I	0.15

Scheme 61. Ethylation of the potassium salt of ethyl acetoacetate by different ethylating agents.[127c]

Heiszwolf and Kloosterziel[129] employed the PLNM to rationalize the increasing O/C ratio in alkylations of enolate ions with increasing reactivity of the alkylating agent. This suggestion, which is in agreement with the qualitative Marcus analysis in Figure 4, has been rejected by Gompper and Wagner,[6b] because they found 1-fluorobutane, the least reactive 1-halobutane to give the highest percentage of O-alkylation (Scheme 62). While the increase in the O/C ratio in Scheme 62, as the solvent polarity increases, can again be rationalized by the solvation of the ions, we cannot currently rationalize the dependence of the O/C ratio on the nature of the electrophile. Knowledge of the experimental details of Scheme 62 would be needed for a detailed discussion, but they are not accessible to us.

As a consequence of the high O–H bond energy, the energy differences between carbonyl groups and their enol



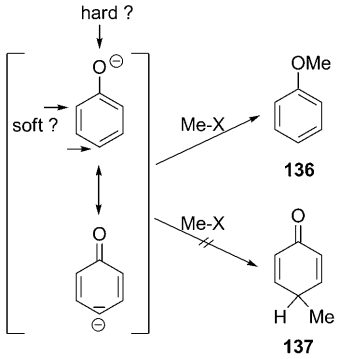
X	% *O* attack HMPT	DMSO	Et_2O
I	15	10	1
Br	40	23	5
Cl	67	46	18
OSO_3Me	83	–	11
OTs	85	44	20
OPO_3Bu_2	93	78	36
F	96	–	–

Scheme 62. Proportion of O-butylation in the reaction of an enolate with different *n*-butyl derivatives in different solvents.[6b] Ts = toluene-4-sulfonyl.

tautomers[130] are smaller than those between carbonyl groups and the isomeric enol ethers (Table 1, entry 12). As a consequence, the $\Delta\Delta G^0$ term favors C-protonation over O-protonation to a smaller extent than C-alkylation over O-alkylation. For that reason, kinetically controlled protonations of enolates occur generally at the oxygen atom, the intrinsically favored site of attack as mentioned at the beginning of this Section.[115]

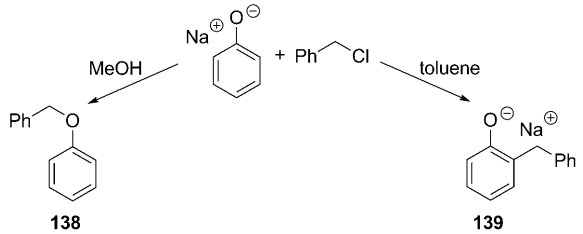
3.4.3. Phenoxides and Phenols

Phenolates contain the enolate substructure, and one can expect analogous control mechanisms for their ambident reactivity. The synthesis of phenol ethers by treatment of phenolates with soft haloalkanes as well as with hard dialkyl sulfates is a well-known procedure.[131] To explain within the HSAB approach why soft electrophiles also prefer to attack at the oxygen atom, a correction for the unfavorable loss of aromaticity in the case of C attack (**137**) had to be made (Scheme 63).



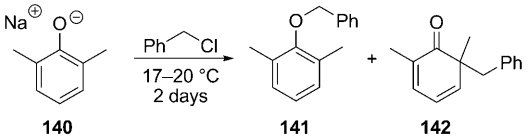
Scheme 63. Methylation of the ambident phenolate anion.

Marcus analysis of the alkylations of phenolate anions reveals that the attack at the oxygen atom is preferred thermodynamically ($\Delta\Delta G^0 = 28.9$ kJ mol^{-1}; Table 1, entry 13) and intrinsically ($\Delta\Delta G_0^{\neq} = 51.6$ kJ mol^{-1}, Scheme 4), again in line with the Hoz rule. Therefore, kinetically controlled alkylations generally occur at the oxygen atom. However, in nonpolar solvents, oxygen attack may be blocked by the counterion, and C-alkylation may occur.[132–134] Thus, Claisen and co-workers reported that treatment of sodium phenoxide with benzyl chloride in methanol yields benzyl phenyl ether (**138**), while the corresponding reaction in toluene solution leads to **139** as the main product (Scheme 64).[133]



Scheme 64. Benzylation of the ambident phenolate anion.[133]

Analogously, in the benzylation and alkylation reactions of sodium 2,6-dimethylphenolate (**140**) the highest percentage of C attack was obtained in toluene, whereas O attack was almost exclusive in THF (Scheme 65).[134a]

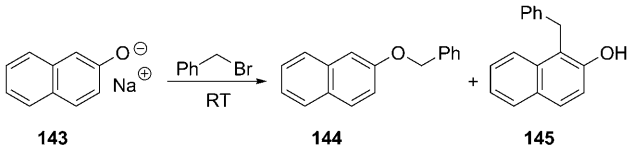


140 **141** **142**

Solvent	C/O ratio
toluene	4.2
Et_2O	0.36
dioxane	0.03
THF	0.01

Scheme 65. Reaction of sodium 2,6-dimethylphenolate (**140**) with benzyl chloride in different solvents.[134a]

As a consequence of the smaller loss of aromaticity in the initial step of C-alkylation of the naphthoxide **143**, C attack becomes more likely than in phenoxides. Thus, Scheme 66 shows that the ether **144** is formed exclusively in the dipolar aprotic solvents DMF and DMSO. Attack at the carbon atom



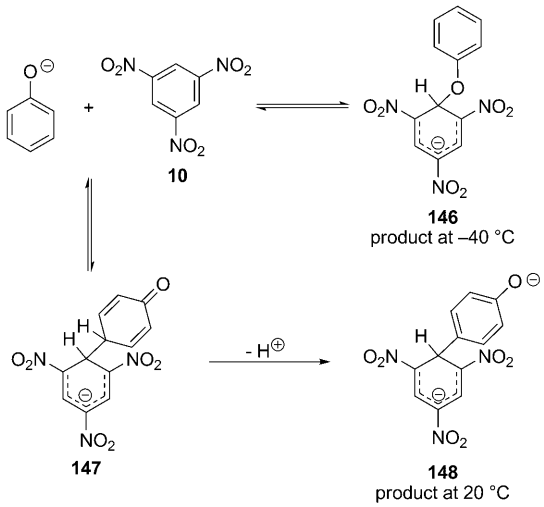
143 **144** **145**

Solvent	O/C ratio
DMF	97 : 1
DMSO	95 : 1
dimethoxyethane	70 : 22
THF	60 : 36
MeOH	57 : 34
EtOH	52 : 28
water	10 : 84
CF_3CH_2OH	7 : 85

Scheme 66. Dependence on the solvent of the site of benzylation in sodium 2-naphthoxide.[134h]

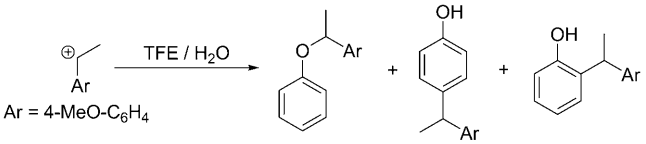
competes with attack at the oxygen atom in nonpolar solvents (dimethoxyethane, THF) where oxygen is coordinated to Na^+, and may even become dominant in protic solvents (ROH, H_2O), which block O attack by hydrogen bonding.[134e–h] Kornblum and Berrigan summarized that in solvents such as water, phenol, and fluorinated alcohols "*the oxygen of the phenoxide ion is so intensely solvated that the availability of the oxygen for nucleophilic displacement is greatly decreased; as a consequence, displacements employing the otherwise unfavored ortho and para carbon atoms can compete successfully.*"[134g] Accordingly, the site of benzylation can be completely inverted by variation of the solvent (Scheme 66).

Even the "very soft" electrophiles trinitrobenzene (**10**) and trinitroanisole attack the hard phenolate oxygen atom under kinetically controlled conditions to give **146** at −40 °C.[135] Rearrangement to **147** and **148**, the products of electrophilic aromatic substitution, takes place at ambient temperature, accompanied by decomposition (Scheme 67).[135b,136] Analogous behavior, namely, kinetically controlled attack at the phenolate oxygen atom and subsequent rearrangement to the product of electrophilic aromatic substitution has been reported for the reactions of phenolates with the highly electrophilic nitrobenzofuroxans and nitrobenzotriazole-1-oxides.[52b,137]

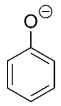
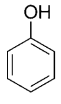


Scheme 67. Ambident reactivity of the potassium phenolate anion towards 1,3,5-trinitrobenzene (in CD_3CN/[D_{10}]-dimethoxyethane 1:1 (v/v)).[135]

Richard and co-workers studied the reactions of phenol and phenolate ions with the 1-(4-methoxyphenyl)ethylium ion (**149**) in trifluoroethanol/water mixtures.[138] The low selectivity for the reaction of **149** with the phenolate anion (Scheme 68) was explained by diffusion control. A much higher selectivity was found for the reaction of **149** with phenol, showing that O attack is also kinetically preferred in the reaction with the neutral phenol.[138]

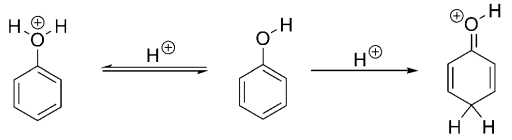


149 **150** **151** **152**

+ 	2	2	1
+ 	230	20	1

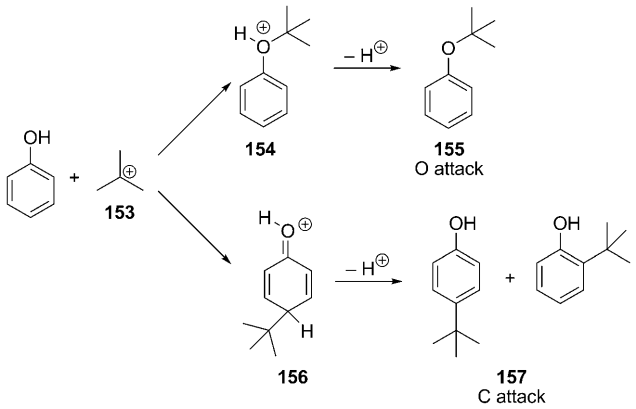
Scheme 68. Relative product ratios for alkylations of phenolate and phenol in TFE/H_2O (1:1) by the 1-(4-methoxyphenyl)ethylium ion.[138] TFE = 2,2,2-trifluoroethanol.

Olah and Mo[139] showed that the protonation of phenol in HF containing traces of SbF_5 at −105 °C initially also occurs at the oxygen atom. However, O-protonation is reversible, and a rearrangement to the thermodynamically more stable hydroxybenzenium ion takes place upon warming to −40 °C; hydroxybenzenium ions were also observed in 70% perchloric acid and fluorosulfuric acid (Scheme 69).[140]



Scheme 69. Protonation of phenol according to Olah and Mo.[139]

In the gas phase, where solvent effects are absent, phenol is also preferentially attacked by the *tert*-butyl cation (**153**) at the oxygen atom to form *tert*-butyl phenyl ether (**155**) under conditions of kinetic control (i.e., at high pressure and in the presence of NH_3 for an effective collisional deactivation). At lower pressure, 2- and 4-*tert*-butylphenols (**157**) dominated among the reaction products, thereby indicating reversible formation of **154** and the higher thermodynamic stability of **156** compared to **154** (Scheme 70).[141]

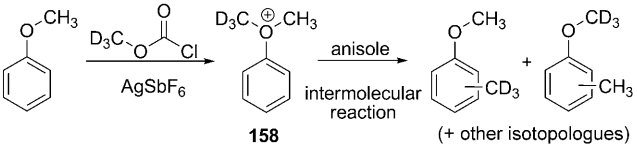


	O/C ratio
kinetic control	8 : 1
thermodynamic control	1 : 4

Scheme 70. Gas-phase reaction of phenol with the *tert*-butyl cation.[141c]

Beak et al.[142] reported labeling experiments which showed that the methylation of anisole in chlorobenzene also proceeds via the initial formation of the dimethylphenyloxonium ion (**158**). Subsequent intermolecular reactions with anisole give a mixture of unlabeled, [D_3]-, and [D_6]-labeled methylanisoles (Scheme 71).

In summary, the ambident reactivity of phenolates is analogous to that of enolates: O-alkylation of phenolates is intrinsically favored over C-alkylation unless the oxygen atom is blocked by coordination to metal ions or by hydrogen bonding in protic solvents. Reactions with strong electrophiles, which proceed under diffusion control, are unselective and occur at the oxygen atom as well as at the *ortho*- and *para*-carbon atom. Thus, we can conclude that O attack is also intrinsically favored over C attack in alkylations of phenols and phenol ethers, but C-alkylation leads to the thermodynamically preferred products.

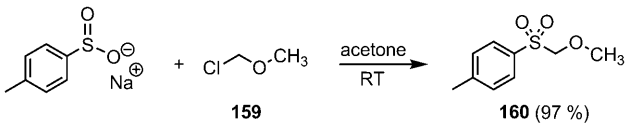


Scheme 71. Methylation of anisole by [D_3]-methyl chloroformiate (in chlorobenzene at 30 °C).[142]

3.5. Oxygen versus Sulfur Attack

3.5.1. Sulfinate Anions

Although sulfinate anions are ambident anions with nucleophilic sites at the oxygen and sulfur atoms, these anions were believed for a long time to react exclusively at the sulfur atom with formation of sulfones.[143] Already in 1880, Otto reported the formation of sulfones by the reaction of alkali salts of aromatic and aliphatic sulfinic acids with a variety of alkyl halides in ethanol at 80 °C.[144] Tertiary alkyl halides did not alkylate sulfinate anions and underwent elimination reactions with formation of olefins.[145] In an extensive study, Schank showed that primary and secondary alkyl halides, α-halocarbonyl compounds, as well as α-haloethers exclusively attack at the sulfur atom of *p*-toluenesulfinate anions (Scheme 72).[146]



Scheme 72. Reaction of sulfinic acid salts with chloromethyl methyl ether (**159**).[146]

Lindberg derived exclusive S attack from the kinetics of the reactions of *m*- and *p*-substituted sodium arenesulfinates with bromoacetate and bromoacetamide in water.[147]

Other displacement reactions at saturated carbon atoms, for example, epoxides[148] or β-propiolactones,[149] and nucleophilic aromatic substitutions of *p*-nitrochlorobenzene also proceed at sulfur to give sulfones exclusively.[150] Sulfones are also the only reaction products in Michael-type additions of sulfinate anions to acceptor-substituted alkenes such as chalcones,[151] haloacrylonitriles,[152] or nitroolefins,[153] which are often reversible.[143]

On the other hand, Meek and Fowler observed concomitant S and O attack in reactions of *p*-toluenesulfinate anions with various methylating agents (Table 7).[154] As an interconversion between the resulting methyl sulfinic esters and the isomeric methyl sulfones was shown not to occur under the reaction conditions, the product ratios given in Table 7 are the result of kinetic control.

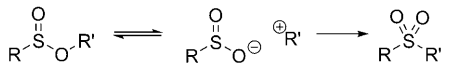
Table 7: Methylation of *p*-toluenesulfinates ($TolSO_2^-$) with different methylating agents.[154]

Entry	Substrate	Methylating agent	Solvent	% O	% S
1	$TolSO_2H$	CH_2N_2	Et_2O/MeOH (9:1)	100	0
2	$TolSO_2^-$	$TsCHCHP(OMe)_3^+$	none	95	5
3	$TolSO_2Na$	$(MeO)_2SO_2$	DMF	84[a]	16[a]
			DMF	88[b]	12[b]
4	$TolSO_2Na$	MeOTs	DMF	77	23
5	$TolSO_2Na$	$(MeO)_2SO_2$	MeOH	69	31
6	$TolSO_2Na$	MeOTs	MeOH	54	46
7	$TolSO_2Na$	MeI	MeOH	2	98
8	$TolSO_2Na$	MeI	DMF	7	93
9	$TolSO_2Ag$	MeI	DMF	9	91

[a] After 30 min. [b] After 17 h.

Although the preferred or exclusive O attack by the in situ generated methyldiazonium ion (Table 7, entry 1), dimethyl sulfate (entries 3 and 5), and methyl tosylate (entries 4 and 6) on the one hand and the preferred S attack by methyl iodide (entries 7 and 8) on the other might be explained by the HSAB principle, it should be noted that the silver salt of *p*-toluenesulfinic acid also reacts with methyl iodide at the sulfur atom with high selectivity (Table 7, entry 9). Attack at the oxygen atom of the sulfinate anions has also been observed in their reactions with triethyloxonium tetrafluoroborate,[155] acetyl chloride,[146] or ethyl chloroformiate.[144c]

Can these findings also be rationalized on the basis of Scheme 2? According to MP2/6-311 + G-(2d,p) calculations (Table 1), dimethyl sulfone is 50.4 kJ mol^{-1} ($\Delta\Delta G^0$) more stable than the isomeric methyl methanesulfinate. In line with this calculated energy difference, alkyl,[156] alkenyl,[157] and alkynyl[158] sulfinic esters rearrange to the thermodynamically more stable sulfones. For allylic sulfinic esters this rearrangement is believed to proceed by a [2,3] sigmatropic shift,[157,159] whereas the rearrangement proceeds through ionization and ion pair recombination if R^+ is a stabilized carbocation (Scheme 73).[13f,156] Independent of the mechanism of the rearrangement, these observations demonstrate the higher thermodynamic stabilities of the sulfones.



Scheme 73. Rearrangement of sulfinates to the corresponding sulfones.

On the other hand, higher intrinsic barriers for sulfur attack are indicated by the identity reactions summarized in Scheme 4 ($\Delta\Delta G_0^{\neq} = 34.7$ kJ mol^{-1}). As sulfur and oxygen are in the same group of the periodic table, and crystal structures indicate that O-alkylation requires larger geometric changes than S-alkylation, we assume that steric interactions are responsible for the higher intrinsic barriers of the S-alkylations.[160]

The exclusive S attack observed in the reaction of sodium benzenesulfinate with ordinary Michael acceptors and highly stabilized benzhydrylium ions (Figure 12) can, therefore, be explained by thermodynamic product control. From the plot of lg k versus the electrophilicity parameters E of the benzhydrylium ions one can extrapolate that the diffusion limit is reached when the electrophilicity E of the carbocations exceeds values of approximately -2.[13f] The observed mixtures resulting from O and S attack of more reactive benzhydrylium ions ($E > -2$, Figure 12) can, therefore, not be explained by classical transition-state models, and a similar situation should hold for reactions with other carbocations.

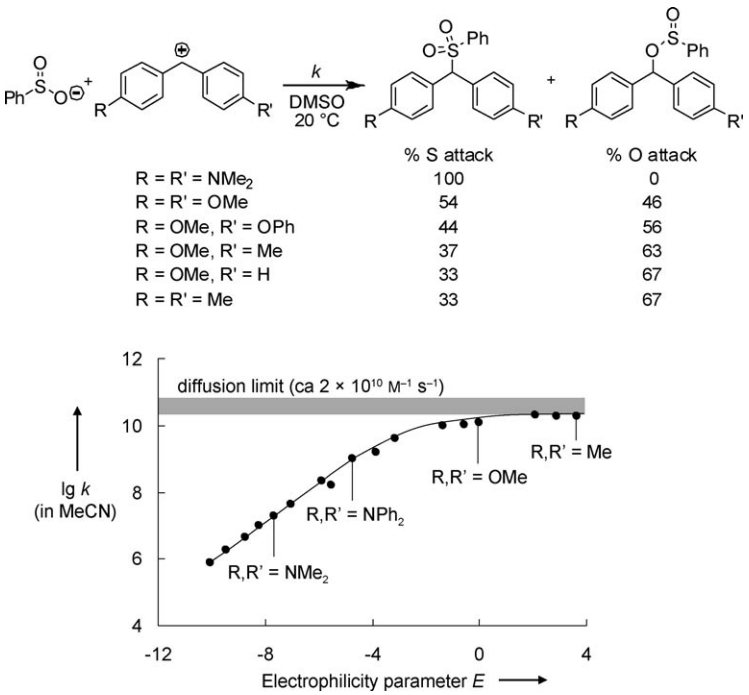


Figure 12. Plot of lg k for the reactions of the benzhydrylium ions with the benzensulfinate ion versus the electrophilicity parameters E (in MeCN at 20 °C).[13f]

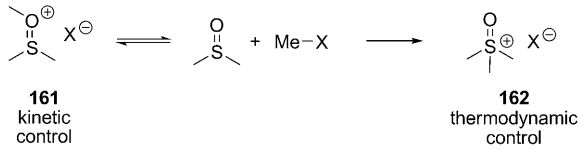
From the experimental rate constants of the reaction of $(p\text{-}MeOC_6H_4)_2CH^+$ with the oxygen atom of the benzenesulfinate anion and of the reverse reaction, an intrinsic barrier of $\Delta G_0^{\neq} = 48$ kJ mol^{-1} was derived from Equation (3). Analogously, intrinsic barriers of $\Delta G_0^{\neq} = 60$–64 kJ mol^{-1} have been calculated from the rate and equilibrium constants for the reactions of amino-substituted benzhydrylium ions with the sulfur atom of $PhSO_2^-$. Although a small fraction of this difference can be assigned to the different nature of the carbocations, it is remarkable that the difference between these two intrinsic barriers is close to 50 % of the difference of the calculated barriers of the corresponding identity reactions (Scheme 4),[13f] as expected from the combination of Equations (3) and (7).

In summary, sulfinate anions are attacked at the sulfur atom under conditions of thermodynamic control. Mixtures

of sulfones and sulfinates are typically obtained in diffusion-limited reactions, while in activation-controlled reactions it depends on the reaction partner and the reaction conditions, whether S or O attack dominates (Figure 4).

3.5.2. Sulfoxides

A similar situation as described for sulfinates is also found for sulfoxides. When DMSO was treated with methyl brosylate, methyl tosylate, or methyl nitrate, O-methylation (**161**) was observed exclusively.[161] On the other hand, only products of S attack (**162**) were isolated when methyl iodide was used as the methylating agent.[161,162] From the observation that the O-alkyl derivatives **161** tend to isomerize in solution to the S-alkyl derivatives **162** and that the tendency of such isomerization decreases in the order $X = I^- > NO_3^- > OTs^-$, Smith and Winstein concluded that the formation of either **161** or **162** is associated with kinetic and thermodynamic control of the products (Scheme 74). As the formation of **161** is highly reversible in the presence of I^-, the rearrangement **161**-I to **162**-I is so fast that only 7% of the O-alkylated product **161**-I could be observed when methyl iodide was heated in DMSO at 50°C. In contrast, 94% of the O-alkylation product **161**-



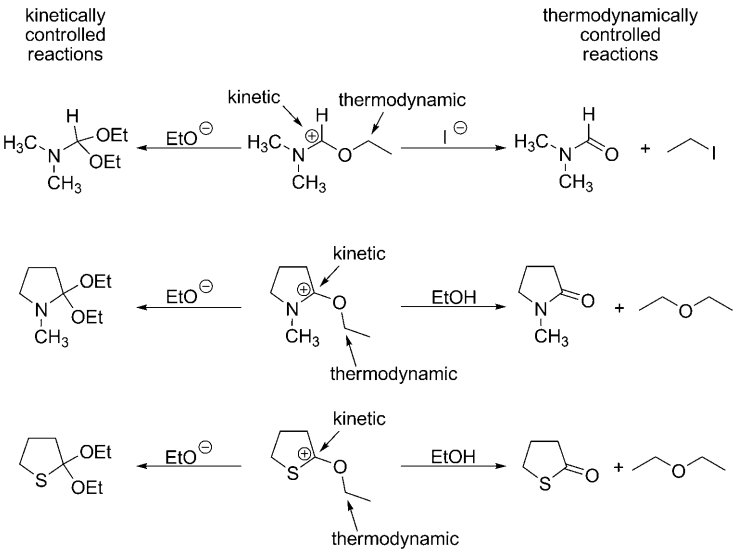
Scheme 74. Methylation of DMSO under conditions of kinetic and thermodynamic control.

OBs was obtained from methyl *p*-bromobenzenesulfonate (OBs, brosylate) in DMSO at 50°C because of the slower rearrangement resulting from the lower nucleophilicity of the *p*-bromobenzenesulfonate anion BsO^-.

4. Ambident Electrophiles

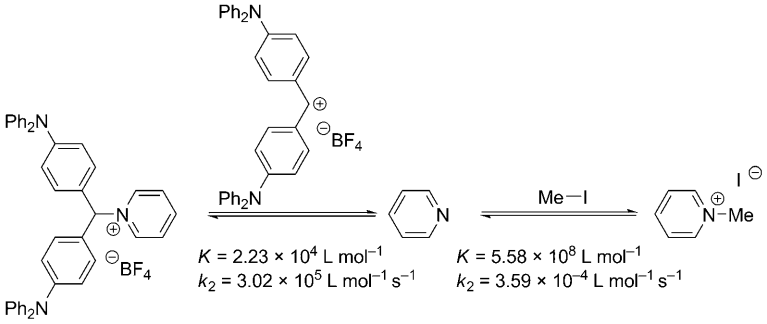
Ambident electrophiles shall not be treated explicitly here because of space limitations. We just want to emphasize that the same procedure which has been applied for rationalizing the regioselectivities of ambident nucleophiles should also be applicable to ambident electrophiles.

In an excellent review published in 1964, Hünig carefully analyzed the modes of reactions of ambident cations derived from amides or esters (Scheme 75). The results of numerous reactions, which gave different products under different reaction conditions, were summarized as follows: "*The structures of the products isolated are determined by competition between a kinetically controlled but reversible reaction and a thermodynamically controlled reaction*".[8]



Scheme 75. Kinetic and thermodynamic product control in the reactions of ambident electrophiles.[8]

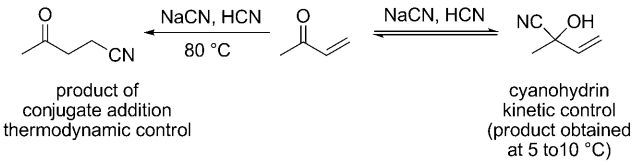
As outlined in Section 2.6, the formation of different products under conditions of kinetic and thermodynamic control implies that the "kinetic" products are intrinsically preferred. In numerous experimental studies, it has been shown that additions of nucleophiles to C_{sp^2} centers (carbocations or Michael acceptors) generally have low intrinsic barriers.[163] In contrast, S_N2 reactions, where a σ bond must be broken in the rate-determining step, require more reorganization and are characterized by higher intrinsic barriers. This relationship is quantitatively illustrated in Scheme 76, which compares the rate and equilibrium constants of the reactions



Scheme 76. Reactions of pyridine with a benzhydrylium ion and methyl iodide.[163a,164]

of pyridine with different electrophiles. Although the equilibrium constant for the reaction with methyl iodide is four orders of magnitude larger than that of the reaction with the benzhydrylium ion, methyl iodide reacts 10^9 times more slowly.[163a,164] This comparison clearly illustrates that the intrinsic barrier for the S_N2 reaction is much larger than the intrinsic barrier for reactions with carbocations.

If 1,4-additions of organocuprates, which follow a special mechanism,[165] are disregarded, most 1,4-/1,2-selectivities in α,β-unsaturated carbonyl compounds can also be rationalized by the competition of kinetic versus thermodynamic product control, as illustrated for cyanide additions to methyl vinyl ketone in Scheme 77.[113b,166] Additions to a C–C double bond



Scheme 77. Ambident reactivity of the cyanide anion toward methyl vinyl ketone.[113b]

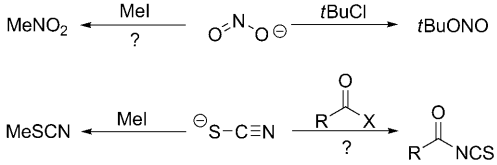
are generally more exergonic than additions to a C–O double bond. For that reason, Michael additions are thermodynamically favored over additions to the carbonyl group. On the other hand, 1,4-additions require much more structural reorganization, and are therefore intrinsically disfavored.

As a consequence, nucleophiles with high Lewis basicity, which react irreversibly, usually give the intrinsically favored 1,2-adducts, whereas nucleophiles with low Lewis basicity eventually yield the thermodynamically more stable Michael adducts because their reactions are reversible with the carbonyl group.[167]

5. Conclusions

The HSAB treatment of ambident reactivity may be considered as a generalization of Kornblum's rule, which states that the site of attack at ambident nucleophiles is related to the S_N1/S_N2 character of the reaction. The main support for Kornblum's rule was the observation that silver cyanide as well as the silver salts of 2-pyridone and of other carboxamides give different products than the corresponding alkali salts. There is convincing evidence, however, that the change of selectivity triggered by the silver salts is not due to a switch from an S_N2 to an S_N1 mechanism but due to blocking of the carbon atom in CN^- and of the nitrogen atoms in the amide and 2-pyridone anions by Ag^+. Furthermore, we have presented examples that show that silver ions do not have any or only marginal effects on the regioselectivities of the reactions with nitrite, sulfinate, and 4-pyridone anions.

Ironically, the two examples which prompted Klopman to develop the concept of charge- and frontier-orbital-controlled reactions[5a] do not proceed as formulated in Scheme 78. Methyl iodide reacts with sodium nitrite to give a mixture of nitromethane and methyl nitrite,[86] and seven years before Klopman's work, Ruske provided evidence that SCN^- is attacked at the sulfur atom by acyl chlorides to give acyl thiocyanates, which may rearrange to the corresponding isothiocyanates under certain conditions.[75] As not even the behavior of the prototypes of ambident nucleophiles can properly be described in this way, the rationalization of



Scheme 78. The questionable experimental basis which triggered the development of the concept of charge- and frontier-orbital-controlled reactions.[5a]

ambident reactivity by the HSAB or the Klopman–Salem concept has to be abandoned.

A consistent approach to ambident reactivity is suggested in Scheme 2. In the first step, it should always be examined whether the isolated products are the result of kinetic or thermodynamic control. In the case of kinetic product control, one has to find out whether the reactions proceed with or without activation energy. This differentiation can be made on the basis of the reactivity parameters N, s_N, and E [Eq. (1)]. As most ambident anions analyzed in this Review undergo diffusion-controlled reactions with carbocations that are less stabilized than the tritylium ion, transition-state models are inappropriate to rationalize the resulting regioselectivities.

Marcus theory, which derives the Gibbs energy of activation $\Delta G^{\neq}$ from the Gibbs energy of reaction ΔG^0 and the intrinsic barrier $\Delta G_0^{\neq}$, has been shown to be suitable for predicting the regioselectivities of kinetically controlled reactions, which proceed over an energy barrier. A rule of thumb for deriving the intrinsically preferred site of electrophilic attack at ambident nucleophiles is provided by the Hoz rule: The further right the nucleophilic reaction center in the periodic table, the lower the intrinsic barrier. Application of the PLNM, which compares geometrical parameters in reactants and products, leads to the same ordering of intrinsic barriers. Our attempts to rationalize ambident reactivity on the basis of Guthrie's "No-Barrier-Theory"[168] have so far not been successful, but efforts are ongoing.

The success of Marcus theory to rationalize ambident reactivity ($\Delta G^{\neq}$) by a combination of intrinsic ($\Delta G_0^{\neq}$) and product stability effects (ΔG^0) suggests that Marcus theory should be employed more generally for analyzing structure–reactivity relationships. Whereas the influence of ΔG^0 on $\Delta G^{\neq}$ is well known and is quantitatively described by Brønsted correlations,[169] the Bell–Evans–Polanyi principle,[170] or the Leffler–Hammond relationship,[171] much less is currently known about intrinsic barriers ($\Delta G_0^{\neq}$)—the second term which controls the rates of chemical reactions [Eq. (3)]. Promising approaches to elucidate the magnitude and origin of intrinsic barriers as described by Bernasconi,[172] Bordwell,[173] Hoz,[23] Kreevoy,[20d] Lewis,[174] Murdoch,[175] Richard,[16a] and Terrier[176] should, therefore, be further developed.

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