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Ambident Nucleophiles

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Marcus Analysis of Ambident Reactivity**

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Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Pearson's principle of hard and soft acids and bases (HSAB)[1] and the related Klopman–Salem concept of charge- and frontier-controlled reactions[2] has been considered to provide a consistent rationalization for ambident reactivity. In a series of experimental investigations we have shown, however, that the reactivities of SCN^-,[3] CN^-,[4] NO_2^-,[5] OCN^-,[6] $R_2C{=}NO_2^-$,[7] and $PhSO_2^-$,[8] that is, the typical ambident nucleophiles, cannot be described by these concepts. In the cited articles,[3–8] we quoted older experimental studies that had already indicated the inconsistency of applying the HSAB principle. In the new edition of his groundbreaking monograph,[9] Fleming has accepted our analysis, and referred to "*other factors which are at work*" which are responsible for the failure of HSAB predictions. As a model which fails in more than 50% of the cases, it eventually has to be abandoned; therefore we have searched for a more consistent rationalization of ambident reactivity and now suggest Marcus theory as the better alternative.

Marcus theory[10] and related concepts consider reactant and product nestling in a parabolic bowl, and the transition state is approximated as the point of intersection of the two bowls. For electron-transfer reactions, that is, the types of reactions that led to the formulation of the Marcus equation, the parabolic displacements refer to the movement of solvent molecules around the reactants and products. In the case of group-transfer reactions [Eq. (1)], which are depicted in Figure 1, a major contribution to the parabolic term comes from the A−X and B−X vibrations.[10e]

$$A{-}X + B \rightarrow A + X{-}B \tag{1}$$

The points of intersection of the parabolas in Figure 1 can be expressed by the Marcus equation [Eq. (2)]. The Gibbs energy of activation, $\Delta G^{\neq}$, is therefore expressed by a combination of the Gibbs energy of the reaction, ΔG°, and the intrinsic barrier $\Delta G_0^{\neq}$, which corresponds to the $\Delta G^{\neq}$ of an identity reaction, where $\Delta G^{\circ} = 0$ (Figure 1). In other words: $\Delta G_0^{\neq}$ reflects the kinetic contribution to $\Delta G^{\neq}$ from which the thermodynamic component has been eliminated. Marcus suggested calculating the intrinsic barrier of a non-identity reaction as the average of the two corresponding identity reactions.[10c,d,11]

$$\Delta G^{\neq} = \Delta G_o^{\neq} + 0.5\,\Delta G^{\circ} + (\Delta G^{\circ})^2/16\,\Delta G_o^{\neq} \tag{2}$$

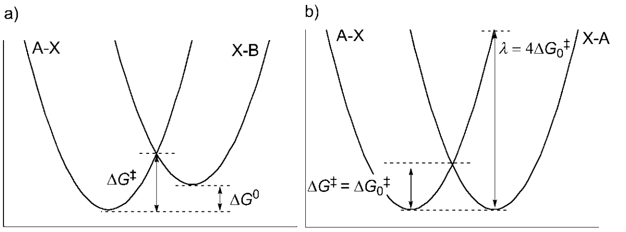

Figure 1. Definition of the intrinsic barrier $\Delta G_0^{\neq}$ for a) a non-identity reaction, and b) an identity reaction.

Application of this so-called additivity principle to methyl-transfer reactions yields Equation (6), wherein the intrinsic barrier $\Delta G_0^{\neq}$ for the S_N2 reaction in Equation (3) is calculated as the average of the activation energies of the identity reactions in Equations (4) and (5).

$$X^- + H_3C{-}Y \rightarrow X{-}CH_3 + Y^- \tag{3}$$

$$X^- + H_3C{-}X \rightarrow X{-}CH_3 + X^- \tag{4}$$

$$Y^- + H_3C{-}Y \rightarrow Y{-}CH_3 + Y^- \tag{5}$$

$$\Delta G_0^{\neq}\ [\text{Eq. (3)}] = 0.5(\Delta G_0^{\neq}\ [\text{Eq. (4)}] + \Delta G_0^{\neq}\ [\text{Eq. (5)}]) \tag{6}$$

The validity of this approach has been confirmed computationally and experimentally. In 1981 Wolfe, Mitchell, and Schlegel[12] reported RHF/4-31G calculations showing that the S_N2 barriers for Equation (3), estimated by the Marcus approach [Eqs. (2) and (6)], agreed well with the explicitly computed barriers for these reactions. Using various high-level theoretical methods, Gonzales, Allen, Schaefer III, et al. confirmed these results and reported that the explicitly calculated barriers differed from those derived by the Marcus approach by less than 12 kJ mol^{-1}.[13]

This agreement implies that there are no variable hard–hard or soft–soft interactions between the different groups in Equations (3)–(5), which is in perfect agreement with Brauman's seminal investigations on the kinetics of methyl- and benzyl-transfer reactions in the gas phase.[10d,14] Directly measured rate constants for gas phase S_N2 reactions

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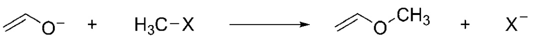
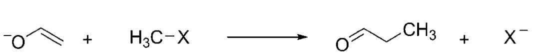
[Eq. (3)] deviated only slightly from those calculated by using Equation (2) using ΔG° and the rate constants for the corresponding identity reactions [Eqs. (4) and (5)].[14c]

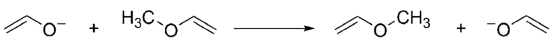
As an example for the use of Marcus theory to analyze ambident reactivity, first consider the O and C methylation of an enolate [Eqs. (7O) and (7C)]. In analogy to Equation (6), the intrinsic barrier for O methylation [Eq. (7O)] is obtained by the average of the Gibbs energies of activation for the identity reactions [Eqs. (4) and (8O)] as expressed by Equation (9O). According to Equation (9C), the intrinsic barrier for C methylation [Eq. (7C)] is obtained as the average of the identity reactions [Eqs. (4) and (8C)].



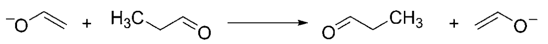
(7O)



(7C)



(8O)



(8C)

$$\Delta G_0^{\ddagger}[\text{Eq. (7O)}] = 0.5(\Delta G_0^{\ddagger}[\text{Eq. (8O)}] + \Delta G_0^{\ddagger}[\text{Eq. (4)}]) \quad (9\text{O})$$

$$\Delta G_0^{\ddagger}[\text{Eq. (7C)}] = 0.5(\Delta G_0^{\ddagger}[\text{Eq. (8C)}] + \Delta G_0^{\ddagger}[\text{Eq. (4)}]) \quad (9\text{C})$$

As illustrated for the identity reaction [Eq. (4)] in Figure 2, $\Delta G_0^{\ddagger}$ can either be defined with respect to the free reactants ($\Delta G_0^{\ddagger}$) or with respect to the reactant complexes [$\Delta G_0^{\ddagger}(\text{RC}) = (\Delta G_0^{\ddagger} - (\Delta G^0(\text{RC})]$. According to theory, intrinsic barriers should be considered with respect to reactant complexes [$\Delta G_0^{\ddagger}(\text{RC})$]. However, previous theoretical[12b,13c] and experimental gas-phase[14b,15] investigations demonstrated the advantages of using $\Delta G_0^{\ddagger}$, that is, the intrinsic barrier with respect to the free reactants. Furthermore, ΔG^0 for the formation of the reactant complex is rather small in solution, which makes the interpretation of reactions in solution simpler if it is based on $\Delta G_0^{\ddagger}$ and not on $\Delta G_0^{\ddagger}(\text{RC})$. Since calculations at the G3(+) and MP2/6-311+G(2d,p) levels of theory showed the same trends, the following discussion will be restricted to the G3(+) results. The results at the MP2 level can be found in the Supporting Information.

As previously recognized by Hoz and co-workers,[16] our calculations also show that the intrinsic barriers of the identity reactions [Eq. (4)] increase dramatically when one moves from right to left in the periodic table (Table 1, $\Delta G_0^{\ddagger} = 15\,\text{kJ}\,\text{mol}^{-1}$ for F^-, 78 for MeO^-, 124 for Me_2N^-, and 206 for H_3C^-). Uggerud correlated this trend with the ionization energy of the nucleophile X^-.[17] Those nucleophiles that form bonds to carbon atoms with stronger electrostatic character give rise to lower barriers due to decreased electron repulsion in the transition state.

Furthermore, Hoz et al. noticed that the intrinsic barriers $\Delta G_0^{\ddagger}$ change only slightly as one moves from top to bottom within one group in the periodic table. This trend, which is also revealed by our calculations (Table 1; F, Cl, Br 15–31 $\text{kJ}\,\text{mol}^{-1}$ and HO^-, MeO^-, HS^-, MeS^- 78–92 $\text{kJ}\,\text{mol}^{-1}$) has been rationalized by Arnaut, Formosinho, et al.:[18] When moving from top to bottom within the periodic table the C–X bond length increases, thereby leading to increasing the separation of the parabolas and a rise of the energy of the transition state. At the same time, in moving from the top to the bottom of the column the force constants decrease, which causes a flattening of the parabolas and a lowering of the transition-state energy. Both effects obviously compensate each other and result in almost constant values of $\Delta G_0^{\ddagger}$ within one group.

Table 1: Intrinsic barriers $\Delta G_0^{\ddagger}$ ($=\Delta G^{\ddagger}$) for the identity reaction [Eq. (4)] and Gibbs energies $\Delta G^0(\text{RC})$ of the formation of the reactant complexes (G3(+); $\text{kJ}\,\text{mol}^{-1}$).[a]

X	$\Delta G_0^{\ddagger}$	$\Delta G^0(\text{RC})$	$\Delta G_0^{\ddagger}(\text{RC})$	X	$\Delta G_0^{\ddagger}$	$\Delta G^0(\text{RC})$	$\Delta G_0^{\ddagger}(\text{RC})$
F	+14.7	−38.5	+53.2	**N**H_2	+146	−36.3	+183
Cl	+31.2	−26.8	+58.0	**N**Me_2	+124	−18.3	+142
Br	+24.7	−22.3	+47.0				
				CH_3	+206	−11.1	+218
OH	+81.4	−98.6	+180				
OMe	+77.6	−20.4	+97.9	**O**CHCH_2	+77.0	−19.7	+96.7
SH	+85.8	−24.6	+110	**C**H_2CHO	+181	−28.8	+210
SMe	+92.1	−21.1	+113				

[a] $\Delta G_0^{\ddagger}(\text{RC}) = \Delta G_0^{\ddagger} - \Delta G^0(\text{RC})$.

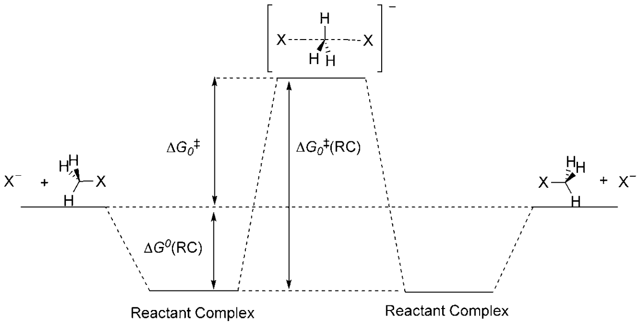


Figure 2. Definition of the intrinsic barrier in identity reactions with respect to the free reactants ($\Delta G_0^{\ddagger}$) or the reactant complex [$\Delta G_0^{\ddagger}(\text{RC})$].

The last two entries of Table 1, which reflect $\Delta G^{\ddagger}$ for Equations (8O) and (8C), that is, special cases of Equation (4), show the same trend: The intrinsic barrier for O attack (77 $\text{kJ}\,\text{mol}^{-1}$) is much lower than that for C attack (181 $\text{kJ}\,\text{mol}^{-1}$).

Let us now examine the suitability of the Marcus approach for deriving the activation Gibbs energies ($\Delta G^{\ddagger}$) for Equations (7O) and (7C). For that purpose, we have directly calculated $\Delta G^{\ddagger}$ for Equations (7O) and (7C) and listed them in the last column in Table 2. Comparison of the

Table 2: Gibbs reaction energies (ΔG^0) and Gibbs activation energies ($\Delta G^{\ddagger}$) for the O and C methylation of the enolate of acetaldehyde [Eqs. (7O) and (7C); G3(+); kJ mol^{-1}].[a]

X in MeX	O attack of enolate [Eq. (7O)] $\Delta G_0^{\ddagger}$ [Eq. (9O)]	ΔG^0	$\Delta G^{\ddagger}$ [Eq. (2)]	$\Delta G^{\ddagger}$ (direct)
F	+45.9	+57.0	+78.8	+71.7
Cl	+54.1	−78.4	+22.0	+16.0
Br	+50.9	−110	+10.8	+6.9
OH	+79.2	+130	+158	+146
OMe	+77.3	+116	+146	+136
SH	+81.4	+3.4	+83.1	+85.7
SMe	+84.6	+41.2	+106	+108

X in MeX	C attack of enolate [Eq. (7C)] $\Delta G_0^{\ddagger}$ [Eq. (9C)]	ΔG^0	$\Delta G^{\ddagger}$ [Eq. (2)]	$\Delta G^{\ddagger}$ (direct)
F	+97.9	−25.1	+85.8	+89.3
Cl	+106	−160	+41.1	+34.4
Br	+103	−192	+29.4	+18.2
OH	+131	+48.4	+156	+155
OMe	+129	+34.0	+147	+150
SH	+133	−78.6	+96.6	+95.9
SMe	+137	−40.8	+117	+115

[a] For clarity, only Gibbs energies referring to the free reactants are given. The corresponding data referring to the reactant complexes are given in the Supporting Information.

two right columns of Table 2 shows that the directly calculated $\Delta G^{\ddagger}$ values agree within a mean unsigned error of 5.1 kJ mol^{-1} with those derived from the Marcus equation using ΔG^0 and $\Delta G_0^{\ddagger}$. In accord with the results of theoretical and experimental investigations of ordinary S_N2 reactions, which are discussed above,[12b,13c,14c] Marcus theory can therefore be used to elucidate the trends underlying ambident reactivity.

Table 2 shows that the difference between the intrinsic barriers ($\Delta G_0^{\ddagger}$[Eq. (7O)]−$\Delta G_0^{\ddagger}$[Eq. (7C)]) for O and C attack is independent of the nature of the electrophile, because the electrophile-specific terms $\Delta G_0^{\ddagger}$ [Eq. (4)] cancel when subtracting Equation (9C) from Equation (9O). The fair agreement between directly calculated $\Delta G^{\ddagger}$ (last column of Table 2) and $\Delta G^{\ddagger}$ derived from the Marcus equation (Table 2, column 2 from right) therefore implies that the "hardness" of the electrophile has little influence upon the C/O alkylation ratio. In line with our analysis, Houk and Paddon-Row concluded from quantum-chemical calculations (HF/6-31G*) in 1986 that "*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 'hardness' or 'softness' of the alkyl halide, but to the ability of the halide to influence the structure of metal enolate aggregates.*"[19]

The middle column of Table 2 shows that for all electrophiles the product stability term (ΔG^0) highly favors C attack over O attack. However, the much higher intrinsic barrier $\Delta G_0^{\ddagger}$ for C attack compensates for this effect; as a result, $\Delta G^{\ddagger}$ is similar for O and C attack independent of the methylating agent (Table 2, right columns). It depends upon the reaction conditions whether the site of attack is controlled by the thermodynamic or the intrinsic term.

For an analogous Marcus analysis of the ambident reactivities of CN^-, OCN^-, SCN^-, and NO_2^- we have calculated the activation energies of the corresponding identity reactions [e.g., Eqs. (10C) and (10N)] with respect to the free reactants and to the reactant complexes, which are listed in Table 3 as $\Delta G_0^{\ddagger}$ and $\Delta G_0^{\ddagger}$(RC), respectively.

$$NC^- + H_3C{-}CN \rightarrow NC{-}CH_3 + {}^-CN \tag{10C}$$

$$CN^- + H_3C{-}NC \rightarrow CN{-}CH_3 + {}^-NC \tag{10N}$$

The relationship between intrinsic barrier and location of the attacking atom of the nucleophile in the periodic table noted by Hoz et al.[16] and confirmed by Table 1 also controls ambident reactivity. According to Table 3, $\Delta G_0^{\ddagger}$ and $\Delta G_0^{\ddagger}$(RC) are generally smaller when the attacking site of the nucleophile (correspond to the departing site of the leaving group) is located further to the right in the periodic table. Therefore, intrinsically favored are N attack by CN^-, O attack by NCO^-, and S attack by NCS^-.

Table 3: Intrinsic barriers $\Delta G_0^{\ddagger}$ (=$\Delta G^{\ddagger}$) for the identity reactions, e.g. in Equations (10C) and (10N), and Gibbs energies ΔG^0(RC) of the formation of the reactant complexes (G3(+); kJ mol^{-1}).

X	$\Delta G_0^{\ddagger}$	ΔG^0(RC)	$\Delta G_0^{\ddagger}$(RC)[a]	X	$\Delta G_0^{\ddagger}$	ΔG^0(RC)	$\Delta G_0^{\ddagger}$(RC)[a]
CN	+156	−29.3	+185	**S**CN	+52.2	−36.5	+88.7
NC	+93.8	−32.9	+127	**N**CS	+93.7	−25.3	+119
OCN	+21.6	−40.7	+62.2	**N**O_2	+61.4	−35.5	+96.8
NCO	+78.4	−23.6	+102	**O**NO	+61.1	−19.2	+80.2

[a] $\Delta G_0^{\ddagger}(RC) = \Delta G_0^{\ddagger} - \Delta G^0(RC)$.

An exception is NO_2^-, where $\Delta G_0^{\ddagger}$ (with respect to the free reactants) is almost the same for N and O attack. The higher stability of the reactant complex of NO_2^- with $H_3C{-}NO_2$ than with $H_3C{-}ONO$ accounts for the fact that $\Delta G_0^{\ddagger}$(RC) is again smaller for O attack than for N attack.

Use of the additivity principle [Eqs. (6), (9O), and (9C)] yields the intrinsic barriers $\Delta G_0^{\ddagger}$ for the reactions of CN^-, OCN^-, SCN^-, and NO_2^- with CH_3Cl (Table 4) using the $\Delta G_0^{\ddagger}$ values of the identity reactions in Table 3 and $\Delta G_0^{\ddagger}$ for the chloride exchange (Table 1, entry 2). Table 4 shows that cyanide prefers C attack thermodynamically (ΔG^0) and N attack intrinsically ($\Delta G_0^{\ddagger}$). As the differences of the intrinsic terms are much smaller than the differences in the Gibbs reaction energies ($\Delta\Delta G^0$), free cyanide ions always preferentially attack C electrophiles with the carbon atom (for a rationalization of the reaction with AgCN, see Ref. [4]).

N attack is favored by the ΔG^0 term in the reactions of NCO^- and NCS^-, and in both cases attack at the chalcogen terminus is preferred intrinsically (Table 4 and Figure 3). The large thermodynamic preference for N attack at NCO^- is not overcompensated by the intrinsic term, and NCO^- generally reacts faster at the nitrogen atom. In contrast, $\Delta\Delta G^0$ for S and

Table 4: Gibbs energies of reaction (ΔG^0), intrinsic barriers ($\Delta G_0^{\ddagger}$), and Gibbs energies of activation ($\Delta G^{\ddagger}$) for the methylation of ambident nucleophiles with MeCl [Eqs. (6), (10C), and (10N); G3(+), kJ mol^{-1}].[a]

X	$\Delta G_0^{\ddagger}$	ΔG^0	$\Delta G^{\ddagger}$	X	$\Delta G_0^{\ddagger}$	ΔG^0	$\Delta G^{\ddagger}$
CN	+93.6	−131	+39.6	**S**CN	+41.7	+87.1	+96.6
NC	+62.5	−29.8	+48.5	**N**CS	+62.5	+71.7	+103
OCN	+26.4	+119	+119	**N**O$_2$	+46.3	−18.1	+37.7
NCO	+54.8	+3.2	+56.4	**O**NO	+46.2	−9.2	+41.7

[a] For clarity, only Gibbs energies referring to the free reactants are given. The corresponding data referring to the reactant complexes are given in the Supporting Information.

N attack for isocyanate is rather small, such that kinetically controlled alkylations of NCS$^-$ occur preferentially at the intrinsically preferred site (S) to give thiocyanates, which may rearrange to isothiocyanates under thermodynamically controlled conditions (Figure 3).

Finally, nitroalkanes are more stable than alkyl nitrites; however, under conditions of kinetic control methyl halides and NO$_2^-$ usually give mixtures resulting from O and N attack.

Unfortunately, this analysis cannot be used to predict how variation of the electrophile affects the product ratio. The reason is that the gas-phase calculations do not provide correct absolute values of ΔG^0 and $\Delta G_0^{\ddagger}$ for reactions in solution. Instead of introducing quantitative solvation models into this treatment, we suggest using the results of this investigation qualitatively to interpret ambident reactivity through the combination of reaction Gibbs energy ΔG^0 and intrinsic barrier $\Delta G_0^{\ddagger}$. Whenever a product obtained under kinetic control is thermodynamically less stable, it must be favored intrinsically.

We have demonstrated that attack at the atom that is further right in the periodic table is usually preferred intrinsically. An alternative approach to relative intrinsic barriers comes from the principle of least nuclear motion, because according to Figure 1 the reorganization energy λ is the four-fold value of the intrinsic barrier, as explicitly discussed by Hine.[20] The coincident conclusions from both approaches will be reported in a subsequent review.

More than three decades ago, Gompper and Wagner[21] emphasized that the HSAB concept does not differentiate between kinetic and thermodynamic control though it has long been known that in many cases ambident systems give different products under kinetic and thermodynamic product control. The clear differentiation between kinetic and thermodynamic control,[22a] which used to be common in the past,[22b] has been neglected in more recent treatments of ambident reactivity and thus led to considerable confusion. By taking into account intrinsic ($\Delta G_0^{\ddagger}$) as well as the thermodynamic (ΔG^0) contributions to the Gibbs energies of activation ($\Delta G^{\ddagger}$), that is, by considering the role of thermodynamics also in kinetically controlled reactions, Marcus theory provides a consistent approach to understanding ambident reactivity.

Methods

Gibbs energies G were calculated at two different theoretical levels. The first level, termed MP2/6-311+G(2d,p), involves geometry optimizations and frequency calculations at the MP2(FC)/6-311+G(2d,p) level of theory. Thermal corrections to 298.15 K have been calculated using unscaled harmonic vibrational frequencies in this case. The second level, termed G3(+), is identical to the standard G3 compound model,[23] but adds additional sets of diffuse basis functions on all nonhydrogen atoms in geometry optimizations. Thermal corrections have therefore been calculated at the RHF/6-31+G(d) level (instead of RHF/6-31G(d)), keeping the scaling factor for vibrational frequencies constant at 0.8929. All subsequent single-point calculations of the G3 Scheme were performed on geometries optimized at the MP2(FULL)/6-31+G(d) level (instead of MP2-(FULL)/6-31G(d)). All calculations were performed with Gaussian 03.[24]

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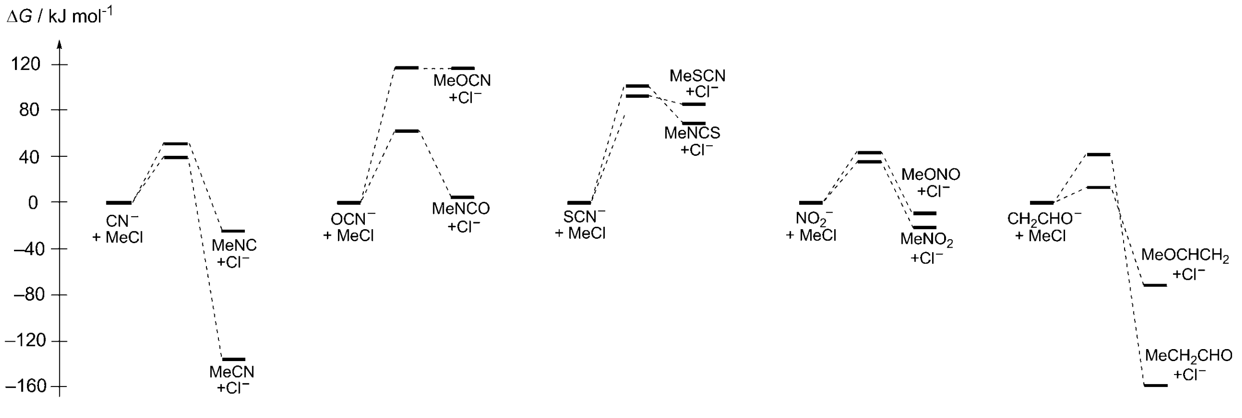

Figure 3. Gibbs energy profiles for the methylation of ambident nucleophiles with methyl chloride in the gas phase [G3(+)].

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