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THE EFFECT OF CATIONS ON NUCLEOPHILIC ADDITIONS TO CARBONYL COMPOUNDS: CARBONYL COMPLEXATION CONTROL VERSUS IONIC ASSOCIATION CONTROL. APPLICATION TO THE REGIOSELECTIVITY OF ADDITION TO α-ENONES

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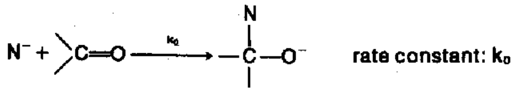
Abstract—The fundamental influence of cations in nucleophilic additions to carbonyl compounds is discussed in terms of either carbonyl complexation or ionic association with the nucleophile. Since loose ion pairs react essentially under complexation control while tight ion pairs react under association control, an experimental criterion is proposed to determine which factor controls the reactivity (complexation or association) based on the kinetic effects of cryptand or crown-ether addition.

An application of this duality is then examined for the regioselectivity of nucleophilic additions to α-enones and correlated with perturbational arguments based on *ab initio* calculations. Under complexation control, attack at carbon 2 is favoured, especially when a soft nucleophile is involved and the counter-ion is Li^+ rather than Na^+. Under association control two cases are considered according to whether the cation is directly bound or not to the nucleophilic center; in addition, the influence of hard or soft metals and the possibility of a cationic bridge in the transition state have been discussed. Several kinetic controlled reactions have been examined and interpreted in this way. An extension of this concept to other reactions will be considered.

Recently several authors have noticed the fundamental effect of alkaline cations during nucleophilic additions to aldehydes and ketones.[1–4] The cation can interact either with the carbonyl compound (carbonyl complexation) or with the nucleophilic reagent (ionic association). Depending on the reagent and the substrate properties, one can figure out 3 limiting mechanisms for the nucleophilic addition to carbonyl compounds.

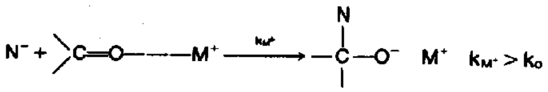
Case (a). Naked ion N^- addition to a free carbonyl compound:



$$N^- + \rangle C{=}O \xrightarrow{k_0} -\overset{\displaystyle N}{\overset{|}{\underset{|}{C}}}-O^- \qquad \text{rate constant: } k_0$$

This situation occurs when there is a weak interaction between the cation and the substrate or the nucleophile, for example, by using a large cation (NR_4^+, crowned M^+) or performing the reaction in a medium of important dissociating and basic powers (HMPA).

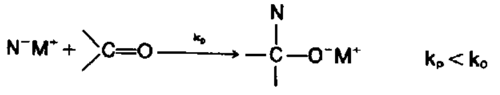
Case (b). Naked ion N^- addition to a carbonyl complexed compound: **(complexation effect)**



$$N^- + \rangle C{=}O\text{-----}M^+ \xrightarrow{k_{M^+}} -\overset{\displaystyle N}{\overset{|}{\underset{|}{C}}}-O^- \;\; M^+ \qquad k_{M^+} > k_0$$

The complexation effect enhances the electrophilicity of the carbonyl group by increasing the carbon charge and lowering the energy level of the LUMO (lowest unoccupied molecular orbital: $\pi^*(C{=}O)$).[5] In these conditions, there is an electrophilic assistance ($k_{M^+} > k_0$). This effect is observed during the carbonyl reduction using $M^+AlH_4^-$ in DME or THF.[1–4]

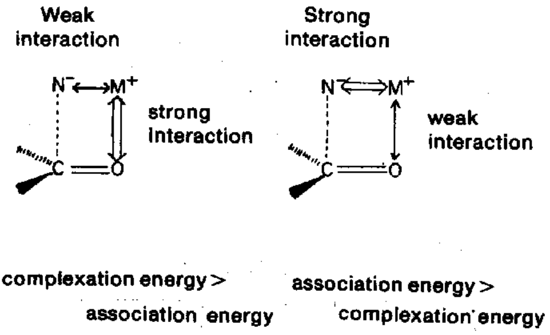
Case (c). Ion pair N^-M^+ addition to a free carbonyl compound: **(association effect)**



$$N^-M^+ + \rangle C{=}O \xrightarrow{k_p} -\overset{\displaystyle N}{\overset{|}{\underset{|}{C}}}-O^-M^+ \qquad k_p < k_0$$

The ion-pair association effect diminishes the nucleophilicity of the anion by decreasing the charge of the nucleophile and lowering the energy level of its HOMO (highest occupied molecular orbital).[7,8] In these conditions, there is an ion-pair inhibition ($k_p < k_0$), and this effect is observed in the addition of the enolate from phenylchloracetate to benzaldehyde in THF at −80°C.[9]

It is obvious that these 3 situations are limits; when the cation plays a role the actual situation can be represented either by one of the two last mechanisms (b and c) or by a combination of them both at the same time (simultaneous association and complexation in a disymmetric cationic bridge).



Consequently, cation intervention on this kind of reaction can induce opposite kinetic effects; the dominant effect will depend on the relative importance of association and complexation energy. Therefore, the problem is to evaluate which one of complexation or association is the more important factor.

From an analysis of available reactivity data based on the reactant structures or bonding, we shall propose an experimental criterion to determine the dominant factor. As a result, it becomes possible to predict the global reactivity of carbonyl compounds under a variety of nucleophilic reaction conditions.

I. *Influence of the reactant structure on the relative importance of association and complexation and in control of the reaction*

(a) *Cation-anion association.* It can exist different kinds of ion-pairs according to the nature of the ions and the media.[10] They are characterized by more or less strong interaction energies.

Weak interaction energy: *loose ion pairs.* They are either solvent separated ion pairs in aprotic media having a low dissociating power and a not too strong basicity (e.g. $Li^+AlH_4^-$ in THF at 25°C),[11] or contact ion pairs between two large (soft) ions (e.g. $Bu_4N^+AlH_4^-$ in THF at 25°C).[11]

Strong interaction energy: *tight ion pairs.* They are contact ion pairs between two hard sites (e.g. lithium alkoxides in ethanol).[12]

These different kinds of ion pairs are in thermodynamic equilibrium; the equilibrium is shifted toward loose ion pairs by (a) increasing the dissociating power and basicity of the solvent, e.g. the association energy in $Li^+AlH_4^-$ and $Li^+BH_4^-$ is larger in ether than in THF,[11] (b) lowering the temperatures ($\Delta H^{-50°C}_{\text{dissociation}} = -0.6$ kcal/mole and $\Delta H^{0°C}_{\text{diss}} = -5.6$ kcal/mole for $NaAlH_4$ in THF),[11] (c) increasing the ionic radia of the species involved (*cf.* coulombic energy), i.e. because BH_4^- is smaller than AlH_4^-, $Li^+BH_4^-$ is more "associated" than $Li^+AlH_4^-$ in THF.[11]

(b) *Cation-carbonyl complexation.* The stability of the $>C{=}O{-}{-}{-}M^+$ complex is increased as the Lewis acid character of the cation increases ($Li^+ > Na^+ > K^+$) and as the dissociating power of the solvent decreases.[14] So, from IR data,[13] carbonyl-lithium complexes are shown to be tighter bonded than those with sodium.

The reactions involving Li^+ seem to be the most interesting ones because the cation is able to give stable complexes with the carbonyl group as well as interact more or less strongly with the nucleophile.

(c) *Application to the nucleophilic addition to carbonyl compounds.*

By loose ion pairs. In this kind of ion pairs, the N^-M^+ association energy is relatively weak the carbonyl complexation energy. So, the complexation equilibrium (I) is competitive with the association one (II).

$$[I]\qquad >C{=}O + M^+ \rightleftharpoons\ >C{=}O{-}{-}{-}M^+$$

$$[II]\qquad N^- + M^+ \rightleftharpoons N^-/\!/M^+ \text{ (loose ion pairs).}$$

According to Curtin–Hammett principle, the reaction must take place between the most reactive species, i.e. the free anion and the metal-carbonyl complex (case b). These conditions are under *complexation control.*

By tight ion pairs. In this kind of ion pairs, the N^-M^+ association energy is very strong and much more important than the complexation energy. The ionic dissociation equilibrium is shifted toward intimate ion pairs. So, the cation is not available to form a complex with carbonyl and, as a result, the reaction must take place between the ion pair and the free carbonyl compound (case c). These conditions are under *association control.*

As we previously noticed, the actual situation is not so clear; both complexation and association may be involved by the way of a cationic bridge. It is not easy to choose between complexation vs association control by the lack of knowledge of the energetic disymmetry in the transition state (predominant cationic interaction with nucleophile or oxygen).

II. *An experimental criterion*: *kinetic effect of cryptands or crown ethers*

To determine the controlling factor—association or complexation—one can use the kinetic effect of the addition of crown ethers[15] or cryptands.[16] In this situation, the cations M^+ are trapped and, therefore, we have to deal with the reaction of a naked ion and a free carbonyl compound[a] (case a).

We can face two possibilities:

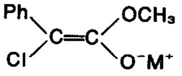
(a) under *complexation control* (loose ion pairs), the cryptand effect must be a rate decrease because the electrophilic assistance is removed;

(b) Under *association control* (tight ion pairs), the cryptand effect must be a rate increase because the nucleophilicity of the anion is magnified.

Examples

(a) $LiAlH_4$ reductions in THF or DME (loose ion pairs). During the $LiAlH_4$ reduction of ketones and aldehydes, in the presence of cryptand 2.1.1, (specific to Li^+ [16]), a large decrease in rate was observed. The magnitude of this effect is dependent on the carbonyl substituents: the rate of reduction is less decreased for aromatic compounds[4] than for aliphatic ones.[3,4] These results are consistent with a complexation control.

(b) Enolate **1** addition to benzaldehyde in THF (tight ion-pairs).



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The addition of the enolate from methyl-phenyl-chloracetate **1** to benzaldehyde in THF at low temperature (≤ −80°) is accelerated in the presence of cryptands. This result is consistent with an association control.

All these results have been rationalized[4,9] in terms of frontier orbital control[19] by considering the cation effects upon the energy level differences between the frontier orbitals. They emphasize the fundamental influence of the association nature between N^- and M^+.

This criterion can be extended to other reactions of the same kind, such as nucleophilic addition to epoxides and episulfides. For instance, Hogen-Esch *et al.*[20] noticed that the reaction of ethylene oxide with fluoradenyl salts (which are solvent separated ion pairs) is made slower by addition of crown ethers: this reaction is therefore

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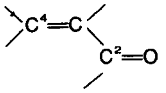
[a] Actually, there is still a weak interaction between the crowned or crypted cation either with the carbonyl group or the anion,[17,18] still the reactivity of these species is closest to those indicated in case a.

complexation controlled. On the other hand, the anionic polymerization of ethylene sulfide in THF is accelerated in the presence of cryptands, which is explained by the observed tight ion pairs:[21] this is an example of association controlled reaction.

III. *Regioselectivity of nucleophilic additions to α-enones*

α-Enones **2** are ambident electrophiles, the two reactive sites being carbons 2 (carbonyl addition) and 4 (Michael-type addition).



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Regioselectivity of nucleophilic additions to α-enones has been extensively studied.[22] Theoretical interpretations have been proposed in terms of the Klopman theory[19a] by Nguyen Trong Anh *et al.*[23–26] Simply stated, the theory says that reactions at carbon 2 are under charge control (hard site) while reactions at carbon 4 are under frontier control (soft site).

Nevertheless, as previously shown, in the case of simple carbonyl compounds, in nucleophilic additions to α-enones, the cation M^+ could also play a role either by complexation or association effects. Now we are going to examine the association-complexation influences by considering only experimental results under kinetic control (predictions for reactions under thermodynamic control cannot be taken into account).

Particular stress will be placed on the $M^+AlH_4^-$ and $M^+BH_4^-$ reductions, since these are known to be irreversible processes, as well as other nucleophilic additions for which kinetic control is checked.

(A) *Complexation control* $>C{=}C{-}C{=}O{-}{-}{-}M^+$

(a) ***α-Enone electronic structure dependence on*** M^+. We have done ***ab initio*** STO-3G calculations[27] in order to determine the electronic structure of acrolein uncomplexed and complexed with Li^+ or Na^+. Results are listed in Table 1.

From these results, we noticed important changes in the acrolein electronic structure when complexation takes place:

—an increase in total and π positive charges on carbon 2 and on carbon 4,

—a noticeable lowering of the LUMO energy level,

—an inversion of the atomic coefficients in the LUMO between carbons 4 and 2: while the larger coefficient is on carbon 4 for free acrolein, it is on carbon 2 for acrolein interacting with Li^+ or Na^+. Such an inversion has been already noticed by Houk and Strozier,[29] and has been interpreted by Fujimoto and Hoffmann[30] when acrolein is protonated.

These changes are more marked with Li^+ than with Na^+ in connection with a larger complexation energy

Table 1. Electronic structures of acrolein and its complexes with Li^+ and Na^+ *ab initio* (STO-3G) calculations[27]

Substrate	Total energy (a.u.)	LUMO energy level (a.u.)	A.O. coefficients in Lumo $\lvert C_2 \rvert$	$\lvert C_4 \rvert$	Total charges q_2	q_4	π Charges q_2^π	q_4^π
$CH_2{=}CH{-}CH{=}O^b$	−188.29723	0.221	0.492	0.642	0.122	−0.111	0.081	0.043
$CH_2{=}CH{-}CH{=}O{-}Na^{+b}$	−348.14612	0.046	0.638	0.597	0.191	−0.064	0.202	0.148
$CH_2{=}CH{-}CH{=}O{-}Li^{+b}$	−195.57086	−0.047	0.613	0.419	0.261	−0.035	0.310	0.215

[a] 1 a.u. = 627.71 kcal/mole.

[b] Standard geometry[28] has been used for the acrolein molecule. Only the *s-trans* conformer was calculated. For the complexes, standard geometry and conformation of acrolein has not been modified. The following bond length and angles have been optimized: O–M^+, $\angle C_2OM^+$, $\angle C_3C_2OM^+$ (dihedral angle). Optimum structure for $CH_2{=}CH{-}CH{=}O{-}{-}Na^+$: O–$Na^+$ = 2.0 Å, $\angle C_2ONa^+ = 150°$, $\angle C_3C_2ONa^+ = 180°$. Optimum structure for $CH_2{=}CH{-}CH{=}O{-}{-}Li^+$: O–$Li^+$ = 1.63 Å, $\angle C_2OLi^+ = 180°$.

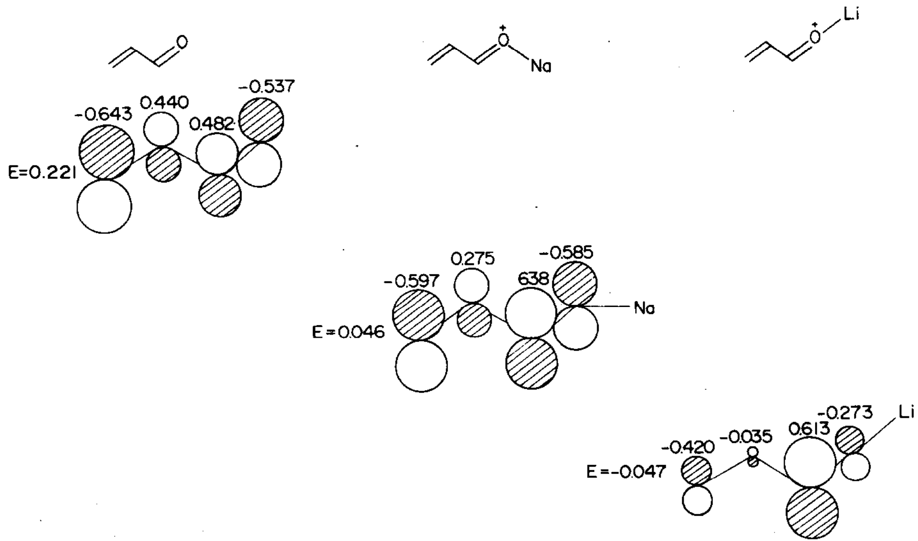


Fig. A. LUMO energies (a.u.) and coefficients for acrolein and its complexes with Na^+ and Li^+.

[Li$^+$-acrolein: −86.6 kcal/mole; Na$^+$-acrolein: −40.3 kcal/mole-calculated values: see Table 3].

From a reactivity point of view, when α-enone complexation takes place, our calculations lead us to the following predictions:

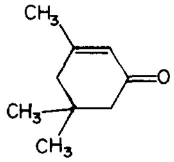
(i) Regioselectivity of attack in favour of carbon 2, is as much under charge control as under frontier orbital control; the selectivity is more marked with Li$^+$ than with Na$^+$.

Thus Handel and Pierre[31] observed 82% attack at carbon 2 for 2-cyclohexenone reduction in DME using LiAlH$_4$, in contrast to only 60% using NaAlH$_4$. Similarly LiBH$_4$ leads to 65% attack at carbon 2 and NaBH$_4$ to 55%. These results are consistent with complexation control. Furthermore adding M$^+$Br$^+$ (where M$^+$ is a common cation, Li$^+$ or Na$^+$) causes no change at all in regioselectivity. These results suggest an effective complexation between 2-cyclohexenone and M$^+$ during reductions, which is consistent with the existence of loose ion pairs M$^+$AlH$_4$ or M$^+$BH$_4^-$.[11]

(ii) Electrophilic assistance by M$^+$ for both attack at carbon 2 and carbon 4.

Deschamps[78] noticed that electrophilic assistance favours both carbonyl attack as well as double bond attack by comparing the reactions of [(EtO)$_2$P(O)CHCN]$^-$ Li$^+$ and K$^+$ with different α-enones in THF. Likewise, Handel and Pierre[31] observed that 2-cyclohexenone reductions by M$^+$AlH$_4^-$ and M$^+$BH$_4^-$ (M$^+$ = Li$^+$, Na$^+$) in DME are considerably slowed by the addition of cryptand. All these results are in agreement with a complexation control.

When approach at carbon 2 is hindered, it must be possible to observe electrophilic assistance by M$^+$ for carbon 4 attack. So, during the addition of PhCHCN$^-$, Li$^+$ to isophoron 3 carbon 2 attack is sterically inhibited due to the interaction between the phenyl ring and the gem dimethyl groups.



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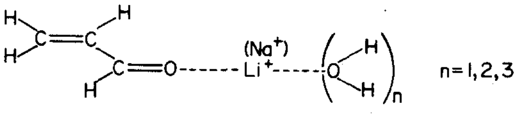
This electrophilic assistance appears clearly in the results of Sauvetre and Seyden-Penne[32] who found that after 1 min at −70°C the yields are 45% in THF and 10% in THF–HMPA 80–20. PhCHCN$^-$, Li$^+$ is expected to be loose ion-pair[33] so that complexation Li$^+$-isophoron inducing electrophilic assistance could occur. On the other hand, this complexation is unlikely in THF–HMPA due to the solvating and basic powers of HMPA (Li$^+$ is strongly solvated), therefore electrophilic assistance is suppressed. This result shows us the importance of electrophilic assistance, especially noteworthy because generally in HMPA nucleophilic reactions are strongly accelerated.[34]

(iii) A change in regioselectivity under frontier control which depends if complexation occurs between M$^+$ and α-enone (*cf.* A.O. coefficients in LUMO, Table 1).

So when PhCHCN$^-$, Li$^+$ is added to benzalacetone or 2-cyclohexenone in THF, additions at both carbons 2 and 4 occurs but in HMPA only addition at carbon 4 takes place.[32]

Accordingly, we can predict, if a reaction occurs at carbon 4, a change of regioselectivity by adding some Lewis acid (increasing attack at carbon 2). Salt free additions of ynamines, R–C≡C–NR$_2$, to 2-cyclohexenone lead only to carbon 4 addition;[35] by adding MgCl$_2$,[36] the attack of carbon 2 becomes the most dominant one.[35]

(b) M$^+$ *solvation effects on α-enone complexation. Ab initio* STO-3G calculation results concerning the electronic structure of the acrolein-Li$^+$(Na$^+$) complexes as a function of the cation solvation are shown in Table 2.



From these results, it appears that the previous conclusions are not altered if we take into account the cation solvation. The preference for the additions on the α-enone carbon 2 is confirmed. With an increase in cation solvation, we notice a gradual lowering of the effects (increase in total and π positive charges, lowering of LUMO energy level, inversion of the atomic coefficients in the LUMO). These changes are coupled with the complexation energies as we calculated them (see Table 3).

As might be expected, we note that M$^+$-α enone complexation energy is diminished as the cation is better solvated either through basicity effects, e.g. diethylether < THF,[37] or important chelation, DME. Consequently, an increase in solvating power must imply a reduction in carbon 2 attack. This fact is effectively emphasized by considering the regioselectivity of 2-cyclohexenone reduction by LiAlH$_4$ in different solvents:

Diethylether: 98% of carbon 2 attack[31,38]
DME: 82% of carbon 2 attack[31]
THF: 78% of carbon 2 attack[26].

Table 2. Influence of the solvent on the electronic structure of acrolein–M$^+$ complexes $CH_2{=}CH{-}CHO{—}M^+(OH_2)_n$

M$^+$ =	n =	LUMO energy level (a.u.)	A.O. coefficients in LUMO $\lvert C_2\rvert$	$\lvert C_4\rvert$	Total charges q_2	q_4	π Charges q_2^π	q_4^π
Li$^+$	0	−0.047	0.613	0.419	0.261	−0.035	0.310	0.215
	1	−0.008	0.655	0.494	0.248	−0.046	0.284	0.190
	2	+0.021	0.659	0.539	0.232	−0.056	0.254	0.167
	3	+0.051	0.644	0.589	0.213	−0.066	0.222	0.144
Na$^+$	0	+0.046	0.638	0.597	0.191	−0.064	0.202	0.148
	1	+0.058	0.628	0.600	0.186	−0.068	0.192	0.139
	2	+0.071	0.613	0.605	0.178	−0.074	0.176	0.126
	3	+0.082	0.598	0.610	0.171	−0.079	0.160	0.115

Table 3. Complexation energies for the exothermic process: acrolein + $M^+(H_2O)_n \rightarrow$ acrolein − $M^+(H_2O)_n$

Complexes M^+ =	n =	$E_{total}^{complex}$ (a.u.)	$E_{total}^{M^+(H_2O)_n}$ (a.u.)	$E_{complexation}$[a] (kcal/mole)
Li^+	0	−195.57086	−7.13540	−86.6
	1	−270.64489	−82.22598	−76.4
	2	−345.69587	−157.30061	−61.5
	3	−420.72597	−232.35376	−47.1
Na^+	0	−348.14612	−159.78462	−40.3
	1	−423.16994	−234.81505	−36.8
	2	−498.18302	−309.83841	−29.7
	3	−573.18679	−384.85133	−24.0

[a] The complexation energies have been calculated by the following formula: $E_{complexation} = -E_{total}^{acrolein} - E_{total}^{M+(H_2O)_n} + E_{total}^{complex}$.

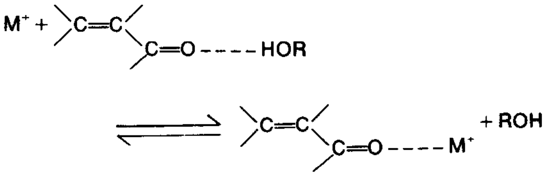
We have to emphasize the great influence of basicity on the 2-cyclohexenone reduction by $NaBH_4$: for example, 45% of carbon 4 attack is observed by Handel and Pierre in DME[31] against 100% by Kadin in pyridine,[39] very strongly basic media. Likewise, Cueille and Jullien[40] noticed the same phenomenon for the bicyclo (3.1.0) hexen-3-one-2 reduction.

(c) *Influence of enone solvation in protic media.* C=C–C=O---HOR. The nature of the borates isolated in the reduction of a simple carbonyl compound (cyclohexanone) by $NaBH_4$ in alcoholic media[41] demonstrates the electrophile assistance by a protic solvent (the isolated borates derive from the solvent and not from the alcohol obtained by ketone reduction, in conditions where no exchange between the alcoxy groups of borates occurs). This electrophilic assistance by alcohol has been pointed out during α-enones reductions by $M^+BH_4^-$ in methanol: the reaction takes place even in presence of cryptands, in contrast to the reactions in aprotic media.[31]

In order to estimate the effect upon regioselectivity caused by electrophilic assistance in protic media, we calculated the electronic structure of acrolein interacting with one water or methanol molecule (Table 4).

These results show that the acrolein electronic structure is slightly modified by the interaction with H_2O or CH_3OH: the larger atomic coefficient in the LUMO still remained at carbon 4. Consequently, the regioselectivity should be nearly the same when the α-enone is free or in interaction with protic solvent. In both cases one would predict a high yield of attack in position 4 under orbital control. It is effectively what is observed: while reduction by $M^+BH_4^-$ under kinetic conditions in ether solvents leads chiefly to attack at carbon 2, reduction in protic media gives a higher percentage of attack at carbon 4.[42,44] An example is the reduction of 2-cyclohexenone by $LiBH_4$ which gives 65% carbon 2 attack in DME and 73% carbon 4 attack in CH_3OH.[31] To explain this difference in regioselectivity, we do not have to introduce arguments based on steric hindrance[31] but simply to consider α-enone complexation with Li^+ in DME and with the solvent in CH_3OH.

Therefore, in protic media we can expect that salt effects could modify the experimental regioselectivity by shifting the complexation equilibrium further to the right:



and this should be more important with Li^+ than with Na^+ (see Tables 1 and 2).

Accordingly, by adding salt in the media, an increase in attack at carbon 2 is predicted, and this is confirmed by Handel and Pierre[31] for 2-cyclohexenone reductions in methanol.

$$LiBH_4 \longrightarrow 27\% \text{ of carbon 2 attack}$$

$$LiBH_4 + 20 \text{ eq. } LiBr \longrightarrow 70\% \text{ of carbon 2 attack}$$

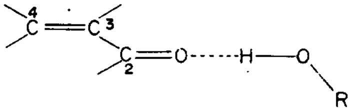
$$NaBH_4 \longrightarrow 26\% \text{ of carbon 2 attack}$$

$$NaBH_4 + 20 \text{ eq. } NaBr \longrightarrow 50\% \text{ of carbon 2 attack.}$$

Nevertheless it should be noticed there is no salt effect on regioselectivity for 2-cyclopentenone reduction, with the major attack always is at carbon 4.[31] It seems like this enone, for some particular reason, give no complex with M^+. Such an effect is certainly in relation with the very high yields of carbon 4 attack, always observed with this enone in aprotic media.[26,31,44,45]

(d) *Influence of the anion structure.* By using the PMO method of Klopman,[19a] it is possible to estimate inter-

Table 4. Electronic structure of acrolein in interaction with ROH



Substrate	LUMO energy level (a.u.)	A.O. coefficients in LUMO		Total charges		π Charges	
		$\lvert C_2\rvert$	$\lvert C_4\rvert$	q_2	q_4	q_2^π	q_4^π
Acrolein	0.221	0.492	0.642	0.122	−0.111	0.081	0.043
Acrolein–H_2O	0.204	0.521	0.636	0.137	−0.104	0.100	0.054
Acrolein–$HOCH_3$	0.204	0.521	0.636	0.137	−0.103	0.100	0.054

Standard geometry and *s-trans* conformation have been used for the acrolein molecule. Starting from $\angle C_2OH = 120°$, $\angle C_3C_2OH = 180°$, O–H bond lengths have been optimized: 1.826 Å (for R = H); 1.838 Å (for R = CH_3). These results show no difference between water and methanol but differences might appear if multisolvation is taken into account.

action energies (E_{int}) between an anion N^- (simulated by one orbital of a variable energy E_{HO}) and carbon 2 or carbon 4 of an α-enone[23] by taking in account all the unoccupied MO of the α-enone.

On Fig. B we have plotted the values $E_{int}(2)$-$E_{int}(4)$ vs $E_{HO}(N^-)$ when acrolein is free or interacting with Li^+, Na^+ or H_2O.

From these results, we can draw the following conclusions:

1. Without complexation, carbon 4 attack is favoured if the HOMO energy of N^- is very high (a soft anion according to Klopman); the lowering of the HOMO energy of N^- (an increase in the anion hardness) favours increasing attack at carbon 2 [Fig. B, a].

2. The solvation of the enone by H_2O or CH_3OH slightly modifies these conclusions giving an orientation at carbon 4 for a high E_{HO} anion and at carbon 2 for a low E_{HO} anion. We observed a slight displacement of the curve toward high HOMO, i.e. for a given anion, a lowering of regioselectivity in 4 [Fig. B, b].

3. Complexation with Li^+, more so than with Na^+, induces a change in regioselectivity: attack on carbon 2 is always the major one. However, a substantial dependance upon the increasing hardness of the anion N^- is still observed [Fig. B, c and d]. In these cases, orientation in position 2 remains always dominant but it diminishes as the level of the HOMO lowers.

From these calculations it becomes possible to explain the difference in experimental regioselectivity of $LiAlH_4$ and $LiBH_4$ reductions (e.g. $LiAlH_4$ reduction of 2-cyclohexenone in DME gives 82% attack at carbon 2 against only 65% for $LiBH_4$ reduction). Since the reaction involves loose ion pairs, it is under complexation control. Calculations[46] show that AlH_4^- HOMO is higher in energy than that of BH_4^- (AlH_4^- is then softer than BH_4^-); consequently, we increase the regioselectivity of attack on carbon 2 by using $LiAlH_4$ rather than $LiBH_4$.

This type of explanation is opposed to that of Nguyen Trong Anh *et al.*[24] who consider a free α-enone, although $M^+\alpha$-enone complexation seems to be experimentally proved, and postulate BH_4^- softer than AlH_4^-, which does not agree with calculations.[46]

In conclusion, the nature of the nucleophile N^- can have opposite effects on regioselectivity, determined by the existence of complexation enone-M^+ or the uncomplexed form.

—in the absence of complexation, attack at carbon 4 is the major one for soft anions (high HOMO) and is less and less favoured when anion hardness increases,

—in the presence of complexation, attack at carbon 2 is always the major one but regioselectivity is lowered when anion hardness increases.

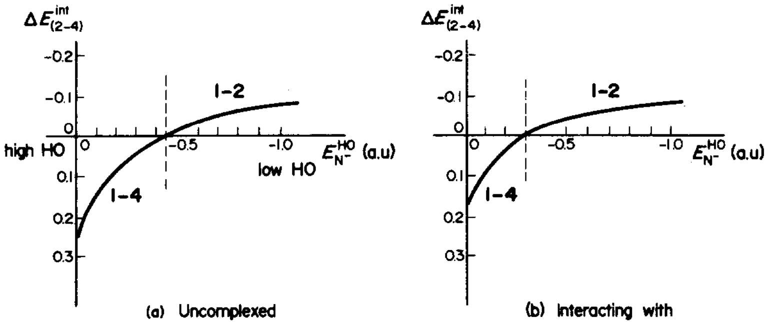
B. *Association control*

It is the situation when there is a strong association energy in the ion pairs (tight ion pairs). We now examine the reaction between an uncharged species and a free α-enone.

Two possibilities must be considered:

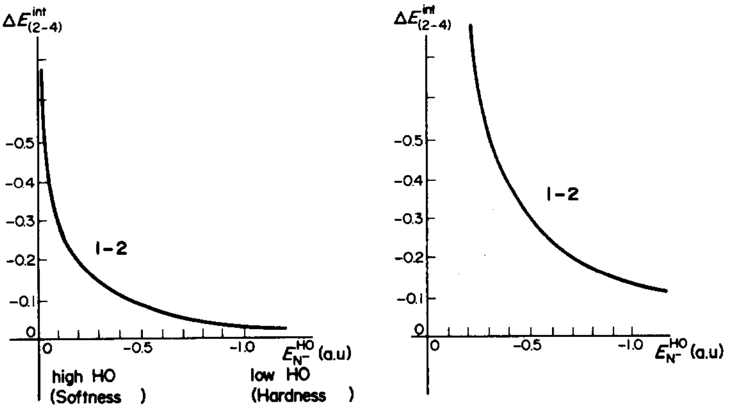
(a) the metal is directly bound to the nucleophilic center (e.g. organometallics)

(b) the metal is not bound to the nucleophilic center (e.g. metal enolates).



(a) Uncomplexed

(b) Interacting with H_2O or CH_3OH

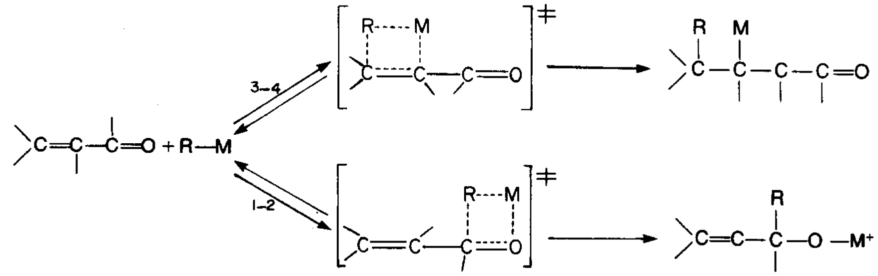


(c) Complexed with Na^+

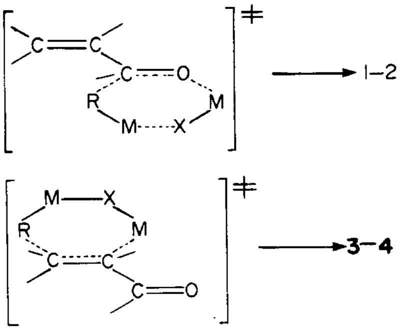
(d) Complexed with Li^+

Fig. B. Differences in interaction energies between N^- and the C2 and C4 centers of acrolein according to its complexation state.

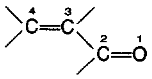
(a) *Additions of organometallic reagents* R–M. During the addition of organometallic reagents to a carbonyl compound, there is rupture of the carbon-metal bond. As this is a strong bond,[47] it contributes in a large part to the activation energy. Therefore, we suggest the necessity of some type of assistance for the C–M bond breaking either involving the α-enone or another organometallic molecule. An α-enone assistance implies a 4 center cyclic mechanism,[48] and consequently 1–2 or 3–4 additions,[49] depending on the interaction between the organometallic compound and either the carbonyl bond or the double bond.[50]



For the assistance by another molecule of organometallic reagent, Ashby has proposed this type of interaction for 1–2 addition of mixed magnesiens.[54]



Other things being equal, these mechanisms imply a fundamental influence nature of the reacting metal.



Ab initio calculations suggest α-enone possesses 2 centers where the interaction with an electrophile should be favoured: the oxygen—hard center (net charge: −0.206; atomic coefficient in HOMO = 0.420) and the carbon 3—soft center (net charge: −0.082; atomic coefficient in HOMO: 0.546).[b] Hard metals should then have a better interaction with oxygen and soft ones a better interaction with carbon. We must emphasize that complexation (π or σ) between metal and α-enone can occur either with the double bond or the carbonyl according to the type of metal. For instance, alkaline metals give σ-complexes with carbonyl[55] while $Fe(CO)_4$ of $NaHFe_2(CO)_8$ (very soft metallic complexes) give π-complexes only with the α-enone double bond.[56,57]

Experimental results are in good agreement with these predictions:

(1) organoalkalines—hard metals[58]—give 1–2 additions,[22]

(2) organocadmium,[59] cuprates[60–63] and palladium compounds[64]—soft metals[58]—lead to the attack of carbon 4.

(3) organomagnesium and organoaluminum—medium metals—give a half way behaviour.[22,65]

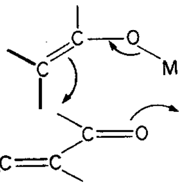
(b) *Additions of metal enolates.*[c] Alkaline enolates are *O*-metalled species which react with α-enones by their carbon atom. The metal is not bound directly to the nucleophilic center. House *et al.*[66] showed by spectroscopy the different kinds of ionic association between enolate and cation according to the nature of the partners and medium. The ion pairs can be of loose type (e.g. in polar solvents or strongly solvating, and also, for some structural reason, such as *Z* or *E* isomers) or of tight type.

So, for the addition to α-enone, we will deal with 2 possible situations:

(1) *Loose enolate*-M$^+$ *ion pairs.* The cation is free to be eventually complexed by α-enone, which implies a major attack on carbon 2. This situation is the same as the reduction, already discussed.

(2) *Tight enolate*-M$^+$ *ion pairs.* In this case, two mechanisms were proposed for addition:

A six center cyclic mechanism. This kind of mechanism was introduced for explaining aldolisation stereochemistry under kinetic conditions[9,68] a cationic bridge occurs between the two oxygen atoms (one from enolate, the other from carbonyl). Considering the nature of the cation (in general alkalines, hard), this kind of mechanism must involve the α-enone carbonyl and, consequently, we must observe 1–2 additions.



In order to support this possibility, salt effects on the regioselectivity of α-enone attack should not be observed.

A non cyclic mechanism. It was emphasized by Felkin *et al.* that it is impossible to understand the observed stereochemistry of the reactions of allyl magnesium

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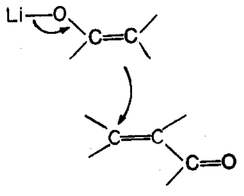
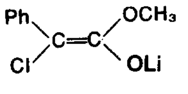
[b] These predictions are not affected by complexation between metal and α-enone; at the opposite, there are bigger differences between oxygen and carbon 3 [enone–$MgCl_2$ complex: charges: oxygen = −0.273, carbon 3 = −0.087; atomic coefficient in HOMO: oxygen = 0.370, carbon 3 = 0.618].

[c] The case of *C*-metalated species (with soft metal) such as certain organozinc[67] or mercuric compounds[66] is roughly the same as organometallic one as we previously discussed in the last section.

compounds with epoxides[69] or carbonyl derivatives[70] by a cyclic mechanism and they proposed a non cyclic mechanism.

Such a mechanism, when applied to α-enones reactions, implies there is no complexation of enone with cation: so, we must observe the attack at carbon 4. Likewise, one can expect an accelerating cryptand effect and a regioselectivity change by adding Lewis acids in the media.





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Such a mechanism is certainly implied in the addition of enolate **1** to α-enone: there is only addition at carbon 4 to chalcone and benzalacetone in THF at −78°C[71] and an accelerating cryptand effect is observed during the reaction with benzaldehyde in THF at −80°C.[9] We have already mentioned the change in regioselectivity by addition of MgCl$_2$ during addition of ynamines to 2-cyclohexenone.[35]

The results in the literature are very diversified, indicating either attack at carbon 2[72–74] or carbon 4.[75–77] As precise structures of the reactive species are rarely known in the reaction conditions, and as medium effects (solvent, cryptants and salts) are not systematically investigated, it seems to us, at the present time, impossible to decide between these different mechanistic possibilities.

CONCLUSIONS

All these considerations show the fundamental influence of the cation on the regioselectivity of nucleophilic attack on α-enones, and underline the prime importance of the type of association between the cation and the anionic nucleophile.

Reactions with loose ion pairs, in a poorly dissociating and basic medium (e.g. THF, DME) are complexation controlled, which implies a preference for carbon 2 attack on α-enones: it is essentially what happens for reductions in ether media. This regioselectivity in favour of carbon 2 (more important with Li$^+$ than Na$^+$) is connected with a larger A.O. coefficient in LUMO on this atom. This selectivity is not modified by adding salts with common cation but cryptands or crown ethers will induce a decrease rate. When an interaction between the α-enone and a protic solvent occurs, regioselectivity is shifted toward carbon 4 and then salt effects will reverse this regioselectivity.

Reactions with tight ion pairs (or covalent compounds) are association controlled. Two possibilities can be considered:

(a) The metal is bound directly to the nucleophilic center (e.g. organometallic compounds, C-metalled ketones). As α-enone is an ambident ligand for metallic ion, the orientation for R–M addition to α-enone is cation nature dependent: attack at carbon 2 for hard cations (e.g. alkaline) and at carbon 4 for soft ones.

(b) The metal is not directly bound to the nucleophilic center (e.g. alkaline enolates): Attack at carbon 4 is expected in a non cyclic fashion. Salt effects might inverse the regioselectivity and cryptand kinetic effect must cause an acceleration; Attack at carbon 2 is expected by a six-center cyclic mechanism; salt effects would not modify the regioselectivity but cryptand kinetic effects are difficult to predict because of the energetic disymmetry in O–Li interactions.

This study can allow the rationalization of a great number of experiments under kinetic control. Furthermore, it implies a knowledge of the ion-pair structure (site and energy of association between cation and nucleophile) and the possibility of cation–carbonyl complexation during the addition (solvent, cryptand and salt effects).

An application of this duality concept can certainly be extended to other reactions. Moreover, it was noticed a parallelism exists between 1) the regioselectivity of α-enone attack, and 2) the stereochemistry of nucleophilic attack of 4-tbutylcyclohexanon, axial or equatorial,[79] and 3) the stereochemistry of S$_N$2 reactions at a silicon center, inversion or retention,[80] according to the reactive species.

We are presently interested in generalizing this approach.

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