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Ab Initio Theoretical Study of Metallo-dehydrogenation and Nucleophilic Addition of Methyllithium and Methylpotassium with Crotonaldehyde Dimethyl Acetal

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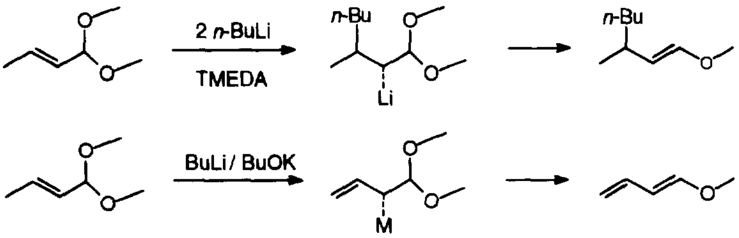
Abstract: The metal-hydrogen exchange reactions of lithium and potassium methide with the dimethyl acetal of crotonaldehyde are compared with the competing additions to the double bond. In the case of lithium the nucleophilic addition reaction is clearly preferred; in contrast, potassium methide shows two barriers of comparable height, with a slight preference for addition, and free methide is more inclined to act as a base. The results appear to be consistent with available experimental evidence and suggest that (i) the alkyl carbon must be in an almost carbanion-like state to exhibit the reactivity actually observed when a superbase is used; (ii) RK is a poor model for a RLi/R'OK superbase. Therefore, potassium alkoxides appear to operate not only by encouraging a deaggregation of alkyllithium oligomers, but also by promoting a weakening of the C^{-}–Li^{+} interaction. © 1997 Elsevier Science Ltd.

Metallo-dehydrogenation reactions are processes of synthetic interest, by which an organic substrate undergoes a metal-hydrogen exchange at a relatively acidic position.[1] The subsequent reaction with an electron-deficient site allows the construction of a new carbon-carbon bond. Such an approach requires the availability of strong and selective organic bases. Common metalating agents are organolithium compounds, which are commercially available and simple to handle, but their reactivity results diminished owing to their oligomeric structure. The activating effect of electron-donating chelating agents, as TMEDA or DABCO increases reactivity of organolithium reagents by deaggregating oligomeric structures. However, an important improvement in the field of organometallic bases was achieved with the discovery of Schlosser's LICKOR superbases (equimolar mixture of alkyllithium and potassium alkoxide), which show a high and selective metalating power.[2] Alkyl metals can behave not only as metalating agents, but also as alkylating reagents in giving nucleophilic addition to carbon-carbon multiple bonds. This reaction can compete with metalation, provided the substrate is structurally apt to undergo such an attack, the multiple bond being substituted at one end either by a π electron attracting group, as carbonyl, or by a good nucleofuge.[3]



Scheme

In fact, α,β-unsaturated acetals, as dialkyl acetals of crotonoaldehyde (Scheme), have been experimentally found to undergo either metallo-dehydrogenation or nucleophilic addition, depending on structure and reaction conditions.[4] 1,1-Dimethoxy-but-2-ene would therefore be a suitable substrate for carrying out a theoretical comparative study of the two competing reactions, in order to evidentiate a different behaviour with different basic/nucleophilic reagents. In the experiments, addition to the double bond is the outcome when butyllithium is utilized; in contrast, metallo dehydrogenation reaction takes place when the mixed reagent BuLi / BuOK is employed (both reaction are followed by elimination of a $RO^- M^+$ couple; Scheme). Due to the size of the substrate, the two alkyl metals used in the present study, to investigate their reactivity toward crotonaldehyde dimethyl acetal, are as simple as possible: lithium methide, chosen as a model for BuLi,[5,6] and potassium methide. In the latter case, BuK might be assumed to be the active reactant, or at least considered as the more active part of a more complex reactant. In this case, the model can obviously be an oversimplification of the experimental situation (in which the substrate reacts in the presence of both lithium and potassium cations, as well as the alkoxide ion).[7] Therefore, the purpose is to offer some insight, on one hand, into the relative inclination of different simple metal alkides toward metalation or addition, on the other hand, maybe in a negative fashion, on the nature of the active LICKOR species.

The present study is articulated in the following steps. (i) The reactivity as nucleophiles of methyllithium and methylpotassium is investigated, by considering the addition reaction to the carbon-carbon double bond of crotonaldehyde dimethyl acetal (eq 1, M = Li, K).

$$CH_3^-M^+ + CH_3CH{=}CHCH(OCH_3)_2 \rightarrow (CH_3)_2CH{-}CH(M)CH(OCH_3)_2 \qquad (1)$$

(ii) The reactivity of MeLi and MeK as bases with the same substrate is studied (eq 2, M = Li, K).

$$CH_3^-M^+ + CH_3CH{=}CHCH(OCH_3)_2 \rightarrow [CH_2CHCHCH(OCH_3)_2]^-M^+ + CH_4 \qquad (2)$$

(iii) The data so collected allow a comparison with the results previously obtained in two recent theoretical investigations: a study of some aggregations of different stoichiometry of LiMe and KOMe components, which has indicated as possible active LICKOR species a mixed tetramer, $LiMe(KOMe)_3$;[7] a model study on propene, carried out to assess the different inclinations of simple lithium and potassium alkyls toward dehydrogenation and addition reaction.[8]

METHOD

The study of the two model reactions was performed by determining on the energy hypersurface the critical points relevant to stable and transition structures. This was accomplished by way of complete gradient optimization[9] of the geometrical parameters at the Hartree-Fock level of theory, using the Huzinaga split-valence shell sp basis set[10] (enriched with d polarization functions on carbon and oxygen atoms), which will be denoted as [53/331/31/2] in the following. The critical points were characterized as minima or first-order saddle points, through diagonalization of the analytically calculated Hessian matrix (vibrational frequencies calculation). In the Figures of the following Section the reported interatomic distances are in ångströms, and angles in degrees (dihedral angles in parentheses). The geometries thus obtained were used to recompute the relative energies by introducing correlation effects through perturbative MP2 computations,[11] in conjunction with the mentioned Huzinaga basis set.[10] The electron distribution was examined in terms of NAO charges (Natural Population Analysis),[12] which are reported in the Figures in parentheses, for some selected cases. The GAUSSIAN94 system of programs[13] was used throughout, on IBM RISC/6000 computers, at both Dipartimento di Chimica Generale ed Organica Applicata and DCMR.

RESULTS AND DISCUSSION

The dimethyl acetal of crotonaldehyde forms a complex with methyllithium or methylpotassium, which is held together by electrostatic interaction between the cation and the two oxygen atoms of the acetalic group (structure not shown). This complex is used as a reference for the determination of the energy barriers of the two reactions examined: indeed, both processes can be thought of as originating from this structure. Energy values are reported in Table 1. Only MP2 values will be discussed, while RHF values are reported for sake of reproducibility. It can be noted that electron correlation lowers significantly all energy barriers; all reactions are also described as more exoergonic.

Nucleophilic Addition to the Carbon–Carbon Double Bond. The transition structure of the nucleophilic addition of methyllithium to the carbon-carbon double bond of crotonaldehyde dimethyl acetal is shown in Figure 1. As methyl anion is adding to the β carbon of the substrate, lithium adds to the α carbon, while maintaining its interactions with only one of the two oxygen atoms. The main NAO charges are reported in parentheses. The energy of this structure is 14.1 kcal mol^{-1} above the reference complex. An intermediate, located 19.2 kcal mol^{-1} below the reference complex, follows this transition structure (geometry not shown). From this species, an elimination reaction can follow, leading in principle to final products of different stereochemistry, (the stereochemistry of the elimination step could offer interesting aspects, but its study is beyond the scope of this work).

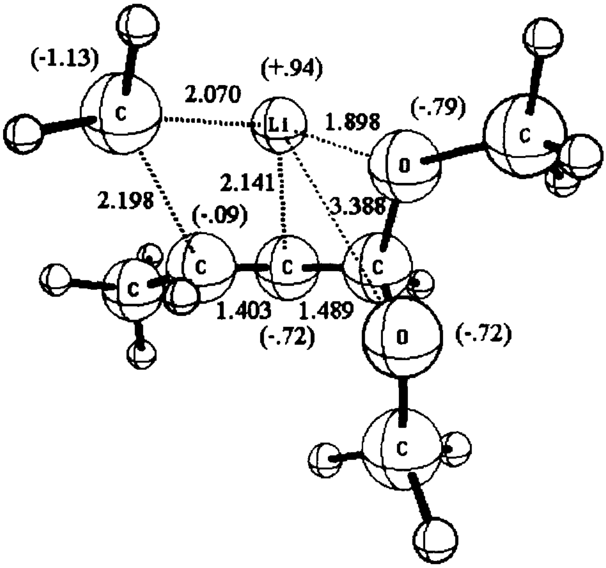


Figure 1. The transition structure for CH_3Li addition to the CC double bond.

The transition structure for nucleophilic addition of methylpotassium to the carbon-carbon double bond is shown in Figure 2. The geometrical features of this species are similar to those observed in the transition structure with methyllithium. The differences in C^{-}–C^3 and C^2–C^3 distances suggest an earlier K transition structure. It can also be noted that K, in contrast with Li, is able to maintain both interactions with the acetalic oxygens, as in the initial complex.

The related energy barrier, 8 kcal mol^{-1}, is lower than that of **1** by ca. 6 kcal mol^{-1}, consistently with the earlier geometrical features. An intermediate follows (whose structure is not shown), which is located at 31 kcal mol^{-1} below the complex. The addition reaction is thus not only easier than for lithium, but also significantly more exoergonic (−12 kcal mol^{-1}). The differences with respect to the lithium reaction were less pronounced in the attack of MeLi and MeK to propene:[8] there the barriers were less than 17 kcal mol^{-1} (K) and 19 (Li), the reaction energies −19 and −14, respectively (MP2 data). The enhanced ΔE differences can originate from differences in the metal cation-acetalic oxygens interactions. Addition is easier in the acetal, although in transition structure **1** one of the two lithium-oxygen interactions present in the complex is lost. The addition step is exoergonic for both acetal systems, although they have no way of efficiently delocalize the negative charge.

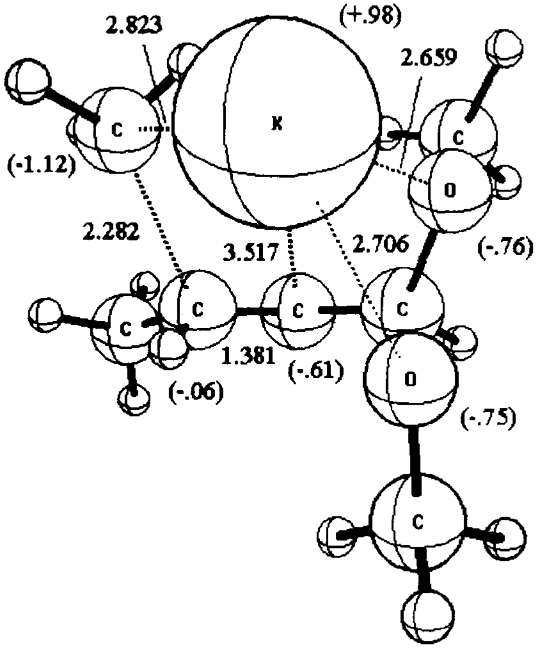


Figure 2. The transition structure for CH_3K addition to the CC double bond.

Metal–Hydrogen Exchange. The metallo-dehydrogenation transition structure for methyllithium is shown in Fig. 3. Its energy is 37.6 kcal mol^{-1} above the reference complex. As a consequence, the calculations describe this reaction as disfavoured with respect to the addition reaction, as experimentally observed.[4] Also this reaction leads to an intermediate, located 2.9 kcal mol^{-1} below the complex, from which elimination can take place. The intermediate is an allylic carbanion, to some extent π-delocalized, but the geometrical parameters indicate that it is deviates significantly from the structure of the parent allyllithium monomer. The main geometrical parameters of the intermediate are: C^2–C^3 = 1.462 Å (from 1.357 in the TS), and C^3–C^4 = 1.341 Å (from 1.434 in the TS). This allows optimum interaction of Li^+ with C^2 (Li–C^2 = 2.088 Å) and one of the two acetalic oxygens (Li–O = 1.862 Å). The other oxygen is at more than 3.5 Å from lithium. Electron density comes out to be rather localized on carbons 2 and 4, with NAO charges not very different from those reported for the TS (maximum variation: –0.08 on C^3).

The barrier and reaction energy computed for the MeLi / propene system in ref. 1 were 22 and –7.5 kcal mol^{-1}, respectively (MP2). The present reaction might be to some extent more difficult and endoergonic due to a relatively larger stabilization of the starting complex and to lack of resonance stabilization in the rather localized carbanionic intermediate.

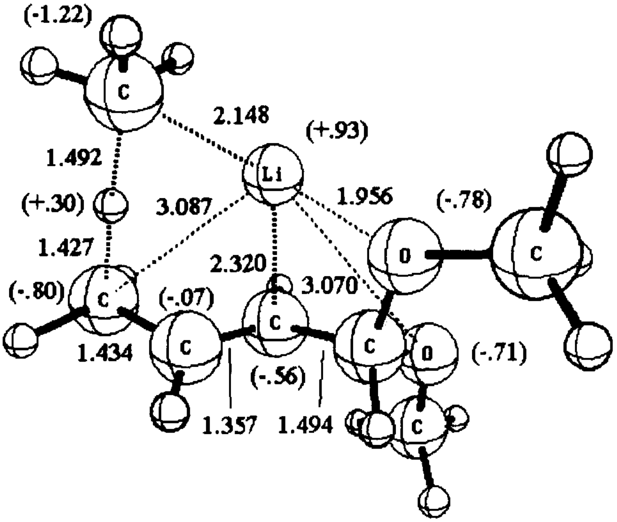


Figure 3. The transition structure for metallo-dehydrogenation operated by CH_3Li.

The metallo-dehydrogenation transition structure for methylpotassium is shown in Fig. 4. Its energy is much lower (−27.3 kcal mol^{-1}) than that of the corresponding methyllithium structure, and quite close to that for nucleophilic addition (10.3 vs 8.3 kcal mol^{-1}). For the simple methylpotassium model reagent the two pathways are almost equivalent (nor taking into account solvent effects in an approximate way helps to discriminate between the two pathways).[14] From the resulting intermediate, as in the lithium case, elimination can take place. Although an allylic carbanion, this intermediate is again quite asymmetric, in the sense that it has one almost single and one almost double allylic C–C bond. The carbon-carbon bond lengths are not very different from those of the lithium intermediate: C^2–C^3 = 1.448 Å (from 1.350 in the TS); C^3–C^4 = 1.350 Å (from 1.449 in the TS). The geometry contrasts its lithium analogue in that K^+ is able to simultaneously keep significant interactions with C^2 (K–C^2 = 2.825 Å) and both acetalic oxygens (K–O = 2.872 and 2.733 Å). The electron density is rather localized on carbon 2, more than in the lithium case. NAO charges on C^4, −0.62, and C^2, −0.79, show a significant reversal with respect to TS **4**; this does not occur in TS **3** and corresponding intermediate. The other charges change at most by −0.05 (C^3).

Comparison with the analogous propene reaction shows this time remarkably close energy differences.[8] The barrier in the acetal (10 kcal mol^{-1}) compares with that for propene (12.5), and the two reaction energies are quit close (−16).

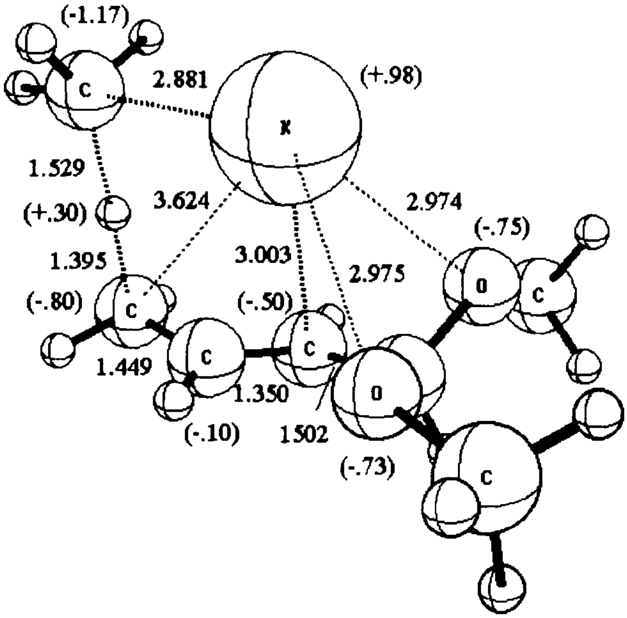


Figure 4. The transition structure for metallo-dehydrogenation operated by CH_3K.

Table 1. Energies[a] and Energy Differences[b]

	Structure		**E(RHF)**	**ΔE**	**E(MP2)**[d]	**ΔE**
Li	complex		–430.445674	0.0	–431.754629	0.0
	addition T.S.	**1**	–430.399860	28.7	–431.732108	14.1
	addition intermediate		–430.459130	–8.4	–431.785317	–19.2
	metalation T.S.	**2**	–430.366335	49.8	–431.694778	37.6
	metalation intermediate[c]		–430.443626	1.3	–431.759280	–2.9
K	complex		–1021.501695	0.0	–1022.812828	0.0
	addition T.S.	**3**	–1021.463781	23.8	–1022.799530	8.3
	addition intermediate		–1021.551400	–18.6	–1022.862262	–31.0
	metalation T.S.	**4**	–1021.461068	25.5	–1022.796409	10.3
	metalation intermediate[c]		–1021.519869	–11.4	–1022.839349	–16.6

(a) Hartrees, [53/331/31/2] basis set; (b) kcal/mole; (c) to which the energy of methane is summed up (RHF : –30.149344; MP2:–40.290678); (d) RHF/[53/331/31/2] geometries.

Figure 5 summarizes the observed trends, by reporting differences in energy barriers for the three cases examined in the present reaction, and in that of propene (positive values: addition preferred; negative values: dehydrogenation preferred). Considering Li and K, the trends are parallel, with a more pronounced preference for nucleophilic addition in the acetal case with respect to propene. It is apparent from the coincidence of the two free anion points, that behavior differences in the two reactions have to be attributed to interactions involving the metal cations, and not simply to the presence (polar effect) of the oxygens.

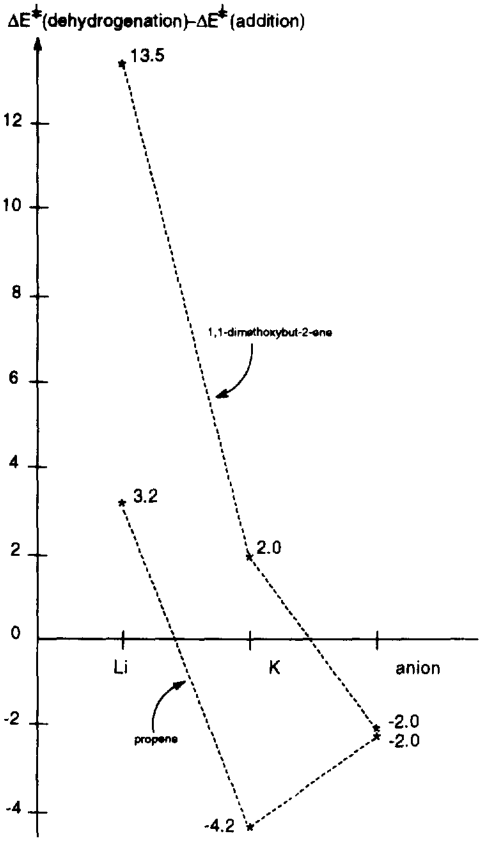


Figure 5

CONCLUSIONS

In 1,1-dimethoxybut-2-ene, both nucleophilic addition to the carbon-carbon double bond in position 3, and metalation in position 4, are more difficult if lithium is the counterion associated to the alkide reactant, and easier if the counterion is potassium. In the lithium case the addition reaction is sharply preferred (by ca. 24 kcal mol^{-1}). In the case of an alkylpotassium reagent the addition reaction is still slightly easier, with a difference between the two energy barriers of only 2 kcal mol^{-1}. In the case of a free methyl anion, dehydrogenation is preferred by ca. 2 kcal mol^{-1}. The last two results indicate that RK is too poor a model for a RLi/R'OK superbase, and that the alkyl carbon must be in an almost carbanion-like state to exhibit the reactivity actually observed when a superbase is used. The hypothesis, put forward in ref. 7, that potassium alkoxide not only brings about a deaggregation of $(LiR)_n$, but also promotes a partial cleavage of the negative carbon-lithium counterion bond, comes out reinforced.

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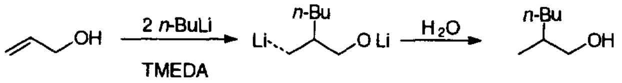
2. See for instance: Schlosser, M. *Mod. Synth. Methods* **1992**, *6*, 227–278; Mordini, A. in *Advances in Carbanion Chemistry*, Snieckus, V. Ed.; JAI Press Inc., Greenwich CT, 1992; Vol.1, pp.1–44. Several experimental data argue against the hypothesis that the mixture of RLi and R'OK might afford a RK and R'OLi. First, butylpotassium does not show the selectivity of Schlosser lithium-potassium bases, and does not discriminate allylic from vinylic proton in alkenes (Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741–744); The BuLi / *t*-BuOK mixture and the BuK reagent exhibit different stability towards ethereal solvents: mixed base is stable for hours in THF at −50 °C, whereas BuK instantaneously metalates THF even at −100 °C (Lehmann, L.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745–748). Finally, recent works on kinetic isotopic effect (k_H / k_D) in metalation of toluene and benzene by BuLi / BuOK base and BuK confirm different behavior of the two: Schlosser, M.; Choi, I. H.; Takagishi, S. *Tetrahedron* , **1990**, *46*, 5633–5648.

3. (a) Effective substituents are for instance: second row elements like sulfur; carbonyl or cyano groups; other conjugated multiple bonds (Michael-type reactions). Also alkenes with an electron donor group in a suitable position (as allylic alcohol, see below) have been reported to readily undergo addition of organolithium.



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10. For K / C,O / Li / H, the basis consists of (13s,8p / 7s,5p,1d / 7s,1p / 4s) gaussians, respectively, which are grouped as: 43321 (s) and 431 (p) for K; 421 (s), 311 (p), and 1 (d, the polarization set) for C and O; 421 (s) and 1 (p) for Li; 31 for H. This provides a [53/331/31/2] basis set.

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