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Ab Initio Theoretical Investigation on the Reactivity as Bases of Mixed LiMe/KOMe Complexes. A Model for Schlosser LICKOR Superbase

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Abstract: The metal-hydrogen exchange reaction of LiMe·KOMe 1 : 1 complex with CH_4 is first examined, and its reactivity is found to be quite similar to that displayed by LiMe alone. On this basis, other possible aggregations are studied. The 1 : 3 complex, in which Me^- and Li^+ are kept *ca.* 3.5 Å apart by three K^+ ions and three negative oxygen atoms, respectively, is particularly interesting. Its formation is computed to be easier than that of the 3 : 1 tetramer. On the basis of its structural and electronic features, this complex can be considered a good candidate as a reactive metalating species.

INTRODUCTION

The metalation reaction is one of the most important transformations in organic synthesis and has become popular owing to the discovery of new organometallic reagents.[1] In particular mixed-metal bases have drawn increasing interest and found many application in synthesis since 1967, when Schlosser showed that the equimolar mixture of butyllithium and potassium *tert*-butoxide (LICKOR reagent) constituted a superbasic reagent with exceptional metalating properties.[2] The first hypothesis on the structure of LICKOR reagent was postulated by Schlosser himself, who considered a 1 : 1 mixed aggregate assumed to be able to enhance the carbanionic character of the organometallic moiety (Chart 1a).[2] More recently Lochmann and coworkers considered three different mechanistic possibilities: (1) a complex like that proposed by Schlosser is formed, but decomposes to yield a lithium alkoxide and an organopotassium compound, which in turn metalates the substrate; (2) the intermediate complex metalates directly the substrate through a multi-center transition structure (Chart 1b); (3) potassium alkoxide just "solvates" organolithium compound, leading to a complex (Chart 1c); the metalation of the substrate produces initially a lithium derivative, which then undergoes lithium-potassium exchange.[3] Some experimental results play against the third hypothesis,[4] and even if in many instances butylpotassium can be considered as the reactive species in mixed-metal metalations, its tendency to autodestruction talks against the role of butylpotassium alone as the true metalating agent.[5] Nevertheless, the nature of metal mixed reagents is still not well-known from both the structural and mechanistic point of views. It can be only assumed that the organolithium reagent and potassium alkoxide undergo a complete reorganization that affords aggregates with various stoichiometries.[1]

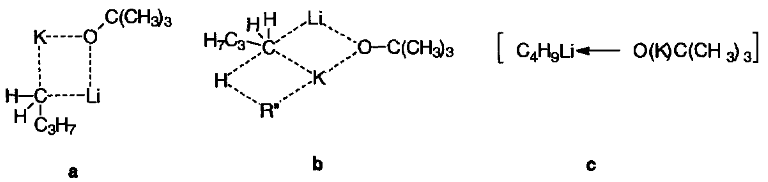
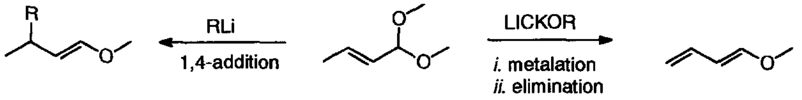


Chart 1

Many examples have shown that the LICKOR reagent is particularly suited for selective deprotonation of resonance active sites (i.e. at allylic and benzylic positions). The regio- and typoselectivity of the reaction are always confirmed: metalation regularly takes place at the allylic terminus of alkenes having also vinylic hydrogens, without traces of addition products. Accordingly with these findings, we have recently reported that α,β-unsaturated acetals derived from crotonaldehyde and 3-methylbuten-2-al in the presence of LICKOR base undergo regioselective metalation at the γ site, that immediately induces a 1,4-elimination reaction affording 1,3-coniugate dienes.[6] On the other hand, studies of Bailey and Zartun,[7] and Mioskowski, Manna and Falck,[8] demonstrate that analogous substrates react with organolithium reagents according to the nucleophilic 1,4-addition pathway of the organometallic reagent to the carbon-carbon double bond (Scheme 1).



Scheme 1

The experimental situation, in which the substrate reacts in the presence of both lithium and potassium cations, as well as the alkoxide ion, can be rather complex, due to possible variety of aggregation modes. It has just been mentioned that the possibility that the complex LICKOR bases react through the intervention of mixed oligomers was first put forward by Schlosser himself. In this study a simple computational model is set up, consisting of dimers, trimers or tetramers of alkyllithium and potassium alkoxide in different stoichiometries. Although higher order oligomers are not considered, this model should be able to offer some insight into the structure and reactivity of LICKOR bases. Due to the size of the larger composite systems, the two component alkyl or alkoxide groups were chosen to be as simple as possible: thus, lithium methide was taken as a model for butyllithium,[9] and potassium methoxide for potassium *tert*-butoxide. Therefore, the present investigation is articulated in two parts. (i) The study of the reactivity as a base of a 1 : 1 complex of methyllithium and potassium methoxide, by considering the metallo-dehydrogenation reaction on methane. (ii) The study of different aggregation possibilities between methyllithium and potassium methoxide, in order to explore possible modes of proton abstraction activation brought about by a synergic effect of the constituent molecules. To this purpose, the structural and electronic features of these aggregates are examined.

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[10] of the geometrical parameters at the Hartree-Fock level of theory, using for all systems a polarized split-valence shell basis set, denoted throughout as 3-21G[*]. This basis set is built from the sp 3-21G basis set,[11a] enriched with d polarization functions on C and O atoms,[11b] while the alkaline ions already carry empty sp functions, which act as a polarization set. 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. The geometries thus obtained were used to recompute the relative energies by introducing correlation effects through perturbative MP2 computations,[12] in conjunction with the more extended Huzinaga split-valence shell sp basis set[13a] (enriched with diffuse p functions and d polarization functions on carbon and oxygen atoms, and with p polarization functions on the alkali metal ions), which will be denoted as [53/331/31/2] in the following.[13b] MP3 and MP4 computations[12] too were carried out on the metallo-dehydrogenation reaction studied. The electron distribution is examined in terms of NAO charges (Natural Population Analysis).[14] The GAUSSIAN92 system of programs[15] was used throughout, on IBM RISC/6000-550 and 360 computers.

RESULTS AND DISCUSSION

Metallo-dehydrogenation brought about by a 1 : 1 complex of MeLi and KOMe

The structure of the equimolecular aggregate MeLi·KOMe is shown in Figure 1. The geometrical parameters are rather close to those of the two separated moieties (not shown). The aggregate is nearly planar, with deviations of the methoxy O and C atoms from the (C, Li, K) plane smaller than 0.001 Å. The methide C–Li distance is slightly longer than that found in the MeLi molecule (2.008 Å). Similarly, the methide C–K distance is slightly longer than that found in the KMe molecule (2.778 Å). The Li–K distance is 2.830 Å. The electron distribution of this mixed aggregate is described by the NAO charges displayed in Table 1. With respect to MeLi, in which methide carries a charge of –0.814, in **1** methide is more negative, consistently with the geometrical features.

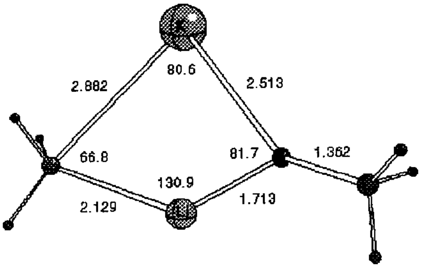


Figure 1. The 1 : 1 complex between MeLi and MeOK

TABLE 1. NAO charges[a]

Structure (stoichiometry)	methide			methoxy		methane	
	Q(Me)[b]	Q(Li)	Q(K)	Q(O)	Q(Me)	Q(H)[c]	Q(Me)
1 (1:1)	-0.923	0.894	0.994	-1.184	0.218	0.214	-0.214
2	-0.921	0.892	0.993	-1.174	0.225	0.248	-0.262
3	-0.6115	0.950	0.998	-1.185	0.228	0.232	-0.6115
4 (3:1)	-0.910 -0.904[d]	0.897 0.865[e]	0.992	-1.177	0.250		
5 (1:2)	-0.9065	0.765	0.953 0.939	-1.061 -1.056	0.185 0.184		
6 (1:3)	-0.975	0.876	0.984	-1.165	0.214		
7	-0.882	-0.882					
8			0.982	-1.150	0.168		

(a) see ref. 14; computed at the RHF/[53/331/31/2] level; methyl group charges computed summing up C and H atomic charges; (b) formal methide; (c) transferred hydrogen; (d) methyl groups bound to one K and two Li ions / methyl group bound to three Li ions; (e) lithium ions bound to oxygen and two methide carbons / lithium ion bound to three methide carbons.

Not unexpectedly, the interaction of methane with **1** does not perturb significantly either the structure or the electron distribution (Table 1). Methane is associated to the aggregate through the interaction of one of its hydrogens with the oxygen atom; it is slightly polarized, and the interacting hydrogen is more positive than in the separated CH_4 molecule. The interaction brings about only a slight elongation (0.02 Å) of the K–O and Li–O distances (Figure 2). The Li–K distance becomes 2.845 Å.

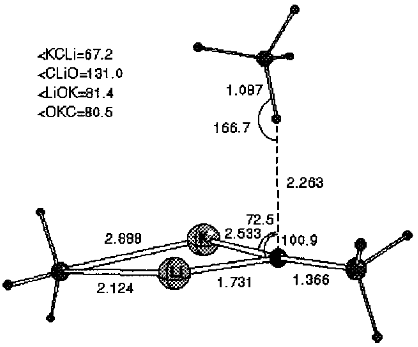


Figure 2. The complex between **1** and methane

The metallo-dehydrogenation transition structure shown in Figure 3 does not appear to be very different from the structures determined in the simpler cases of the reactions of methane with methyllithium or methylpotassium.[16] The transferred hydrogen is half-way from the two involved carbons, C and C', and the structure is rather symmetric, showing quite similar C–Li vs. C'–Li and C–K vs. C'–K distances. These distances are longer than those found in the transition structures for the identity exchange reactions of methane and methyllithium or methylpotassium (C–Li=2.110 Å; C–K=2.770 Å), to an extent which is different in the two cases. On the other hand, the distances of the transferred hydrogen from the two carbons is closer to those determined in the identity reactions (1.478 Å for the lithium reaction, 1.469 Å for that involving potassium). The Li–K distance has shortened to 2.804 Å. The NAO charges show a partition of the negative charge on C and C' to equal extents, while the transferred hydrogen has such a small positive charge (compare with methane) that the process can hardly be defined as a proton transfer.[16,17] The alkaline ions are more positive than in **1**, reflecting the longer distances from the negative carbon; this effect is significant only for lithium.

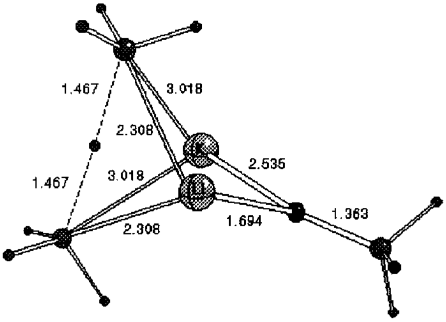


Figure 3. The metallo-dehydrogenation transition structure

From the energy differences shown in Table 2 it can be elicited that the reactivity as a base of the 1 : 1 mixed dimer **1** does not depart from that of the simple MeLi reactant. No synergic effect of the two cations is present.

Table 2. Metallo-dehydrogenation: energies[a] and energy differences[b]

Structure		E(RHF)[c]	ΔE	E(MP2)[d]	ΔE	E(MP3)[d]	ΔE	E(MP4)[d]	ΔE
reactants[e]	**1**	−796.866843	4.9	−800.682407	2.6	−800.728210	−1.2	−800.750500	−2.8
complex	**2**	−796.874689	0.0	−800.686534	0.0	−800.726334	0.0	−800.754984	0.0
T.S.	**3**	−796.809475	40.9	−800.634083	32.9	−800.671322	34.5	−800.700708	34.1

(a) Hartrees; (b) kcal mol^{-1}; (c) optimizations with the 3-21G[*] basis set; (d) [53/331/31/2] basis set; in the MP computations the options "full" and "6d" were set (see ref. 16); (e) the energy of the 1:1 complex **1** is: −756.877344 (HF), −760.388735 (MP2), −760.418023 (MP3), −760.434 525 (MP4), to which the energy of methane is summed up.

In fact, the computed energy barrier for the identity exchange reaction of methane and methyllithium is 40 (RHF or CASSCF) to 32 kcal mol^{-1} (MP2).[16] The analogous reaction of methane and methylpotassium shows lower energy barriers, 32–33 kcal mol^{-1} (RHF and CASSCF) and 24 kcal mol^{-1} (MP2); these values are closer to those computed for the anionic system, in which the exchange is easier, requiring 21 (RHF or CASSCF) or 14 kcal mol^{-1} (MP2).[17]

Complexes of MeLi and KOMe with stoichiometry different from 1 : 1

Given that the reactivity of the 1 : 1 aggregate does not depart significantly from that of the simple MeLi reactant, an investigation on the 1 : 1 mixed tetramer (the dimer of **1**) did not seem to be particularly promising. Instead, mixed oligomers of different stoichiometry were studied, in an attempt to investigate possible structural and electronic reasons of an altered reactivity with respect to **1**.

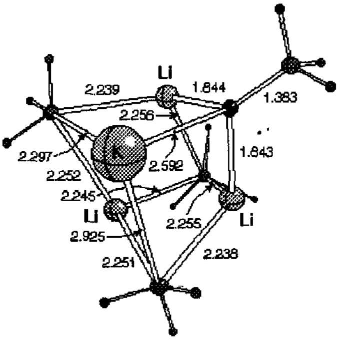


Figure 4. The 3 : 1 tetrameric complex

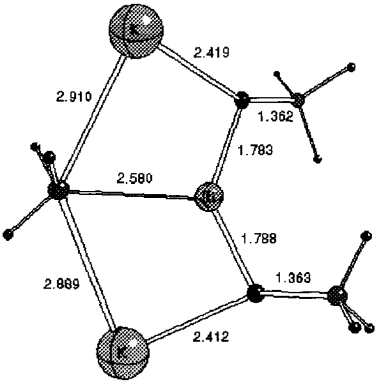


Figure 5. The 1 : 2 trimeric complex

The RLi to ROK ratio decreases from the 3 : 1 mixed tetramer $(MeLi)_3{\cdot}KOMe$, shown in Figure 4, to the trimer $MeLi{\cdot}(KOMe)_2$ (Figure 5), and finally to the 1 : 3 mixed tetramer $MeLi{\cdot}(KOMe)_3$ (Figure 6).

The structure of tetramer **4** is characterized by having two sets of lithium cations (one is bound to three methide carbons, two others are bound to one oxygen and two carbons), as well as two sets of methide carbons (one bound to three lithium ions, the other two bound to potassium and two lithium ions). Thus NAO charges are split consequently (Table 1). The negative charges on methide carbons appear to be slightly lower than in **1**.

It is interesting to assess if a larger separation of methide from its lithium counterion can be achieved through the interaction with a larger number of KOMe units. In fact, the structure of the trimeric complex **5** is such that the C–Li distance, 2.580 Å, is significantly larger than the values of 2.008 Å in MeLi, and 2.129 Å in **1**. However the NAO charges (Table 1) show that the electron density on the methide group is still close to that found in **4**.

The structure of tetramer **6** seems to be particularly interesting. Unconstrained optimization of a non-symmetric aggregate of three KOMe molecules arranged around a single MeLi molecule converged on the symmetric complex shown below. The more striking feature of this tetramer is the *complete* splitting of the lithium and methide ions (dashed line in Figure 6), operated on one hand by the potassium cations (which engage the negative carbon, as well as a couple of oxygen atoms each) and, on the other hand, by the three negative oxygens which surround the lithium cation. It can be noted that the three K–C distances are larger than 3 Å, i.e. longer than those usually encountered (for instance, the K–C distance in MeK is 2.778 Å, in **1** is 2.882 Å). Thus, methide is more loosely bound than in the preceding structures: this is reflected also by the NAO charges reported in Table 1. On this basis, complex **6** can be conceived to act as a carrier of an almost free methyl anion: this, in turn, has been shown to be more inclined toward dehydrogenation than nucleophilic addition.[16] This hypothesis should of course be validated by studying the metalation reaction, as done for the 1 : 1 complex: this reaction will form the subject of further investigation.

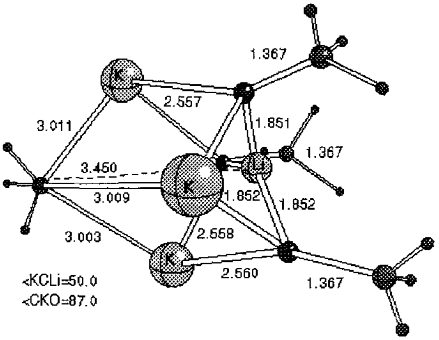


Figure 6. The 1 : 3 tetrameric complex

The question to be faced at this point concerns the stability of aggregate **6**: it would be desirable to assess if this hypothetical reacting species is plausible, or if its formation can be envisaged to be too difficult.

Equations 1 and 2 relate the two aggregates **4** and **6** to the tetramers $(MeLi)_4$ and $(KOMe)_4$. Their purpose is that of providing an estimate of relative stability of these species. The methyllithium and potassium methoxide tetramers optimize as structures composed by two intertwined tetrahedra (Figures 7 and 8). The former had already been studied by Schleyer and coworkers.[9b]

$$3\,\underset{\mathbf{7}}{(MeLi)_4} + \underset{\mathbf{8}}{(KOMe)_4} \longrightarrow 4\,\underset{\mathbf{4}}{(MeLi)_3\cdot KOMe} \tag{1}$$

$$\underset{\mathbf{7}}{(MeLi)_4} + 3\,\underset{\mathbf{8}}{(KOMe)_4} \longrightarrow 4\,\underset{\mathbf{6}}{MeLi\cdot(KOMe)_3} \tag{2}$$

Table 3. Energies[a] of the Species Entering Equations 1 and 2

Structure		RHF/3-21G[*]	MP2/[52/331/3/2]
$(MeLi)_3\cdot KOMe$	**4**	-850.569763	-854.726629
$MeLi\cdot(KOMe)_2$	**5**	-1466.954347	-1467.812358
$MeLi\cdot(KOMe)_3$	**6**	-2177.105829	-2186.958220
$(MeLi)_4$	**7**	-187.274961	-188.606693
$(KOMe)_4$	**8**	-2840.302220	-2853.039874

(a) Hartrees; in the MP2 computations the options "full" and "6d" were set (see ref. 15).

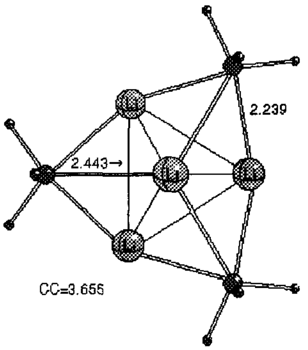


Figure 7. The methyllithium tetramer

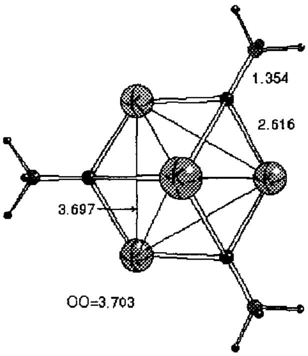


Figure 8. The potassium methoxide tetramer

The energy difference related to Equation 1 is -29.2 kcal mol^{-1} (MP2), while that for Equation 2 is -66.9. Thus, the formation of the two mixed tetramers from **7** and **8** is estimated to be exoergonic by *ca.* 24 kcal mol^{-1} (sum of Equations 1 and 2). Moreover, the formation of **6** is indicated as more advantageous by -16.7 vs. -7.3 kcal mol^{-1} per molecule.

CONCLUSIONS

The metalation reaction operated by a mixed 1 : 1 lithium methide-potassium methoxide complex on methane exhibits a reactivity which is very close to that of methyllithium alone. Therefore, the enhanced basic strength of LICKOR bases with respect to alkyllithiums must be attributed to a different kind of reacting species. The 1 : 3 tetrameric complex is particularly interesting: Me^- and Li^+ are kept *ca.* 3.5 Å apart by three K^+ ions and three negative oxygen atoms, respectively; the charge on Me is also larger than in the other aggregations studied. Its formation is computed to be easier than that of the 3 : 1 tetramer. On the basis of its structural and electronic features, this complex can almost be seen as a "free methide carrier", and appears to be a good candidate as a reactive species in LICKOR metallo-dehydrogenation.

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