Amidolithium-mediated enolization: does proton transfer occur *via* a dimer intermediate with bridging carbonyls?

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Received (in Cambridge, UK) 27th July 2000, Accepted 1st November 2001
First published as an Advance Article on the web 21st December 2000

Ab initio RHF/6-31G* and MP2-fc/6-31G* computations predict that a very shallow local minimum of the $LiNH_2 \cdot OCHMe$ dimer exists in which the carbonyl oxygens adopt the bridging role, and further that the activation enthalpy of acetaldehyde enolization by $LiNH_2$ is significantly lower for such a dimeric intermediate than for an unsolvated monomeric intermediate. Solvation of the monomeric intermediate with dimethyl ether reduces the activation enthalpy of enolization, but not to the near-zero level found for the bridged carbonyl dimer. However, starting from the amide-bridged dimeric global minimum, the solvated monomeric local minimum from which the transition state evolves is more easily accessible than the carbonyl-bridged dimeric local minimum. Inclusion of electron correlation effects is imperative in the determination of the transition state barriers.

Introduction

Enolization, as the first step of the aldol condensation, is one of the most widely practised synthetic procedures in chemistry. Modern synthetic methods often involve the use of amidolithium bases to effect such transformations.[1] Consequently, a large and growing body of knowledge is accumulating in the hope that the selectivities of the reaction will ultimately be controllable and predictable.[2] Due to the efforts of numerous groups worldwide, something approaching a consensus is emerging over some issues in the chemistry of enolization and subsequent aldol addition. It is widely accepted that synthetically important amidolithiums (such as LDA) exist in ether solutions predominantly (and in some cases exclusively) as ring dimers.[3] It is further accepted that the first step in enolization is coordination of the carbonyl group of the enolizable substrate to lithium.[4] There is also considerable evidence that the product enolates are aggregated *via* bridging oxygens, and that immediately after enolization the amine produced by protonation of the amidolithium remains coordinated.[5]

What remains to be settled is the most crucial part: what are the structural and electronic factors at work *during* the actual proton transfer? The original model of Ireland *et al.*[6] was developed to explain the E/Z selectivity of enolizations of simple ketones such as 3-pentanone. The original conjecture of a chair-like six-membered ring transition state has since been modified: *ab initio* computations show that the six-membered ring shows major deviations from the chair form,[7] as a result of the weak directionality of the bonds to lithium, and a preference for a linear geometry about the migrating proton. It was further found that the transition state was very reactant-like, suggesting that an explanation for the E/Z preferences might lie in the conformational preferences of the reactant substrate.[7] More recently, the concept of open-dimer transition structures has gained credence. Here, a larger, 8-membered ring transition state, with less strain at crucial angles, has been suggested.[8] In this case, there is no need for the widely held assumption that the highly abundant dimers dissociate to reactive monomers in (sometimes unobservably) small concentrations. They must simply rupture one Li–N bond, to make available the necessary lone pair on one nitrogen to accept the hydrogen from the ketone. These open dimers have been the subject of crystallographic[9] and NMR characterization.[10] However, the only computational evidence available on their reactivity is at the semi-empirical level.[11]

In the course of studies directed at understanding the nature of enantioselective deprotonation of cyclic ketones,[12] we were forced to consider alternative enolization models. The conformational data collected on the homochiral amidolithium complexes[12] did not explain the observed selectivities. Here we present our investigation of a further possible enolization mechanism: the bridging carbonyl model. In essence, it is similar to the Ireland model, though instead of requiring that the amidolithium dimers dissociate to reactive monomers, they are required merely to undergo a bridge/terminal ligand rearrangement. While the evaluation of the energetics of such bridge/terminal fluxions remains beyond the scope of this work, such intramolecular rearrangements are commonplace in other main-group dimeric complexes.[13] Furthermore, such a putative intermediate is very similar to the crystallographically confirmed bridged enolate structure with coordinated amine.[5] The thesis is that the carbonyl oxygen migrates to a bridging position *before* and not *after* enolization. The oxygen of the substrate now being coordinated to two Lewis acidic lithium ions, its enolizable hydrogen may be expected to be further activated to reaction. The RHF/6-31G* and MP2-fc/6-31G* computations reported here seem to support this thesis, provided that the prerequisite bridge/terminal fluxion is assumed to be a low-energy process. However, when the effect of solvation is included, the situation becomes less clear-cut.

Computational details

Preliminary computations were carried out using TURBOMOLE[14] on a Hewlett Packard 735 workstation. All subsequent calculations were performed using GAMESS 96[15] on the single nodes of an IBM SP2. The freedom to freeze chosen internal coordinates during optimizations with GAMESS enabled the location of transition states using the

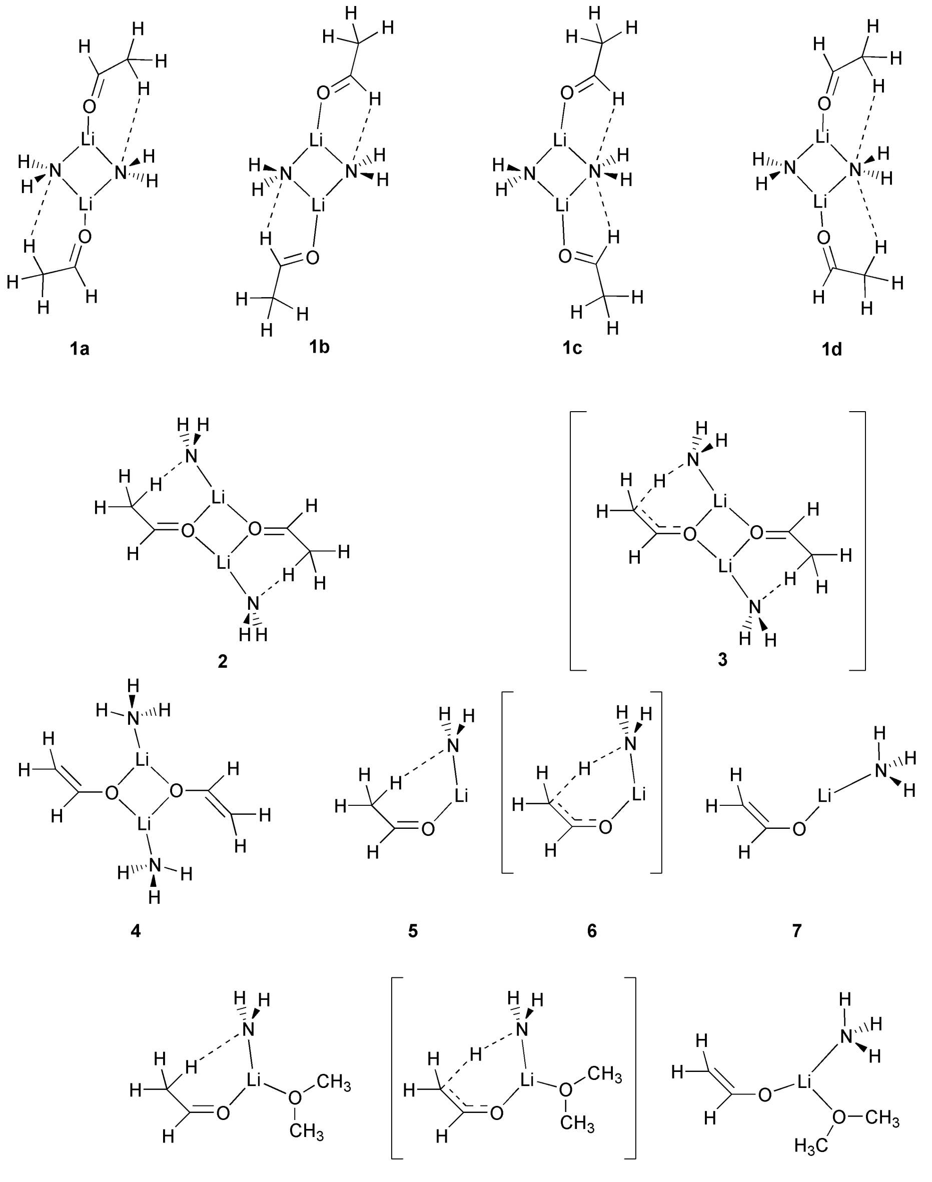
DOI: 10.1039/b003446k

"reaction coordinate" method.[16,17] All calculations performed were either spin restricted Hartree–Fock (RHF) or MP2 frozen core (MP2-fc). These consisted of RHF/6-31G* and MP2-fc/6-31G* optimizations, and also selected higher level estimates at the MP2-fc/6-31+G**//MP2-fc/6-31G*, 6-31G*[18,19] and 6-31+G**[20,21] levels were used. For the 6-31G* computations, 6-31G* basis sets were used on all atoms except the carbons which were modelled with a 6-31G basis set. This choice for carbon reduced the number of basis functions from 168 to 144, thus enabling the performance of calculations at the MP2 level. The reason for this was that any error introduced by this choice of basis set would be minimal when compared to error due to neglect of the crucial effects of electron correlation. As detailed below, the energies were found to be insensitive to changes in basis set beyond the 6-31G level, so that neglect of basis-set superposition error was deemed justifiable. The effects of inclusion of zero-point energies (ZPE) were evaluated, but were found to be minimal, lowering barriers by approximately 1 kcal mol^{-1}. The lowering of the barrier was much smaller than that found on inclusion of correlation, and was almost identical across all possible reaction pathways. In line with recent convention in the area of organolithium computational work, therefore ZPE effects have been neglected in the discussion.

Where minimum stationary points from the optimizations contained imaginary frequencies, symmetry was relaxed until all-real normal modes were obtained.

Results and discussion

The results of our *ab initio* calculations are presented in Fig. 1–3, and Tables 1–3. The discussion continues with respect to the structures from Fig. 1 and relative energies from Fig. 2 and 3. The prototypical amide, $LiNH_2$, and the simplest possible enolizable substrate, acetaldehyde, were chosen for these preliminary computations. This gives rise to four reactant minima, the C_{2h} structures **1a** and **1b**, and the C_{2v} structures **1c** and **1d**. The differences in energy between these are modest, the lowest in energy being **1b**, which minimises the steric repulsions of the methyl group while the carbonyl-bound hydrogen engages in hydrogen bonding with the amide nitrogens. Since this could not happen in the more frequently encountered ketones, and since enolization must proceed with a methyl C–H directed towards the amide, all further dis-


1a **1b** **1c** **1d**

2 **3**

4 **5** **6** **7**

8 **9** **10**

Fig. 1 Structures of reagents, transition states, and products.

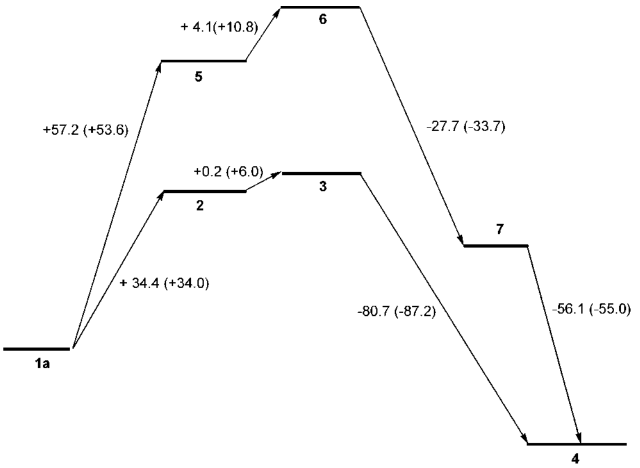


Fig. 2 MP2-fc/6-31G* relative energy profiles in kcal mol^{-1} of unsolvated monomer *vs.* dimer proton transfer pathways (RHF/6-31G* values given in parentheses).

cussion is chosen to be with reference to structure **1a**, in which the methyl groups are appropriately disposed to react, and which is only 1.13 kcal mol^{-1} higher in energy at MP2-fc/6-31G* level than global minimum **1b**.

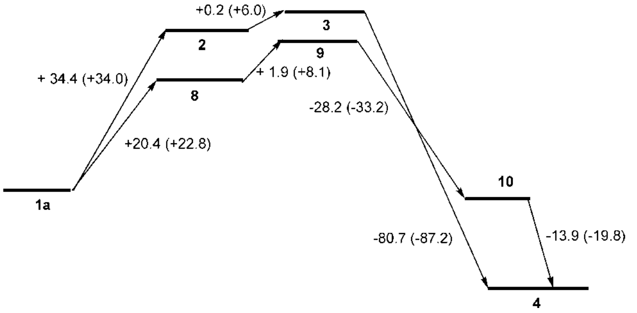


Fig. 3 MP2-fc/6-31G* relative energy profiles in kcal mol^{-1} of Me$_2$O solvated monomer *vs.* dimer plus two free Me$_2$O proton transfer pathways (RHF/6-31G* values given in parentheses).

There is indeed a local minimum **2** with neutral aldehydes bridging the two lithium atoms, despite this arrangement never having been observed crystallographically. This minimum lies 34.0 and 34.4 kcal mol^{-1} above the **1a** reactant local minimum at the RHF/6-31G* and MP2-fc/6-31G* levels, respectively. Most importantly, the transition state of enolization, **3**, was located. At the RHF/6-31G* level, it requires only 6.0 kcal mol^{-1} to reach this reactant-like transition state from the bridged carbonyl intermediate, **2**. Significantly, on inclusion of correlation effects, at the MP2-fc/6-31G* level the barrier decreases to a mere 0.2 kcal mol^{-1}, indicating that the bridged carbonyl intermediate **2** is itself very close to the transition state geometry, and thus that the proton transfer is virtually barrierless from **2**.

In order to check that these results were consistent with the thesis that reaction path geometries are relatively insensitive to basis set, the barrier at the higher MP2-fc/6-31+G**//MP2-fc/6-31G* level was computed. This led to an increase in the barrier height by only 0.2 kcal mol^{-1} (see Table 1), indicating that the result at the MP2-fc/6-31G* level is accurate. A saddle point related to **3**, but which possessed C_i symmetry, represented concerted enolization of both aldehydes simultaneously. It was located at both the RHF/6-31G* and MP2-fc/6-31G* levels, but had two imaginary frequencies, indicating that enolization is a stepwise process. Two such sequential proton transfers lead highly exothermically to the global enolate minimum **4** (see Fig. 1).

For comparative purposes, the corresponding monomer species **5**, **6** and **7**, previously modelled at the uncorrelated RHF/3-21+G level by McKee,[7] were recomputed at the RHF/6-31G* and MP2-fc/6-31G* levels. The effect of using 6-31G basis sets instead of 6-31G* basis sets on the carbon atoms was also evaluated for these species at the Hartree–Fock level: Hartree–Fock calculations at the RHF/6-31G*(full) and RHF/6-31G*(full)//RHF/6-31G* levels, as well as the RHF/6-31G* level, were performed and results compared for geometries, relative energies and vibrational frequencies of the monomers **5**, **6** and **7**. The difference between the 6-31G* and 6-31G*(full) basis sets is that the 6-31G*(full) basis set has 6-31G* basis sets on all atoms, including the carbons.[18] There is, on average, a difference of only 0.1 kcal mol^{-1} between the energies of the optimum RHF/6-31G* and RHF/6-31G*(full) geometries calculated at the RHF/6-

Table 1 Activation energy barriers, $\Delta E^{\ddagger}$ (kcal mol^{-1}), computed for the monomer and dimer proton transfer pathways

	RHF/6-31G*	MP2-fc/6-31G*	MP2-fc/6-31+G**//MP2-fc/6-31G*
Monomer	+10.8	+4.1	+5.2
Monomer (solvated)	+8.1	+1.9	+3.1
Dimer	+6.0	+0.2	+0.4

Table 2 Absolute energies (Hartrees) of free acetaldehyde, free dimethyl ether and **1**–**10**

	RHF/6-31G*	MP2-fc/6-31G*	MP2-fc/6-31+G**//MP2-fc/6-31G*
MeC(O)H	−152.8713	−153.2339	—
1a	−431.9803	−433.0744	—
1b	−431.9837	−433.0762	—
1c	−431.9822	−433.0750	—
1d	−431.9791	−433.0733	—
2	−431.9261	−433.0196	−433.3884
3	−431.9165	−433.0192	−433.3878
4	−432.0555	−433.1478	−433.5083
5	−215.9474	−216.4916	−216.6791
6	−215.9302	−216.4850	−216.6708
7	−215.9839	−216.5292	−216.7113
8	−369.9890	−370.9080	−371.2673
9	−369.9761	−370.9050	−371.2623
10	−370.0290	−370.9499	−371.3032
Me$_2$O	−154.0170	−154.3871	—

Table 3 Selected *ab initio* optimum geometric parameters and vibrational frequencies of free acetaldehyde and structures **1**–**10**; MP2-fc/6-31G* values (RHF/6-31G* values in parentheses)

	C–O/Å	C–C/Å	N–H/Å	C–H–N/°	ν/cm^{-1}
MeC(O)H	1.236(1.197)	1.519(1.498)	—	—	1770.5[a]
1a	1.245(1.205)	1.509(1.491)	2.502(2.645)	159.7(154.8)	1739.3[a]
2	1.258(1.217)	1.488(1.484)	2.064(2.426)	149.9(155.5)	1692.9[a]
3[b]	1.268(1.244)	1.465(1.430)	1.777(1.543)	153.3(157.8)	1611.1[a]
4	1.344(1.317)	1.370(1.340)	1.024(1.007)	147.1(137.6)	1210.2[a]
5	1.250(1.212)	1.506(1.489)	2.408(2.577)	157.0(152.8)	1718.9[a]
6	1.272(1.240)	1.456(1.433)	1.573(1.468)	155.9(157.8)	1605.6[a]
7	1.335(1.306)	1.377(1.348)	1.029(1.009)	145.4(135.6)	1225.7[a]
8	1.248(1.209)	1.507(1.490)	2.315(2.413)	159.4(155.8)	1727.7[a]
9	1.267(1.236)	1.461(1.435)	1.613(1.480)	156.1(158.4)	1621.4[a]
10	1.332(1.302)	1.378(1.349)	1.028(1.009)	149.0(141.9)	1228.1[a]

[a] RHF/6-31G* values only reported, scaled by the single RHF/6-31G* correction factor of 0.8953.[23] [b] Parameters shown relate to the aldehyde undergoing enolization.

31G*(full) level. Strikingly similar geometric parameters confirm this observation. The monomer proton transfer barrier for transition state **6** increases slightly from 10.8 kcal mol^{-1} at the RHF/6-31G* level to 13.3 kcal mol^{-1} at the RHF/6-31G*(full) level. Most importantly, calculations at the RHF/6-31G*(full)//RHF/6-31G* level also gave a barrier of 13.3 kcal mol^{-1}, further indicating the similarity of the reactant path geometries between basis sets. Completion of proton transfer to the enolate monomer **7** takes place with similar exothermic values (RHF/6-31G* = -33.7, RHF/6-31G*(full) = -30.7, RHF/6-31G*(full)//RHF/6-31G* = -30.7 kcal mol^{-1}). For the vibrational frequencies, the C=O stretch of coordinated acetaldehyde in monomer **5** was 52 cm^{-1} lower than in free acetaldehyde at the RHF/6-31G* level, compared with a shift of 55 cm^{-1} at the RHF/6-31G*(full) level. Overall then, all properties calculated are similar between the two basis sets and the exclusion of the d polarisation functions on the carbon atoms for the larger systems is justified.

It requires 19.7 (RHF/6-31G*) or 22.9 kcal mol^{-1} (MP2-fc/6-31G*) to split the dimer **2** into two monomers. Thus, as a putative intermediate, the carbonyl-bridged dimer **2** is competitive in energy with the monomer **5**. Furthermore, the computed activation energy for proton transfer (to reach transition state **6**) is 10.8 kcal mol^{-1} at the RHF/6-31G* level, compared to the significantly smaller 4.1 kcal mol^{-1} barrier at the MP2-fc/6-31G* level. Estimating the barrier height at higher level, as we did for the dimer, the barrier increases slightly to 5.2 kcal mol^{-1} at the MP2-fc/6-31+G**//MP2-fc/6-31G* level (see Table 1). Hence, the monomeric activation energy barriers for proton transfer are 4.8 kcal mol^{-1} higher at the RHF/6-31G* level, 3.8 kcal mol^{-1} higher at the MP2-fc/6-31G* level, and 4.8 kcal mol^{-1} higher at the MP2-fc/6-31+G**//MP2-fc/6-31G* level than the corresponding barriers for the dimeric transition state, **3**. Henceforth, all energetic comparisons shall relate to the MP2-fc/6-31G* level.

For a more accurate assessment of the relative probability of monomeric or dimeric paths for the reaction, account must be taken of the fact that enolization reactions normally proceed in ether solvents. While, in the case of the bulky lithium amides used, the dimeric structures are unlikely to co-ordinate external donors other than the carbonyl substrates, it is likely that monomers will co-ordinate at least one ether molecule. The effect of this on energetic pathways was investigated by computation of reactant solvated monomer **8**, transition state **9** and product **10**. Free dimethyl ether was also computed.

In line with conventional wisdom, both the dimeric reactant **1a** and product **4** were more stable than their solvated monomeric analogues **8** and **10**, by 20.4 and 13.9 kcal mol^{-1}, respectively. Solvation reduces the monomer activation enthalpy of enolization from 4.1 to 1.9 kcal mol^{-1}. While this is still higher than for the bridged dimeric transition state, two solvated reactant monomers **8** are only 20.4 kcal mol^{-1} less stable than dimer **1a** plus two free dimethyl ethers. Hence the solvated monomer reaction precursor **8** is easier to access than the carbonyl-bridged dimeric reaction precursor **2**, which lies 34.4 kcal mol^{-1} above dimer minimum **1a**. Thus, while the bridging carbonyl intermediate is easier to access from the reactant global minimum than an unsolvated monomer intermediate and results in a significant decrease in activation enthalpy relative to the unsolvated monomer intermediate at all levels of theory studied, and both reactant and product dimers resist further solvation by Me_2O, a solvated monomer transition state is more stable. In enthalpic terms therefore, both the postulated dimer **2** and the solvated monomer intermediate **8** seem worthy of further consideration.

Selected geometric parameters of the RHF/6-31G* and MP2-fc/6-31G* optimum structures are displayed in Table 3. The MP2-fc bond lengths are longer due to the inclusion of the effects of electron–electron correlation. The RHF/6-31G* structural details of the dimeric transition state have much in common with those of the monomer described in the earlier work of McKee,[7] and recomputed here as **5**, **6** and **7**. The most notable differences are bond lengths in the pre-enolization intermediates **2** and **5**. In **2**, C–C is shorter, and C=O is longer than in **5** at both levels of theory. This effect, although very small at the RHF/6-31G* level, is greater at the MP2-fc/6-31G* level, where the C–C bond length in **2** is 1.488 compared to 1.506 Å in **5**, and the C=O bond length in **2** is 1.258 compared to 1.250 Å in **5**. This perhaps offers an explanation for the reduced energy barrier to proton transfer at both levels from monomer to bridged dimer, but in particular for the substantial reduction at the MP2-fc/6-31G* level, from 4.1 to 0.2 kcal mol^{-1}. It would appear that placing the ketone in a bridging position perturbs the ground state parameters to be closer to those of the transition state, in which the relative shortening and lengthening of bonds progresses further. As noted by McKee at the RHF/3-21+G level,[7] the transition state is quite reactant-like; it is even more so at the MP2-fc/6-31G* level. Solvation of the monomer **5** to give **8** causes the C–O and C–C bond lengths to be closer to those in **1a**, with which it has in common that the carbonyl is terminally co-ordinating to a three-co-ordinate lithium ion. This, however, does not stop the activation energy from **8** to **9** from being lower than from **5** to **6**. The answer may lie in the increased basicity of the nitrogen in **8** over that in **5**, owing to the fact that, in **8**, the lithium ion has partially loosened its hold on nitrogen in order to bond with the ether oxygen.

A more sensitive probe of the perturbations in bonding is the relative vibrational frequencies of the bonds in question. These were computed for all species at the RHF/6-31G* level and for free acetaldehyde for reference. The standard single RHF/6-31G* frequency scaling factor of 0.8953 proposed by Scott and Radom[23] was applied in each case. For correlated methods, such as MP2, the use of different scaling factors, reflecting the difference in anharmonicity among the vibrational modes, is far more important than for a non-correlated method, such as Hartree–Fock, which can yield reliable vibrational frequencies once a standard single scaling factor has been applied. Accordingly, discussion continues with respect to the RHF/6-31G* singly-scaled frequencies. These scaled vibrational frequencies are presented in Table 3. A decrease of 31 cm^{-1} in the C=O frequency was predicted upon coordination of the aldehyde to the amidolithium, as in **1a**. This is close to that found by Lochmann and co-workers for ester carbonyls,[4] confirming that both the level of our frequency calculations and the single scaling factor applied is adequate for the application in hand. For a closer comparison, $[\{(Me_2CO)_2LiBr\}_2]$, crystallographically confirmed by Dunitz *et al.* to possess terminal acetone carbonyl groups,[24] was re-synthesized for spectroscopic characterization. The infra-red spectrum of crystalline $[\{(Me_2CO)_2LiBr\}_2]$ was recorded from a liquid paraffin mull prepared in an argon-filled glovebox between KBr plates. It showed a coordination shift of 40 cm^{-1} with respect to free acetone, in reasonable agreement with the RHF/6-31G* prediction. The monomer **5**, and the solvated monomer **8**, had similar predicted C=O frequencies to that of **1a**, making infrared spectroscopy of dubious use in differentiating between monomer and dimer structures. Significantly, however, the bridging carbonyl in **2** has a stretching frequency 46 cm^{-1} lower than the terminal carbonyl in **1a**, suggesting that spectroscopic identification of dimer **2** may be feasible, if it exists. Of course, the intermediate will be extremely short lived in any realistic case, with only an extra 0.2 kcal mol^{-1} required to activate **2** on to the ultimate enolate product **4**. It would appear that, despite the fact that the carbonyl-bridged dimer **2** is a minimum with all-real normal modes of vibration, its reaction to form enolate is all but barrierless. For this reason, it is clear why crystallographic evidence of a bridged dimer intermediate has not yet been found. Prospects for obtaining experimental (spectroscopic) evidence will depend upon, at least, stopped-flow methods, together with the selection of amide substrates more likely to adopt terminal positions in the ground state. Such amide substrates come in the form of the diazapentadienyl anion, in which the nitrogen-centred negative charge is delocalized over a 5 atom π-framework.[25] A compound in which the neutral ligand hexamethylphosphoric triamide is found in a bridging role, while the diazapentadienyl anion adopts a terminal position, has been prepared.[25] Currently, only reduced ketones (*e.g.* benzophenone)[26] or minor canonical contributions, such as the ketone-enamide form of a deprotonated enaminone,[27] point to such a bridging capacity of carbonyls between two lithium atoms. We are searching for an analogue which will crystallographically confirm the bridging capacity of a neutral ketone; one recent attempt, in which 2-adamantanone was combined with a diazapentadienyllithium complex, resulted in a dimer with bridging oxygen, but only after the diazapentadienyl anion had acted as a C-nucleophile on the carbonyl carbon.[28] Indeed, our results point to solvated monomers as being at least as likely a route to enolization. This being the case, crystallographic studies may not be the best source of information; this study began because observed enantioselectivities could not be reconciled with crystallographically observed substituent conformations in a dimeric amidolithium complex.[12] These conformations are likely to be different in a reactive monomer.[29] Furthermore, at present, no energetic comparisons exist for the bridged ketone or solvated monomer *vs.* the open dimer models, since the extreme flatness of the potential surface of the open dimers has so far frustrated our attempts to locate transition states with our limited computational resources. The open dimer contains elements of the monomer: its formation is likely to be accompanied by further solvation; the environment around the enolizing nitrogen is monomer-like, leading to probable alteration of substituent conformation. But an open dimer remains dimeric and therefore does not require the full dissociation enthalpy. This compromise may indeed prove to be the answer. A definitive computational treatment will require inclusion of larger substituent groups, and consideration of entropy effects at real temperatures.

Conclusion

MP2-fc/6-31G* computations predict that the dimer **2** with bridging carbonyls is a viable species and, further, that the activation enthalpy of acetaldehyde enolization by $LiNH_2$ is significantly lower for such a dimeric intermediate than for the unsolvated monomeric **5**. Solvation of **5** with dimethyl ether gives **8**, in which the activation enthalpy of enolization is reduced from that for **5**, but not to the very low level found for **2**. The dimers **1a** and **4** are unstable with respect to dissociation and monosolvation by dimethyl ether. However, solvated monomer **8** is more easily accessible than **2** from **1a**. That said, bearing in mind the approximations in the model and the computational methods employed, the safest conclusions must remain that transition states are reactant-like, and activation enthalpies for enolization are very small and similar for all routes considered. IR spectroscopy should provide a tool to distinguish the bridged dimer **2** from other possibilities.

Acknowledgements

Mr A. P. Dickie is thanked for preparing and recording the IR spectrum of $[\{(Me_2CO)_2LiBr\}_2]$. The referees are thanked for constructive suggestions.

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