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Theoretical Study of the Aldol Condensation with Imine-Type Electrophiles

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1. Introduction

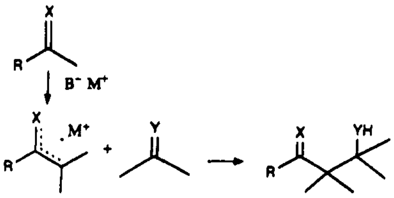
Ionic carbon–carbon bond formation based on the interaction of a carbon nucleophile and a carbon electrophile

$$C^- + C^+ = C–C$$

represents one of the most important building blocks of the synthetic organic chemist. Among the many possibilities offered by this approach the variants using a carbanion incorporated at the terminus of an allylic system as nucleophile and a carbonyl or an azomethyne group as electrophile constitute fundamental methods for C–C bond construction both in biosynthesis as well as in organic synthesis. This family of reactions is the most commonly employed for the creation of 1,3-O,O, 1,3-N,O, and 1,3-N,N relationships in organic chemistry (see Scheme I).

Unfortunately, the above-illustrated reaction is complicated not only because enolization may lead to several structurally and stereochemically isomeric enolate ions but also because the subsequent reaction of each enolate ion may lead to a multiplicity of products. Because of the nucleophilicity of the π-system of the enolate and imine anion one has two ends of potentially comparable reactivity leading to carbon and to oxygen or nitrogen alkylation, respectively. Moreover, the easy removal of a relatively acidic hydrogen leading to the formation of the enolate and the imine anion gives rise to the possibility that the product resulting from the attack on the electrophile will itself be deprotonated and suffer further reaction. Finally, the same reaction product may possibly act as an electrophile yielding concurrent condensation processes. A further source of complication arises from the fact that enolates, not only the most used Li enolates, but also sodium, magnesium, aluminum, boron, and zinc enolates, are found to form dimeric, tetrameric, or hexameric aggregates in the crystal as well as in solution.[1] NMR spectroscopy studies have demonstrated that Li enolate aggregates may be directly involved in reactions, rather than being the preequilibrium precursors of monomeric reactans.[2] The degree of aggregation was clearly correlated with the degree of isomeric products formed (C- vs O-alkylation of Li enolates). Dimeric aggregates turn out to be more reactive than tetrameric ones. Further, while the lithium amides are also known to form aggregates,[3] the amine arising during the deprotonation of a carbonyl compound with a lithium amide strongly complexes with the enolate formed, and the complexation may have an effect upon the reactivity of the enolate.[4] Faced with such complexity it is surprising that a proper choice of the reagents and a careful control of the reaction conditions can lead to preparatively good results. Even more astonishing is the fact that the simple monomeric models normally used for the mechanistic interpretation of these reactions work so well.

Scheme I



R = H, Alkyl, Aryl, OR_1
X and Y = O and/or NR_2
M = Li, MgL, ZnL, BL_2, AlL_2, etc.

The aldol condensation can in principle be performed either under acidic or basic conditions and under thermodynamic or kinetic control. The chemistry and stereochemistry are best documented for the case of the kinetically controlled condensations carried out directly with aldehydes or aldimines and preformed metal enolates of defined geometry. In the mechanism of these kinetically controlled reactions two main types of "monomeric" transition state have been proposed: a peryciclic state I and an "open" transition state II[5] (see Chart I).

The pericyclic transition state I, first proposed by Zimmerman in 1957,[6] has gained widespread acceptance for reactions involving metal enolates (M = Li, MgL, ZnL, AlL2, etc.). The cyclic structure of I is enforced by the organization features of the Lewis acidic metals of the enolates. Although considerably less information is available, the second "open" or acyclic transition state II with the two π-bond moieties in anti arrangement may be preferred in reactions between aldehydes or imines and "nacked" or ion-pair dissociated enolates where the coordinating power of the metal is absent.[7]

In order to obtain information on some aspects of this complex mechanicistic problem we have undertaken a theoretical ab initio study. Theoretical studies of the reaction of acetaldehyde enolate[8] and lithium and boron enolates of acetaldehyde with formaldehyde[8,9] as well as related theoretical studies on the stereochemistry of metalated aldimines have recently been reported.[10] In the present paper we describe the results obtained in a

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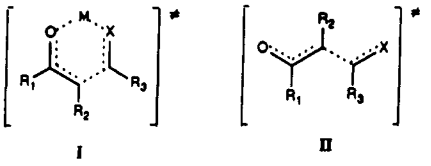
Chart I



R_1, R_2, R_3 = H, Alkyl, Aryl

theoretical study carried out at the ab initio SCF and SCF/MP2[11] level of the aldol condensation between imine-type electrophiles and Li-enolates; consequently, we have limited our study to reaction paths involving transition states of type I. Our work has the following objectives: (a) a comparison between the reaction mechanisms associated with the use of imine and that with the use of formaldehyde to obtain information upon the effect of the electrophile and (b) an investigation of the effect of substituents such as lithium and the silyl group in the imine moiety. The results are then rationalized with an interaction diagram approach.

2. Structure and Energetics

The primary objective of the present study is to obtain information about the mechanistic features of aldol condensations involving imine-type electrophiles, including substituent effects, and to compare that information with the formaldehyde reaction. Thus, we have investigated the following aldol reactions:

(i) the reaction of monomeric lithium acetaldehyde enolate with formaldehyde

$$\mathrm{H_2C{=}CHOLi + H_2C{=}O}$$

(ii) the reaction of dimeric lithium acetaldehyde enolate with formaldehyde

$$\mathrm{(H_2C{=}CHOLi)_2 + H_2C{=}O}$$

(iii) the reaction of lithium acetaldehyde enolate with imine

$$\mathrm{H_2C{=}CHOLi + H_2C{=}NH}$$

(iv) the reaction of lithium acetaldehyde enolate with the substituted imines $\mathrm{H_2C{=}NLi}$ and $\mathrm{H_2C{=}NSiH_3}$.

In our recent MC-SCF[9] study of the aldol reaction of formaldehyde with acetaldehyde boron enolate it was found that this type of reaction is mainly described by a single configuration (the coefficient of this configuration is larger than 0.98 in all cases investigated). Therefore, problems of this type can be correctly described at the SCF level. Thus, all computations were carried out at the SCF and SCF-MP2 levels. As shown in previous studies,[8,9] the general reaction mechanism for this type of reactions in the gas phase involves the critical points associated with the reactants, an electrostatic complex, a transition state, and the products. In the present study the geometries of the reactants, electrostatic complexes, and transition states have been fully optimized using gradient techniques. For the reactions i and iii the various critical points have been optimized at the 3-21G,[12a] 6-31G*,[12b,c] and MP2/6-31G* levels with frequency analysis at the SCF/3-21G level. All computations have been carried out using the Gaussian 88 series of programs[13] on the IBM 3090 of the CINECA computer center of Bologna and the CRAY X-MP at the University of London computer center.

The energetic information for the $\mathrm{H_2C{=}CHOLi + H_2C{=}O}$ and $\mathrm{H_2C{=}CHOLi + H_2C{=}NH}$ reactions is collected in Table I, and the corresponding data for $\mathrm{H_2C{=}HOLi + H_2C{=}NX}$ (X = H, $\mathrm{SiH_3}$, and Li) is given in Table II. The relative energies (in kcal mol^{-1}) are given in two forms. The stabilization energy (SE) is the energy of the electrostatic complex relative to the reactants (RS), and the transition-state relative energy (TSRE) is the energy of the transition state relative to the electrostatic complex (EC). The latter quantities, when they assume positive values, represent activation energies. The most important geometrical parameters are shown in Figures 1–3 while the full geometries are given in the supplementary material.

In order to obtain reliable activation energies for these reactions, the energies have been recomputed at the MP2 level. For the $\mathrm{H_2C{=}CHOLi + H_2C{=}O}$ and $\mathrm{H_2C{=}CHOLi + H_2C{=}NH}$ reactions we have performed both single-point MP2 computations at geometries optimized at the SCF level (MP2/6-31G*//RHF/3-21G and MP2/6-31G*//RHF/6-31G*) and an MP2 geometry optimization (MP2/6-31G*). While the MP2 values of the activation energies are significantly different from those computed at the SCF level, the level at which the geometry is optimized is less critical and value of the correct order of magnitude can be already obtained using a 3-21G geometry. Consequently, in the reactions $\mathrm{H_2C{=}CHOLi + H_2C{=}NX}$ (X = H, $\mathrm{SiH_3}$, and Li), where the effect of imine substituents is investigated, the geometries of the various critical points have been optimized only at the SCF/3-21G level in the case of $\mathrm{H_2C{=}NLi}$ and at the 3-21G*[12d] level in the case of $\mathrm{H_2C{=}NSiH_3}$, with subsequent 6-31G* MP2 calculations at these geometries.

We begin our discussion with a comparison of the $\mathrm{H_2C{=}CHOLi + H_2C{=}O}$ and $\mathrm{H_2C{=}CHOLi + H_2C{=}NH}$ reactions. From Table I it can be seen that for the reaction $\mathrm{H_2C{=}CHOLi + H_2C{=}O}$ some of the values of the relative energies with respect to the electrostatic complex activation energies are negative (MP2/6-31G*//RHF/3-21G and MP2/6-31G*//RHF/6-31G*), indicating that the total energy of the transition state is lower than that of the electrostatic complex. At the MP2/6-31G* level of geometry optimization a transition structure does not exist. The values of the transition-state relative energies are internally consistent (i.e., values computed at the same methodological level are of similar order of magnitude), and one observes that the TSRE for the reaction with imine is larger than the corresponding value for formaldehyde. However, the values of the stabilization energies do not show any clear overall trend. One can say only that

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Table I. Total Energies[a] of the Reactants (RS), Electrostatic Complexes (EC), and Transition Structures (TS) for the Reactions of Li Enolate (Monomer and Dimer) with Formaldehyde and Imine Together with the Stabilization Energies (SE)[b] and the Transition-State Relative Energies (TSRE)[b]

basis set	RS	EC	TS	SE	TSRE
		$H_2C{=}CHOLi + H_2C{=}O$			
3-21G//3-21G	−272.143 00	−272.189 28	−272.184 41	−29.0	3.1
6-31G*//3-21G	−273.659 07	−273.692 00	−273.689 19	−20.7	1.8
MP2/6-31G*//RHF/3-21G	−274.395 68	−274.440 99	−274.448 83	−28.4	−4.9
6-31G*//6-31G*	−273.661 60	−273.696 30	−273.692 54	−21.8	2.4
MP2/6-31G*//RHF/6-31G*	−274.394 81	−274.430 36	−274.435 98	−22.3	−3.5
MP2/6-31G*	−274.410 63	−274.445 46		−28.9	
		$(H_2C{=}CHOLi)_2 + H_2C{=}O$			
3-21G//3-21G	−431.176 86	−431.215 32	−431.205 45	−24.1	8.1
		$H_2C{=}CHOLi + H_2C{=}NH$			
3-21G//3-21G	−252.415 96	−252.467 50	−252.432 04	−32.3	22.3
6-31G*//3-21G	−253.821 73	−253.860 79	−253.831 59	−24.5	18.3
MP2/6-31G*//RHF/3-21G	−254.542 47	−254.596 86	−254.584 19	−34.1	8.0
6-31G*//6-31G*	−253.823 80	−253.863 05	−253.834 00	−24.6	18.2
MP2/6-31G*//RHF/6-31G*	−254.543 20	−254.597 53	−254.584 02	−34.1	8.5
MP2/6-31G*	−254.558 53	−254.600 57	−254.586 46	−26.4	8.9

[a] Values in au. [b] Values in kcal/mol.

Table II. Total Energies[a] of the Reactants (RS), Electrostatic Complexes (EC), and Transition Structures (TS) for the Reactions of Li Enolate with $H_2C{=}NX$ (X = H, SiH_3, Li) Together with Stabilization Energies (SE)[b] and the Transition-State Relative Energies (TSRE)[b]

basis set	RS	EC	TS	SE	TSRE
		X = H			
3-21G//3-31G	−252.415 96	−252.467 50	−252.432 04	−32.3	22.2
6-31G*//3-21G	−253.821 73	−253.860 79	−253.831 59	−24.5	18.3
MP2/6-31G*//RHF/3-21G	−254.542 47	−254.596 86	−254.584 19	−34.1	8.0
		X = SiH_3			
3-21G*//3-21G*	−541.040 93	−541.086 86	−541.059 38	−28.8	17.2
6-31G*//3-21G*	−543.911 71	−543.949 78	−543.925 14	−23.9	15.5
MP2/6-31G*//RHF/3-21G*	−544.706 68	−544.769 39	−544.764 99	−39.4	2.8
		X = Li			
3-21G//3-21G	−259.255 14	−259.312 96	−259.243 54	−36.3	43.6
6-31G*//3-21G	−260.673 98	−260.740 64	−260.676 77	−41.8	40.1
MP2/6-31G*//RHF/3-21G	−261.404 57	−261.489 90	−261.454 23	−53.5	22.4

[a] Values in au. [b] Values in kcal/mol.

the stabilization energies are quite large (about 20–30 kcal/mol) and of similar order of magnitude for the two reactions.

We now turn our attention to the effect of substituents on the imine moiety. The energetic data for the reactions of lithium acetaldehyde enolate with imine, lithium imine, and silylimine are listed in Table II and the relevant geometrical parameters are shown in Figures 1–3. The effect of the substituents is unambiguous. The replacement of the imine hydrogen with lithium increases significantly the activation energy of the reaction, while the replacement with a silyl group lowers the activation energy.

In the preceding study, we have used monomeric lithium enolates. As we have pointed out in the Introduction, several enolates have been shown to aggregate in solution, thus affecting the stereochemistry and the reaction energy. Accordingly, in order to obtain information about the effect of aggregation upon the reactivity of lithium enolates, we have investigated the reaction between the lithium enolate dimer and formaldehyde $(H_2C{=}CHOLi)_2 + H_2C{=}O$ at the SCF/3-21G level. The most relevant geometrical parameters are given in Figure 4, while the total energy values together with the stabilization and activation energies are given in Table I. The most significant change from monomer to dimer is the activation energy which is almost three times larger (8.1 versus 3.1 kcal/mol). The stabilization energy remains almost unchanged. Also, the structures of the various critical points are very similar to those obtained with the monomer.

3. Discussion and Rationalization

The attack of monomeric Li enolate with formaldehyde has already been investigated by Houk et al.[8] at the 3-21G SCF level, where both an electrostatic complex and a cyclic transition state have been found (see Figures 1 and 2). The geometry of the electrostatic complex found by Houk et al. differs somewhat from that found here at the same computational level; however, the potential energy surface in this region is very flat. As already pointed out, the inclusion of dynamic correlation modifies significantly the energy profile of this reaction. In fact, at the SCF level there is an activation barrier of 2–3 kcal/mol; in contrast, the barrier disappears at the MP2 level and the reaction proceeds directly from reactants to product. On the other hand, at all computational levels a minimum corresponding to the electrostatic complex has been found: this minimum is well defined at the SCF level, but just an inflection point at the MP2 level.

The use of monomeric lithium enolates could represent a drastic oversimplification of what happens in solution, since in these conditions there are indications that these species exist as dimers and tetramers. However, the results obtained for the attack of the Li enolate dimer with formaldehyde show that the changes due to aggregation

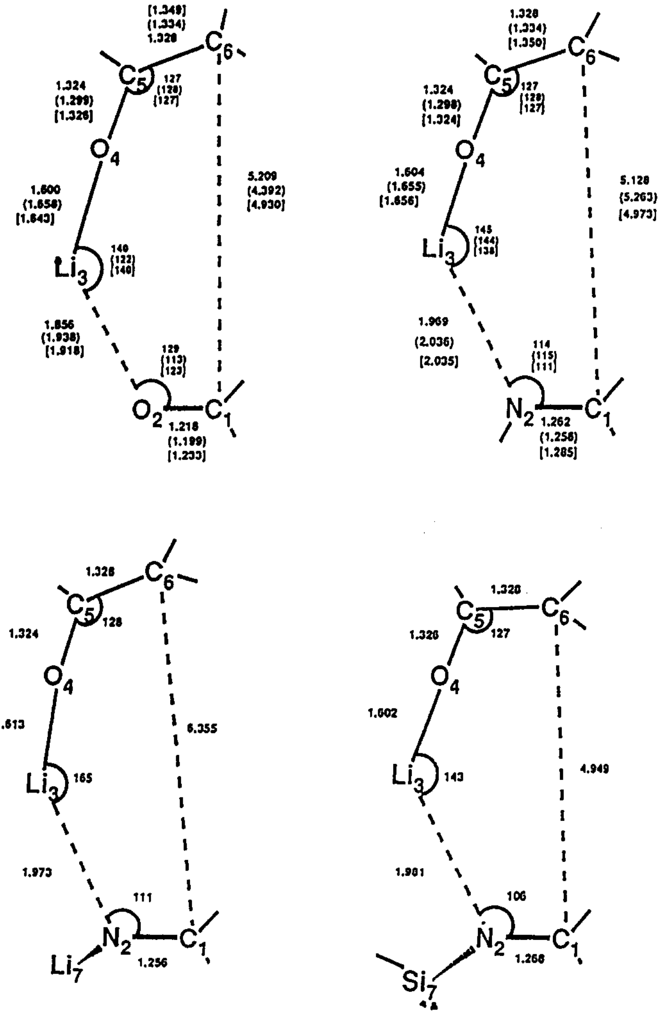

Figure 1. Calculated electrostatic complexes for the reactions with formaldehyde, imine, and substituted imines. The parameters (in Å and deg) are given at the following levels: 3-21G, 6-31G* (in parentheses), and MP2/6-31G* (in square brakets).

are limited mainly to the activation energy. The results of Table I show, in fact, that energetically the most significant change concerns the large increase of the activation energy which is almost three times larger (8.1 versus 3.1 kcal/mol), while the stabilization energy remains almost unchanged. Also the structures of the various critical points are very similar to those obtained with the monomer (see Figure 4). It is found, in fact, that the electrostatic complex is planar and the transition state has a half-chair structure, with similar geometrical parameters. The more relevant structural variations concern the values of the O–Li bonds which are significantly longer than the corresponding values obtained for the monomer. Since the results obtained for the dimer attack are similar to those obtained with the monomer (except for the activation energy), the study of substituent effects on the imines can be adequately simulated with the Li enolate monomer.

The energy profile for the attack of Li enolate with imine is significantly different from that between Li enolate and formaldehyde. In this case, at the SCF and MP2 levels, the reaction involves both an electrostatic complex and a transition state. The stabilization energy is of the same order of magnitude found for the both reactions (about 20–30 kcal/mol). However, while the activation energy is small or nonexistent for the formaldehyde reaction, there is a significant barrier for the imine (about 20 kcal/mol at the SCF level to values of about 9 kcal/mol at the MP2 level). The structures of the electrostatic complex and of the transition state are very similar for both reactions (see Figures 1–3). Thus, both reactions proceed in two stages. In the first stage there is the formation of an electrostatic complex, slightly pronounced in the case of formaldehyde and well defined in the case of imine. In this stage the reaction leads to the formation of the O–Li and N–Li bonds, while in both cases the C–C bond is still very long. The second stage of the reaction involves the formation of the C–C bond. The differences between the imine reaction and the formaldehyde reaction can be rationalized qualitatively. This process can be considered an intramolecular nucleophilic attack of the carbon center of the enolate on the carbon of formaldehyde or imine. Thus, the barrier should depend on the energy of the LUMO (π^*) of the formaldehyde or imine fragment. As the energy of the LUMO is decreased, the barrier is lowered and the transition state shifts toward the reactants. The energy of this LUMO in turn correlates with the electron affinity of the heteroatom. Thus, the reaction is extremely facile in the case of formaldehyde where the large electron affinity of the carbonyl oxygen makes the electron transfer very easy, with the result that the overall process becomes very exothermic, without any activation barrier. The fact that the electron affinity of the imine nitrogen is smaller makes the process more difficult, with the result that in this case there is a significant activation energy. These observations are consistent with the results of our computations which show that for the attack on $H_2C{=}NH$ the activation energy

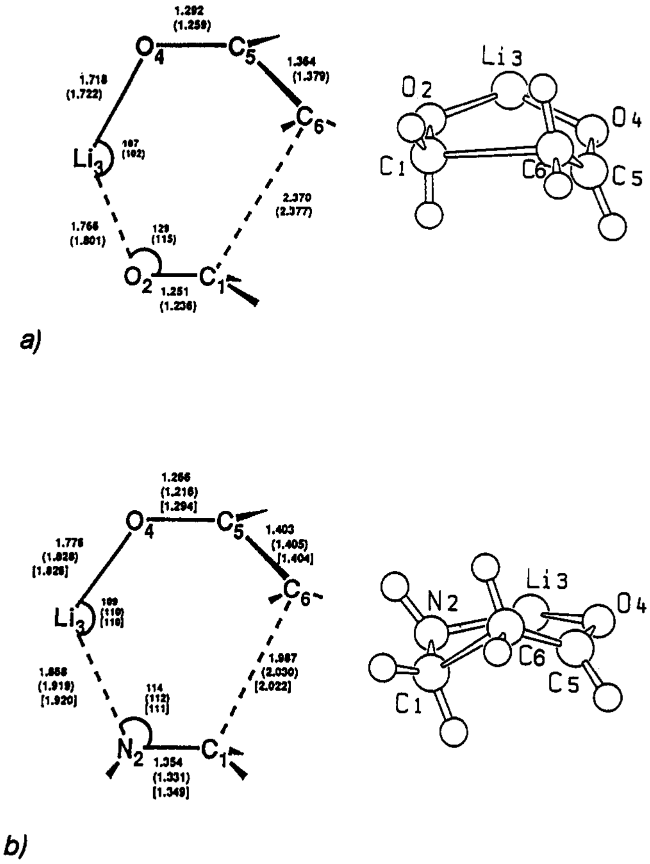

Figure 2. Calculated transition structures for the reactions with formaldehyde (a) and imine (b). The parameters (in Å and deg) are given at the following levels: 3-21G, 6-31G* (in parentheses), and MP2/6-31G* (in square brakets).

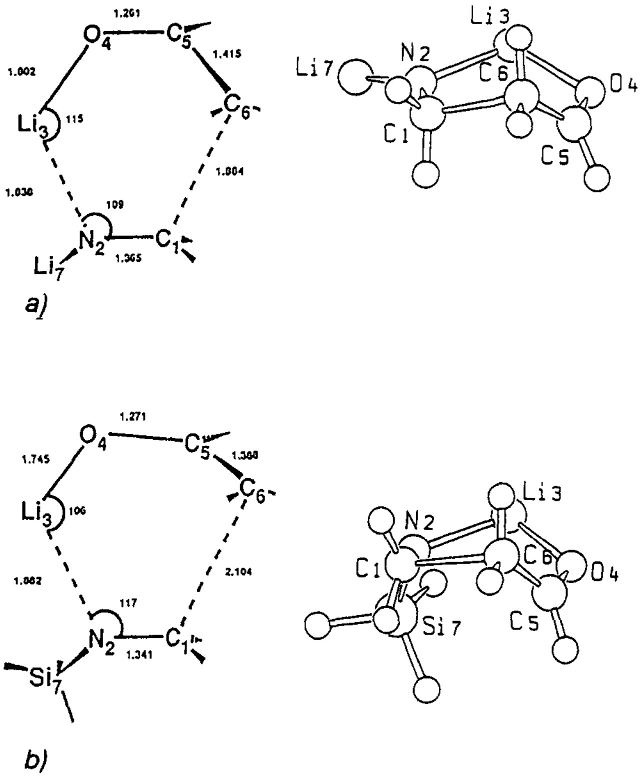

Figure 3. Calculated transition structures for the reactions with lithium imine (a) and silylimine (b). The parameters (in Å and deg) are given at the 3-21G level for lithium imine and at 3-21G* level for silylimine.

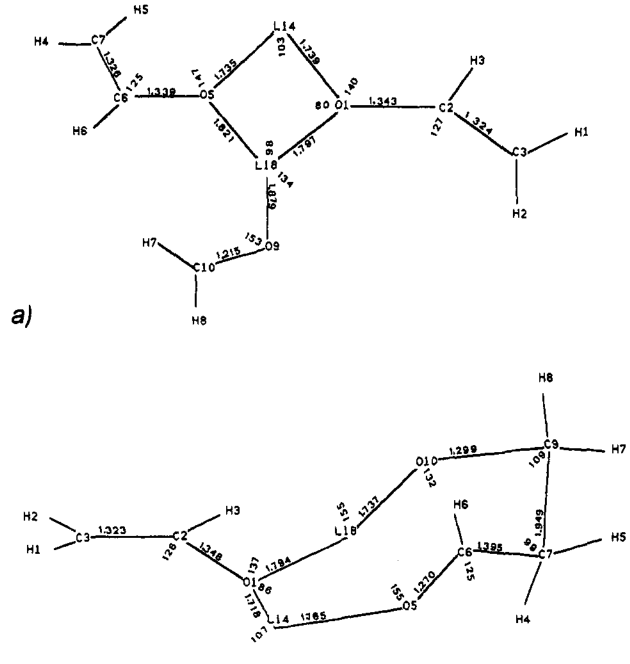

Figure 4. Calculated electrostatic complex (a) and transition structures (b) for the reaction of the lithium enolate dimer with formaldehyde. The parameters (in Å and deg) are given at the 3-21G level.

is larger and the transition structure occurs at smaller values of the reaction coordinate.

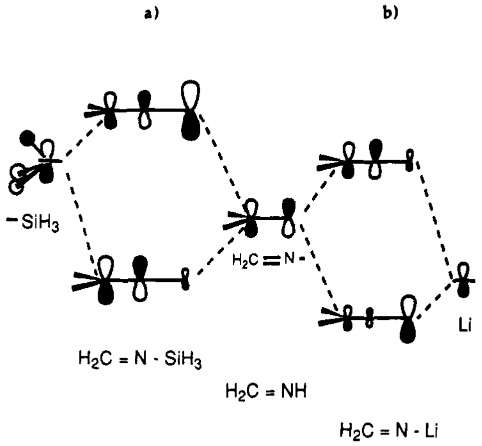

Figure 5. Interaction diagram between (a) the LUMO of imine and the 2pπ orbital of lithium and (b) the LUMO of imine and the π^* MO of the SiH_3 group.

The effect of the substituents in the imine moiety can be rationalized in a similar fashion. The replacement of the imine hydrogen with lithium increases significantly the activation energy of the reaction while the replacement with a silyl group lowers the activation energy. The effect of substituents on the LUMO of the imine can be easily explained in terms of the orbital interaction diagram of Figure 5, which illustrates the effect of the interaction of the LUMO of imine with the $2p_\pi$ orbital of lithium and the $\pi^*(SiH_3)$ MO of the SiH_3 fragment. The key features here are the following: (i) the $2p_\pi$ orbital of lithium is lower in energy than the imine LUMO, and (ii) the π^* MO of the SiH_3 fragment is higher in energy than the imine LUMO. Consequently, lithium raises the imine LUMO and the silyl group lowers the imine LUMO. Consequently, the barrier for the reaction has the trend Li > H > SiH_3, and position of the transition state follows the reverse trend (i.e., C–C distance in the transition state corresponds to SiH_3 (2.1 Å) > H (1.97 Å) > Li (1.88 Å)).

4. Conclusions

In this paper we have investigated the reaction mechanism of the aldol condensation between the acetaldehyde Li enolate and imine at various SCF and SCF/MP2 levels including the effects of substituents in the imine.

The reaction with imine proceeds through the formation first of an electrostatic complex and then of a transition state with an activation energy of about 9 kcal/mol at the MP2/6-31G* level. At the same computational level the transition state for the reaction with formaldehyde disappears and this reaction proceeds directly from reactants to product. In the investigation of the effects of substituents in the imine one finds that the substitution of the imine hydrogen with lithium increases the activation energy, while the substitution with a silyl group lowers it.

The various trends of the activation energies, of the main geometrical features of the transition states, and of the effects of imine substituents can be rationalized in terms of the LUMO of the formaldehyde or imine fragment. The various trends are thus controlled by the electron affinity of the electrophile and provide an explanation of the experimental observation that with a silyl substituent the reaction is very fast. In fact, a preliminary experiment showed that a reaction between equimolecular amounts of the lithium enolate of ethyl isobutyrate, the *N*-trimethylsilylimine and the *tert*-butylimine of benzaldehyde leads to the almost exclusive formation of 3,3-dimethyl-4-phenylazetidin-2-one.[14]

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Supplementary Material Available: Tables 3–17, containing geometrical parameters and energy values (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Cainelli, G.; Panunzio, M. Work in progress.