A Computational Study of the 1,4-Addition of Lithium Enolates to Conjugated Carbonyl Compounds

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The MNDO potential energy surface for the reaction of acetaldehyde lithium enolate with acrolein was studied. Two water molecules were used to mimic ether solvent. Relative energies of stationary points were computed at the 3-21G//MNDO level. Four cyclic eight-membered transition structures **8–11** could be located, which allowed a qualitative rationalization of the observed stereoselectivity trends in the title reaction. The effects of enolate geometry and 3-enone substituent were evaluated at this level. Transition structure geometries were also optimized by ab initio molecular orbital calculations (3-21G) on the unsolvated structures **20–23**. The ab initio optimized geometries were found to be very similar to the MNDO-optimized geometries. The relative energies of **20–23** were computed up to the MP2/6-31G*//3-21G level, which helped to explain the unrealistically high stereoselectivity predicted at the 3-21G//MNDO level.

Introduction

The stereochemistry of the Michael addition of ketone and ester lithium enolates to conjugated carbonyl compounds has recently been the focus of several studies.[1-4] The stereochemical outcome of this reaction appears to be influenced by a variety of factors; however some general trends have been identified.[1] Although some exceptions have been found,[2,3] the configuration of the Michael adducts appears to be determined by the configuration of the reacting partners. In most cases, addition of *E*(*Z*) enolates to *E* acceptors results in selective formation of the syn (anti) diastereomer (Scheme I). With *Z* acceptors the opposite is true, i.e., *E*(*Z*) enolates tend to give the anti (syn) diastereomer, generally with lower selectivity. These trends are usually reinforced by the presence of bulky substituents on the enolate and the acceptor.

The experimental data[1] suggest that at low temperature (−78 °C) these reactions are kinetically controlled. The results of intramolecular Michael addition in aprotic solvents indicate that transfer of the metal ion from the enolate to the acceptor takes place in the transition state. On the basis of these findings, Heathcock and Oare have suggested that the stereochemical outcome of enolate Michael addition can be rationalized by assuming that the reaction occurs through cyclic, eight-membered transition structures (TS), in which the enone moiety takes up the s-cis conformation.

We recently reported that four cyclic eight-membered TSs can indeed be located on the MNDO potential energy surface for the reaction of acetaldehyde lithium enolate with acrolein. Two of them arise from attack on the s-cis conformation of the enone, the other two from attack on the s-trans conformer. The relative 3-21G//MNDO energy differences were also computed and a qualitative rationalization of the observed stereoselectivities was attempted on this basis.[5]

This study has now been expanded to analyze the substituent effect on the relative stability of the TSs. The unsubstituted structures have also been optimized at the HF/3-21G level and their relative energies evaluated at the MP2/6-31G*//3-21G level. Our results are reported herein.

Methods

Computational Methods. Semiempirical calculations were carried out using standard MNDO procedures, as implemented in MOPAC 5.0 or 6.0.[6] Transition structures were located approximately by the reaction coordinate method (vide infra) and refined by minimizing the norm of the gradients. All stationary points were fully characterized by computing analytical force constants.

The major shortcoming in the use of MNDO for calculations involving lithium compounds is the known tendency of this method to predict lithium interactions with carbon too stable by approximately 30 kcal/mol.[7] This can lead in some cases to unrealistic geometries. In particular for lithium enolates, the lithium-bridged forms are overstabilized. In order to minimize this problem, all MNDO calculations were carried out on structures where the lithium moiety is coordinated to two water molecules, mimicking ether solvation.

Ab initio, single-point energies of structures **4–19** were computed with the 3-21G basis set[8] using Gaussian 88 or Gaussian 90.[9] It has been shown that for lithium compounds the use of MNDO geometries followed by a single-point ab initio calculation yields a potential energy surface which reproduces the qualitative features of the fully optimized ab initio surface.[10]

To assess this point in the case at hand, transition structures **20–23** were optimized at the 3-21G level and compared to the MNDO-optimized geometries **8–11**. The HF/3-21G optimized TSs **20–23** (Figure 8) were generated by removing the solvent ligands from **8–11**, partially optimized by constraining the forming C–C bond, and finally optimized to a first-order saddle point using Baker's algorithm.[11] Computation of the analytical Hessians showed that all these critical points are transition structures with the direction of the negative curvature corresponding to the formation of the carbon–carbon bond. Single-point energy calculations for structures **20–23** were carried out with the 6-31G* basis set,[12] and MP2 corrections were applied.[13]

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(1) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227 and references therein.

(2) (a) Viteva, L.; Stefanovsky, Y. *J. Chem. Res., Synop.* **1990**, 232. (b) Viteva, L.; Stefanovsky, Y. *Tetrahedron Lett.* **1990**, 5469.

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(8) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(9) Frisch, M. J., Head-Gordon, M., Trucks, G. W., Foresman, J. B., Schlegel, H. B., Raghavachari, K., Robb, M. A., Binkley, J. S., Gonzalez, C., Defrees, D. J., Fox, D. J., Whiteside, R. A., Seeger, R., Melius, C. F., Baker, J., Martin, R. L., Kahn, L. R., Stewart, J. J. P., Topiol, S., and Pople, J. A., Gaussian 90, Inc., Pittsburgh, PA, 1990.

(10) McKee, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 559 and references therein.

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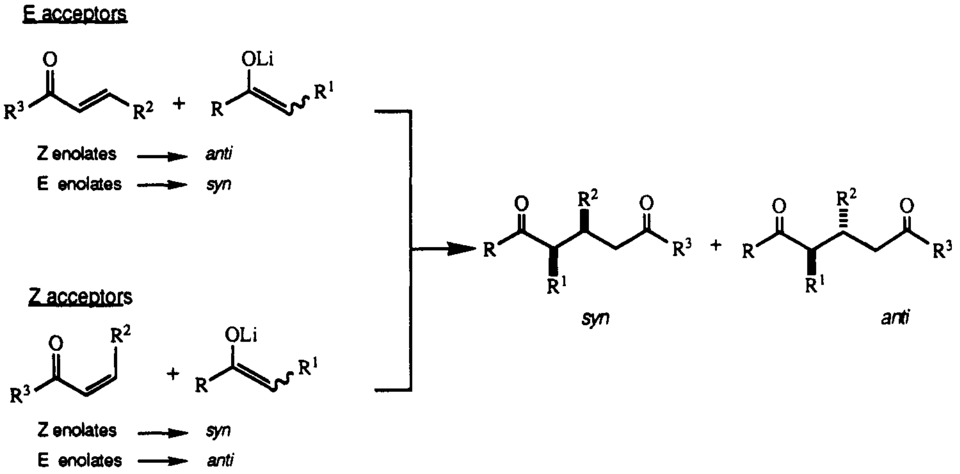
(12) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *16*, 217.

(13) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. De Frees, D. J.; Levi, B. A.; Pollack, S. K.; Hehre, W. J.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4085.

0022-3263/92/1957-7029$03.00/0

Scheme I. Michael Addition of Lithium Enolates to Conjugated Carbonyl Compounds



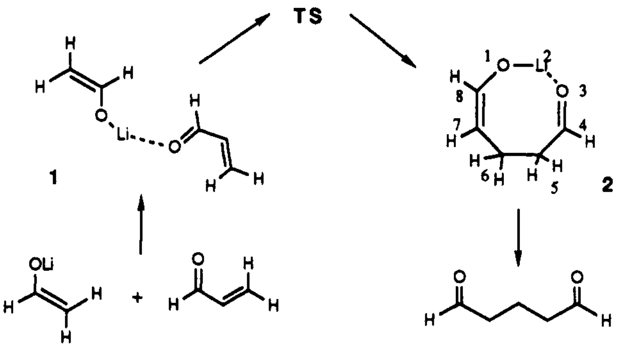


Figure 1. Reaction pathway for the addition of acetaldehyde lithium enolate to acrolein.

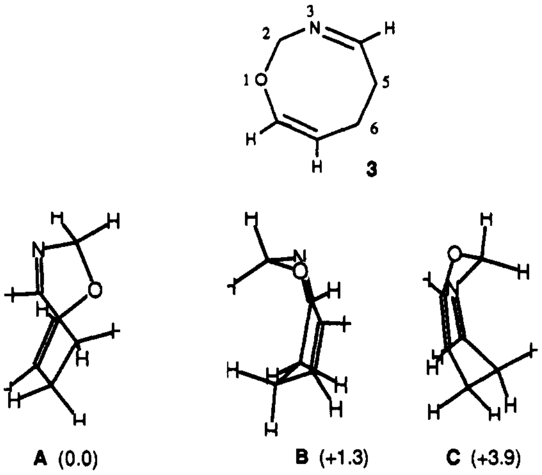


Figure 2. MM2-minimized low energy conformations of model 3 (MM2 relative energies, kcal/mol).

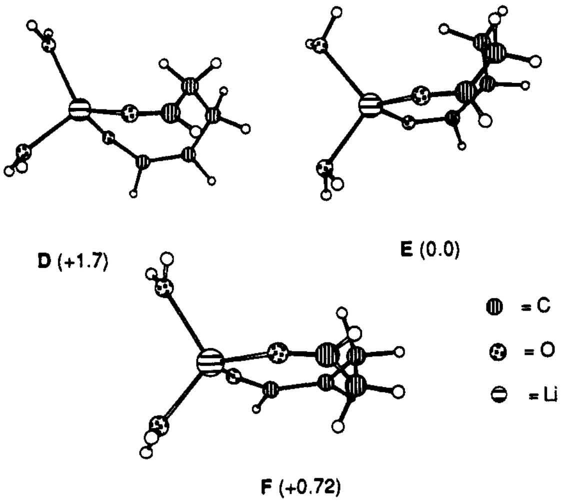


Figure 3. MNDO-minimized conformers of water-solvated 2 (MNDO relative energies, kcal/mol).

The bond distances of structures 4–23 are collected in Table V. Their Cartesian coordinates are available as supplementary material.

TS Location Strategy. Earlier theoretical studies on carbonyl addition reactions of lithium enolates[14] indicate that, in the gas phase, the 1,4-addition pathway should begin with carbonyl–lithium coordination to give complex 1 (Figure 1). From 1, formation of the C–C bond through transition structures TS should lead to the addition product as a lithium enolate. On the assumption that the addition takes place through cyclic structures containing an s-cis configurated enone, the reaction product should appear as an eight-membered ring containing a *Z*-configurated enolate, as depicted in 2.

We chose 2 as the starting point for computing the reaction pathway. This choice greatly simplifies the conformational problems connected with bringing together the two carbon ends of complex 1 to form the cyclic TS.[15]

In order to sample the conformational space accessible to 2, we used molecular mechanics and model compound 3 (Figure 2). A conformational search of 3 using the Multic[16] mode of MacroModel[17] at 30° resolution and the MM2 force field found three structures (**A**, **B**, **C**) within 4 kcal/mol from the global minimum **A**.[15]

Substitution of C-2 with a lithium atom and of N-3 with an oxygen atom gave rise to three conformers of 2. Two water molecules solvating the lithium ion were added at a 2-Å distance, and the three structures were minimized using MNDO to give conformers **D**, **E**, and **F** (Figure 3).

The forming carbon–carbon bond (C5···C6 in 2) was chosen as the reaction coordinate. The reaction path was calculated for the *breaking* of the 5-6 bond, starting for all three minimum structures **D**–**F**, by systematically increasing the bond length value in successive increments and optimizing all the remaining geometrical parameters. The geometries corresponding to the maximum potential energy along the three paths were then fully optimized by gradient minimization routines and characterized as true transition states by calculating force constants. Starting from

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[14] (a) Li, Y.; Paddon-Row, M.; Houk, K. N. *J. Am. Chem. Soc* **1988**, *110*, 3684; *J. Org. Chem.* **1990**, *55*, 481. (b) Leung-Toung, R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, *112*, 1042.

[15] For the conformational analysis of cyclooctane, see: Anet, F. A. L. *Top.Stereochem.* **1974**, *8*, 159. Ferguson, D. M.; Raber, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4371 and references therein.

[16] Lipton, M.; Still, W. C. *J. Comp. Chem.* **1988**, *9*, 343.

[17] Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.

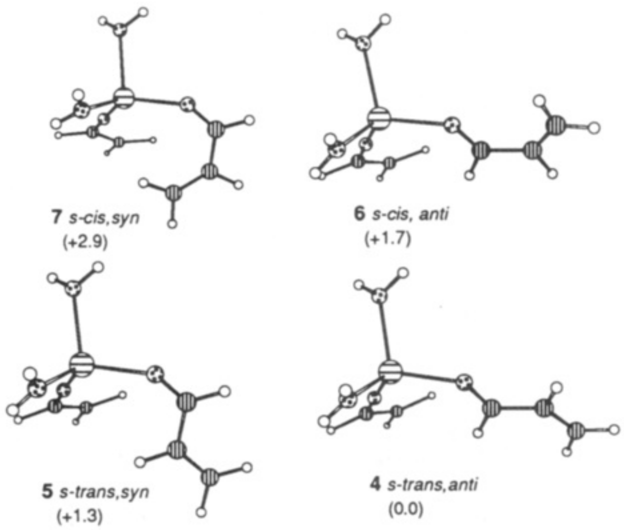


Figure 4. MNDO-optimized geometries of the solvated lithium enolate complex for the reaction of acetaldehyde lithium enolate with acrolein (3-21G//MNDO relative energies, kcal/mol).

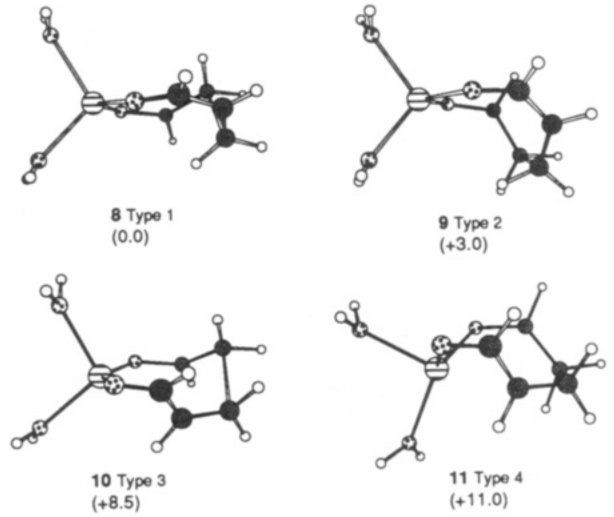


Figure 5. MNDO transition structures for the reaction of acetaldehyde lithium enolate and acrolein. Two water molecules mimic ethereal solvent (3-21G//MNDO relative energies, kcal/mol).

D–F two structures, **8** (from **F**) and **9** (from **D** and **E**), were found (Figure 5).

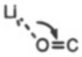
Following the reaction coordinate from **8** to the starting material, the s-cis,syn conformation **7** of the initial complex was localized (Figure 4. The first descriptor refers to the enal conformation, the second to Lewis acid complexation). From **7**, rotation around the single bonds and reoptimization led to the three other possible conformers **4–6**. All the structures in Figure 4 were characterized as true minima by vibrational analysis.

Starting from the s-trans complexes **4** and **5** and following the reaction path for the *formation* of the C–C bond led to two additional TSs, **10** and **11** (Figure 5), which were characterized by the presence of a single negative eigenvalue in their Hessian matrix. Finally, starting from the s-cis,anti complex **6**, the same process led to TS **9**. In general, every attempt to locate transition structures featuring an anti arrangement of the lithium atom and the enone double bond proved to be unsuccessful.

Results and Discussion

In the gas-phase, reaction of a lithium enolate with an aldehyde occurs through carbonyl–lithium complexation to give the reactive complex **1** (Figure 1).[14] The four possible water-solvated, lithium-coordinated complexes (**4–7**) are collected in Figure 4 with their relative 3-21G//MNDO energies.

Table I. 3-21G//MNDO Energies and Geometrical Features of 4–7

str	energy (−au)	rel energy (kcal/mol)	 ϕ (deg)	 χ (deg)	 ω (deg)
4	499.88381	0.0	124.0	−171.3	169.5
5	499.88169	+1.3	132.9	169.3	−28.7
6	499.88108	+1.7	123.7	2.8	172.0
7	499.87914	+2.9	132.8	−14.9	−23.6

These structures differ by the conformation of the enone portion, which is s-cis (χ = ca. 0°, in **6** and **7**, see Table I), or s-trans (χ = ca. 180°, in **4** and **5**), and by the geometry of complexation, i.e., the relative disposition between the lithium atom and the α-carbon of acrolein, which is syn (ω = ca. 0°, in **5** and **7**) or anti (ω = ca. 180°, in **4** and **6**). At the 3-21G//MNDO level the s-trans,anti geometry of **4** is found to be the minimum energy one. Syn metal coordination and the s-cis conformation of the enone "cost" ca. 2 kcal/mol (cf. **4** vs **6**, and **5** vs **7**) and ca. 1 kcal/mol (cf. **4** vs **5** and **6** vs **7**), respectively, with an additive effect in the s-cis,syn isomer **7** (ca. **4** vs **7**).

The structure of lithium-coordinated acrolein was investigated at the 3-21G//3-21G level by Houk,[18] and a 1.9 kcal/mol ΔE was calculated to exist between the s-trans,anti and the s-trans,syn conformers. Both conformers were found to exhibit a linear, planar geometry of complexation, which appears to be a general feature of the ab initio gas-phase calculations of the Li^+ carbonyl complexes.[19] Structures **4–7** are significantly more bent (Table I, $124° \leq \Phi \leq 132.9°$, $24° \leq \omega_{syn} \leq 29°$; $169° \leq \omega_{anti} \leq 172°$). However, it has been suggested[20] that the linear, planar geometry calculated in the gas phase could be an artifact of the unrealistic coordination number of lithium (=2) in these calculations. In fact, a recent inspection of the Cambridge Structural Database[20] has shown that, in the solid state, bent geometries are favored. The average Li–O bond length of 1.99 ± 0.07 Å and the average Li—O=C bond angle of 139 ± 3° reported in this survey compare very well with those calculated for structures **4–7** and collected in Table I.

The structure of the enolate moiety in complexes **4–7** compares favorably with the structures found by previous investigations at various computational levels[10,14] and with the available experimental data.[21–23]

From the s-trans,anti complex **4** to the product **2** (lowest energy conformer, **E**) the reaction is calculated to be exothermic by 18 kcal/mol, with a barrier of 8 kcal/mol (3-21G//MNDO data).

In principle, each activated complex can generate two diastereomeric transition structures, depending on which enantioface of the enolate attacks the enone moiety. This

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(18) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(19) (a) Russegger, P.; Schuster, P. *Chem. Phys. Lett.* **1973**, *19*, 254. (b) Raber, D. J.; Raber, N. K.; Chandrasekhar, J.; Schleyer, P. v. R. *Inorg. Chem.* **1984**, *23*, 4076.

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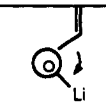
(21) Lynch, T. J.; Newcomb, M.; Bergbreiter, D. E.; Hall, M. B. *J. Org. Chem.* **1980**, *45*, 5005.

(22) (a) Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, 3931. (b) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

(23) (a) It is well known that lithium enolates exist as aggregates in ethereal solutions. For a review, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein. (b) The X-ray structure of tetrameric sodium pinacolonate solvated by pinacolone has been solved, and the informations it gives on how performed ketone–enolate complexes react have been discussed. See ref 14a.

Table II. 3-21G//MNDO Energies and Salient Geometrical Features of 8–11

str	3-21G// MNDO energies (–au)	rel energy (kcal/mol)	r(C···C) (Å)	 α_N (deg)	 α_E (deg)	 ϕ (deg)	 θ (deg)	 χ (deg)	 ω (deg)	 ψ (deg)
8	499.87085	0.0	2.31	108.1	103.7	138.8	–121.4	–12.8	–32.4	–34.5
9	499.86575	+3.0	2.30	114.2	104.1	134.9	–38.7	–10.3	–41.3	79.2
10	499.85730	+8.5	2.31	108.1	102.3	91.0	–51.0	154.6	–37.6	–43.3
11	499.85319	+11.0	2.29	109.6	102.9	86.1	52.9	158.2	–44.1	40.8

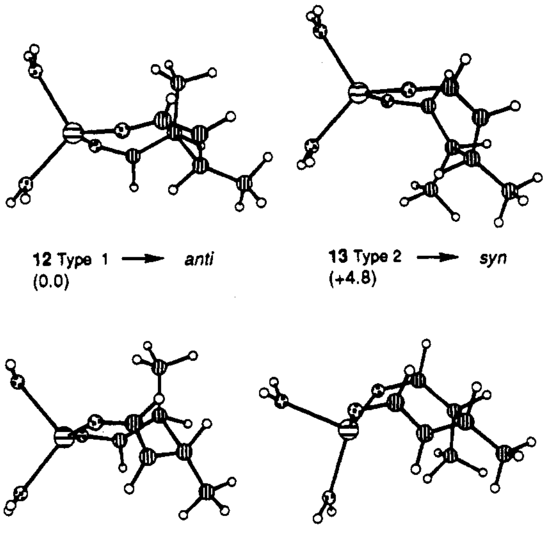
would give rise to eight possible structures (plus their conformational isomers). In fact only four TSs (8–11) (Figure 5) could be located on the MNDO hypersurface, all of them featuring a syn relationship between the metal and the enal double bond ($44° \leq \omega \leq 32°$, see Table II). Their salient geometrical features are collected in Table II, together with their 3-21G//MNDO relative energies.

The lower energy structures **8** (type 1 geometry) and **9** (type 2 geometry) derive from the attack of the enolate to the s-cis configurated acrolein. Type 2 geometry can be described as a half-chair-twist-boat.[16] Type 1, on the other hand, is a very distorted half-chair-chair. Its most striking feature is the total lack of staggering around the forming bond (ϑ = 121.4°). This feature, however, does not appear to be peculiar of the transition state, since the same dihedral angle is also found in the **F** conformation of the product enolate (see Figure 3). The relative stability of **8** compared to **9** appears to be due to the C=C—O—Li torsional angle ψ in the enolate moiety, which is closer to the ideal 0° (ψ_8 = 34.5°, ψ_9 = 79.2°).[10,14,21] Compared to **9**, structure **8** also reduces the repulsion between the lone pairs on the oxygen atoms ($d(\mathrm{O{-}{-}O})_8$ = 3.576 Å, $d(\mathrm{O{-}{-}O})_9$ = 3.362 Å). Apart from the lack of staggering in **8**, these two structures are essentially coincident with those proposed by Heathcock to rationalize the stereochemical outcome of the reaction.[1]

Attack of the enolate to the s-trans,syn (χ = 180°, ω = 0°, see Table II) conformation of the lithium-coordinated acrolein gives rise to the less stable structures **10** (type 3 geometry) and **11** (type 4 geometry). Ground-state studies of Lewis acid-coordinated α,β-unsaturated carbonyl compounds[18,20] and our own calculations on the activated complexes **4–7** suggest that this conformation should be largely favored over the s-cis,syn ($\chi = \omega$ = ca. 0°, see Table II) conformation involved in structures **8** and **9**. However, the s-trans configuration of the enone is equivalent to introducing a trans double bond in the 8-membered ring. This cannot happen without introducing some strain in the molecule. For instance, the O–Li bond lengths stretch from the ca. 2.0 Å found in **8** and **9** (see Table V) to 2.2 and 2.3 Å in **10** and **11**, respectively. Moreover, the C=O—Li bond angle φ in **10** and **11** is close to 90°, a highly unfavorable arrangement that surely contributes to the high energy of these structures.

Another interesting geometrical feature displayed by structures **8–10** is the nearly coplanar disposition of the lithium cation and the four adjacent atoms. This geometry is also observed in the 3-21G transition structure for the 1,2-addition of lithium enolates to carbonyl compounds,[13] and, perhaps more importantly, in the X-ray structures of tetrameric enolate complexes and aldolate products.[22,23] With this in mind, the bending out of plane of the lithium atom which is apparent in structure **11** appears to be rather unlikely and could be originated by the MNDO overestimation of carbon–lithium bond energy, which we have already discussed.

Contrary to the aldol reaction where two chair TSs and two boat TSs can be generated for a given enolate stereochemistry depending on the equatorial or axial position of the aldehyde substituent, the substitution pattern of TSs **8–11** is fixed once and for all by the configuration of the starting material. This means, for instance, that for a given combination of reactants (say a Z-enolate and a E-enone) there can be one and only one (enantiomeric pair of) type 1 TS. Moreover, for a given combination of reactants, each TS type can lead to one and only one (enantiomeric pair of) reaction product. Let us examine for example the addition of propionaldehyde Z-enolate to (E)-crotonaldehyde (Figure 6).



12 Type 1 ⟶ anti (0.0)

13 Type 2 ⟶ syn (+4.8)

14 Type 3 ⟶ syn (+8.6)

15 Type 4 ⟶ anti (+13.3)

Figure 6. MNDO transition structures for the reaction of propionaldehyde lithium enolate (Z-configuration) and (E)-crotonaldehyde. Two water molecules mimic ethereal solvent (3-21G//MNDO relative energies, kcal/mol).

Type 1 TS **12** and type 4 TS **15** (are originated by *ul* approach of the reagents and) give rise to the anti adduct, whereas type 2 **13** and type 3 **14** (formed by the *lk* approach) give rise to the syn isomer. The 3-21G//MNDO relative energies reported in Figure 6 show that preferential formation of the anti adduct is expected from this reaction, which is in qualitative agreement with the experimental findings.

Likewise, addition of the E-enolate of propionaldehyde to (E)-crotonaldehyde occurs through the four TSs depicted in Figure 7.

Type 1 **16** and type 4 **19** (*lk* topicity) lead to the syn reaction product, and type 2 **17** and type 4 **18** (*ul* topicity) lead to the anti isomer. The 3-21G//MNDO relative energies predict preferential syn isomer formation and are again in qualitative accord with the experimental data.

From a more quantitative point of view the energy differences calculated are too large compared with the experimental diastereomeric ratios. The latter are of synthetic value only if either the α enolate substituent R^1

Table III. Salient Geometrical Features of 20–23

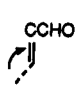
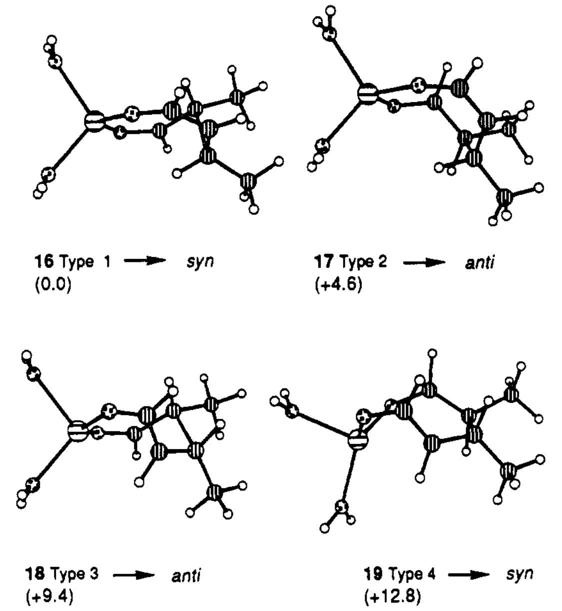
str	r(C···C) (Å)	 α_N (deg)	 α_E (deg)	 ϕ (deg)	 θ (deg)	 χ (deg)	 ω (deg)	 ψ (deg)
20	2.30	110.8	96.7	140.4	−125.5	−9.1	−26.7	−24.4
21	2.28	121.9	92.8	138.3	−52.5	−8.9	−35.6	105.1
22	2.21	108.6	97.7	100.3	−39.0	149.3	−48.3	−49.4
23	2.20	107.7	96.9	97.1	52.2	155.2	−68.8	67.4

Table IV. Total Energies (−au) and Relative Energies (in Parentheses, kcal/mol) of Structures 20–23

str	3-21G//3-21G	6-31G*//3-21G	MP2/ 6-31G*//3-21G
20	348.65040	350.57635	351.58695
(type 1)	(0.0)	(0.0)	(0.0)
21	348.64306	350.57190	351.58152
(type 2)	(+4.6)	(+2.8)	(+3.4)
22	348.63758	350.56824	351.58627
(type 3)	(+8.0)	(+5.1)	(+0.4)
23	348.63481	350.56643	351.58476
(type 4)	(+9.8)	(+6.2)	(+1.4)



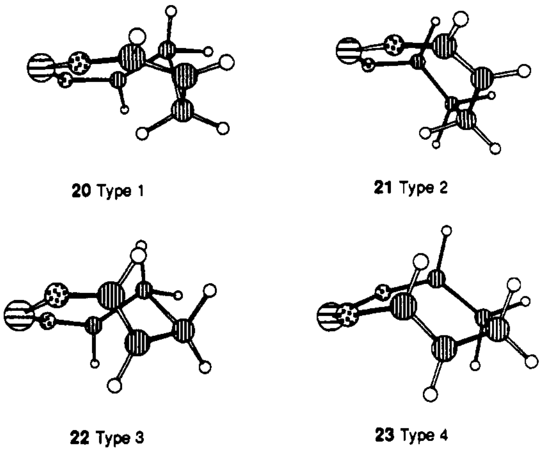
16 Type 1 → *syn*
(0.0)

17 Type 2 → *anti*
(+4.6)

18 Type 3 → *anti*
(+9.4)

19 Type 4 → *syn*
(+12.8)

Figure 7. MNDO transition structures for the reaction of propionaldehyde lithium enolate (E configuration) and (E)-crotonaldehyde. Two water molecules mimic ethereal solvent (3-21G//MNDO relative energies, kcal/mol).



20 Type 1

21 Type 2

22 Type 3

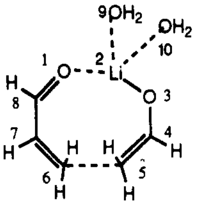
23 Type 4

Figure 8. 3-21G-optimized transition structures for the reaction of acetaldehyde lithium enolate and acrolein.

(see Scheme I) or the enone carbonyl substituent R^3 are bulky groups.[1] In conjunction with the lithium parametrization problems in MNDO, this fact raises some questions on the nature of the TSs we have located.

In order to clarify this point we proceeded to optimize the geometry of the four TSs at the 3-21G level. The solvent molecules were removed at this stage, to speed up calculations. The 3-21G optimized geometries (**20**–**23**) are reported in Figure 8 and Table III. The gross geometrical features of the ab initio optimized (**20**–**23**) and the MNDO optimized TSs (**8**–**11**, Figure 5, and Table II), as well as their 3-21G relative energies (Table IV), are very similar (compare **8** and **20** for type 1 geometry, **9** and **21** for type 2, **10** and **22** for type 3, and **11** and **23** for type 4). However, no bending out of plane of the lithium atom is now observed in type 4 TS **23**, and the Li···O bond lengths are reduced to 1.7–1.8 Å (see Table V), as a consequence of the absence of the external water ligands.

Table V. Calculated Bond Distances (Å)[a]



	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**20**[b]	**21**[b]	**22**[b]	**23**[b]
O_1–Li	2.144	2.134	2.145	2.134	2.064	2.069	2.242	2.289	1.744	1.746	1.816	1.811
O_3–Li	1.843	1.842	1.840	1.844	1.976	1.967	1.988	1.991	1.715	1.724	1.709	1.711
O_3–C_4	1.290	1.290	1.290	1.291	1.271	1.272	1.271	1.272	1.287	1.290	1.276	1.277
C_4–C_5	1.367	1.366	1.366	1.366	1.403	1.402	1.402	1.403	1.370	1.367	1.376	1.373
C_5–C_6					2.313	2.303	2.311	2.300	2.296	2.279	2.208	2.204
C_6–C_7	1.344	1.344	1.344	1.347	1.375	1.376	1.377	1.378	1.375	1.380	1.378	1.378
C_7–C_8	1.489	1.485	1.487	1.480	1.449	1.450	1.472	1.476	1.398	1.396	1.397	1.394
C_8–O_1	1.233	1.231	1.234	1.233	1.244	1.245	1.246	1.245	1.261	1.263	1.268	1.272
O_9–Li	2.178	2.187	2.180	2.201	2.164	2.161	2.179	2.169				
O_{10}–Li	2.158	2.164	2.160	2.174	2.158	2.153	2.159	2.199				

[a] MNDO geometries, unless otherwise noted. [b] 3-21G geometry.

In Table IV we have collected the calculated 3-21G, 6-31G*//3-21G, and MP2/6-31G*//3-21G energies of TSs **20**–**23**. Up to the first two levels, the energy differences between the transition structures do not differ sensibly from what expected on the basis of the 3-21G//MNDO data (see Table II). However, inclusion of electron correlation effects by second-order Møller–Plesset correction shows that type 3 and type 4 TS (both including an s-trans configurated aldehyde moiety) are much more stable than those calculated by 3-21G//MNDO. Since type 3 TS implies the opposite topicity compared to type 1 TS, this has a major implication on the stereochemical outcome of the reaction. In particular the critical dependence of the selectivity on the bulk of the enone carbonyl substituent R^3 could be explained by the well-known ground-state correlation in conjugated ketones between the size of R^3 and the relative population of the s-cis and s-trans conformations of the enone.[24] An increase in the bulk of R^3 has the effect of destabilizing the s-trans conformation by allylic strain, and therefore it increases the relative population of the s-cis conformer. If this feature is carried over to the TS, this should rule out a contribution by type 3 and type 4 geometry when R^3 is large. The stereochemical outcome would therefore depend only on the energy difference between type 1 and type 2 TSs, which are well separated at all computational levels. The effect of the enolate substituent R^1 is much less clear-cut and a detailed analysis of it must await for a higher level of theory calculation of substituted transition structures.

Conclusion

In conclusion, we have shown that four different cyclic, eight-membered transition structures can be located for the conjugate addition of acetaldehyde lithium enolate to acrolein. Their geometrical features and relative energies are similar at the 3-21G//MNDO or the HF/3-21G level.

Their relative stability has been evaluated up to the MP2/6-31G*//3-21G level and can qualitatively account for the experimentally observed stereoselectivity in the Michael addition reactions of ketone and ester enolates. These calculations support the mechanistic rationale invoked by several authors[1] in order to account for the stereochemical outcome of this reaction.

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Supplementary Material Available: Energies and Cartesian coordinates of structures **4**–**23** (9 pages). This material is contained in many 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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Anomeric and Reverse Anomeric Effects in the Gas Phase and Aqueous Solution

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Anomeric stabilization within the (hydroxymethyl)oxonium, (hydroxymethyl)ammonium, and 2-tetrahydropyranosylammonium systems has been explored at both the ab initio (MP2/6-31G**//HF/6-31G**) and semiempirical (AM1) levels of theory. Aqueous solvation effects have been explored using a continuum dielectric model including local field and hydrophobic/hydrophilic effects (AM1-SM2). By analysis of C–O bond rotational coordinates in (hydroxymethyl)oxonium and stationary points for the other two molecules, it is apparent that hyperconjugative delocalization is operative in all instances of favorable orbital overlap; i.e., an anomeric effect exists. It is smaller in the ammonium case by comparison to the oxonium. Aqueous solvation tends to reduce anomeric stabilization, especially for the tetrahydropyranosyl system, where steric and dipole–dipole effects are also in opposition. The combination of these effects is sufficient to outweigh anomeric stabilization and leads to an equilibrium dominated by the equatorially substituted isomer, i.e., the reverse anomeric effect. Implications for the relative basicity of axial and equatorial anomeric substituents are also discussed.

Introduction

Electronegative substituents at C(2) of a pyranose ring (C(1) in sugar notation) have a tendency to prefer axial orientations over equatorial in spite of steric influences which would otherwise favor the converse. This phenomenon, recognized now for nearly a century, has been termed the anomeric effect.[1] It has more recently been generalized to state that in a molecular fragment W–X–Y–Z, where Z is an electron-withdrawing group, X possesses one or more lone pairs, and W and Y are of intermediate electronegativity, the synclinal (gauche) arrangement of atoms is preferred over the antiperiplanar (trans).[2]

Historically, in order to account for this apparent energetic anomaly in pyranose rings, interpretations based

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