geometrical change is again associated with the dihedral angle φ, which becomes quite small (40°). Another interesting feature is the planarization of the two methylene centers and the decrease of the CCC angles. Both the barrier between the trans and gauche minima and that between the gauche minimum and cyclobutane are very low (1.69 and 5.08 kcal/mol relative to the gauche minimum at the STO-3G level).

One of the most interesting observation is that the interfragment C–C distance (R) is almost the same for the [$2_s + 2_s$] coplanar (C_{2v}) second-order saddle point and the gauche and trans fragmentation transition structures. Thus these three structures lie on a "ridge" that separates reactants and products. Figure 6 illustrates the energy profile of this ridge along φ. The curve shows two minima corresponding to the gauche and trans fragmentation transition structures. Thus the main feature for the addition of two ethylene is that the surface is divided into two parts by a ridge occurring at an almost constant value of R (1.92 and 1.76 Å at the STO-3G and 4-31G levels, respectively) for all values of φ.

The origin of this ridge is associated with the intersection of the two diabatic surfaces corresponding to packets A and B. As previously defined, packet A involves configuration I (see Scheme II) plus all related one-electron charge-transfer configurations and packet B configuration II plus all related one-electron charge-transfer configurations. In Figure 7 the behavior of these diabatic curves is shown for the [$2_s + 2_s$] coplanar, the gauche, and the trans approaches. The computations have been performed at the STO-3G level with the optimized geometries of the corresponding second-order saddle points and transition states. In all cases there is a crossing between the two diabatics, which are associated one with two closed-shell ethylenes and the other with two triplet ethylenes coupled to a singlet. In the same figure we have also shown the behavior of the two diabatic curves for the [$2_s + 2_s$] rectangular approach, where the crossing occurs at a larger value of the interfragment distance, in agreement with the results of the geometry optimization.

The other critical points associated with the tetramethylene diradical region, i.e., the gauche and trans minima, the gauche–trans transition state, and the *gauche*-cyclobutane transition state, all lie on the side of the ridge dominated by the diabatic surface associated with packet B. Therefore, the gauche–trans and the *gauche*-cyclobutane transition states originate from conformational effects, while the gauche and trans fragmentation transition states originate from the crossing of the two diabatic surfaces.

IV. Conclusions

In this paper we have presented a detailed ab initio study at the MC–SCF level of the transition-structure region of the reaction of two ethylenes to form cyclobutane.

On examination of the concerted supra–supra approach it was found that no transition structure exists. Rather, one finds only second-order saddle points which have no chemical significance and thus the concept of a forbidden concerted pathway is without foundation. The other concerted pathway corresponding to a [$2_s + 2_a$] approach is inaccessible energetically, since it involves a very high energy transition state. Thus the favored pathway involves a stepwise approach with a diradical intermediate. In this case both a gauche and a trans approach are possible. We have found gauche and trans intermediates and corresponding fragmentation transition structures with small barriers to fragmentation, particularly at the 4-31G level.

There is a ridge separating reactants and products, which is associated with the intersection of two diabatic surfaces, one corresponding to two closed-shell ethylenes and the other to two triplet ethylenes coupled to a singlet. The tetramethylene diradical fragmentation transtition structures and the coplanar C_{2v} second-order saddle point lie on this ridge, while the other critical points associated with the tetramethylene diradical lie all on the side of the ridge dominated by the diabatic surface associated with the two triplet ethylenes coupled to a singlet.


Transition-State Modeling in Acyclic Stereoselection. A Molecular Mechanics Model for the Kinetic Formation of Lithium Enolates

David W. Moreland[*†] and **William G. Dauben**[*]

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. Received February 27, 1984

Abstract: As the initial phase of a study of the aldol condensation, molecular mechanics was used to calculate the energies of model transition states for the formation of cis and trans enolates from a number of ketones and esters. Regression analysis was used to correlate these energies with the corresponding experimentally determined cis:trans enolate ratios reported in the literature for kinetic deprotonation with LDA in THF or in THF:HMPA mixtures at −70 °C. An analysis of the regression equations allowed some comparisons to be made between the geometries of the models and that of the actual transition state. This analysis strongly suggests that the transition state leading to the cis isomer is destabilized by a steric interaction with the base, thus supporting the concept of a cyclic transition state. That this interaction is greatly diminished in the presence of HMPA suggests that the transition state is much more loosely organized in this solvent. The correlation equations can be used to quantitatively predict the cis:trans enolate ratios which would be expected from the kinetic deprotonation of simple ketones and esters with LDA in THF or THF:HMPA mixtures at −70 °C.

Acyclic stereoselection has become an extremely active field of research in recent years and is an increasingly useful synthetic technique.[1] Of the numerous reactions studied in this area, the aldol condensation and its variations have perhaps been the most heavily utilized.[2,3] Since the stereoselectivity of a reaction often
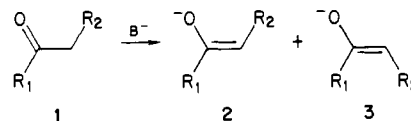
results from a subtle balance of many factors, an understanding of the factors governing a given reaction is essential for its full

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†Current address: Warner-Lambert Company, Pharmaceutical Research Division, 2800 Plymouth Road, Ann Arbor, Michigan 48105.
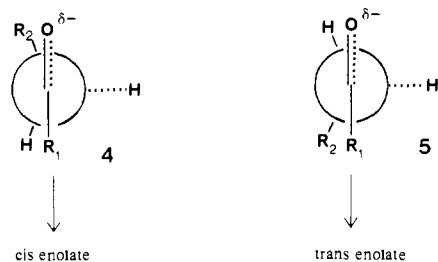
Figure 1. Partial transition-state structures for the deprotonation of ketones and esters.

Figure 2. Carbonyl conformations and enol geometries used as transition-state models.

Table I. Experimental Data for Enolate Formation with LDA in THF at −70 °C

entry	R_1	R_2	cis:trans ratio	ln (ratio)	ref
1	mesityl	Me	5:95	2.944	5a
2	O-*t*-Bu	Et	5:95	2.944	6
3	O-*t*-Bu	Me	5:95	2.944	6
4	OMe	Me	5:95	2.944	6
5	OMe	Et	9:91	2.314	6
6	Et	Me	23:77	1.208	6
7	*i*-Pr	Me	60:40	−0.405	5a
8	adamantyl	Me	>98:2	−4.595	5a
9	*t*-Bu	Me	>98:2	−4.595	5a
10	OMe	*t*-Bu	3:97	3.476	6
11	OMe	Ph	71:29	−0.895	6
12	Ph	Me	>98:2	−4.595	5a
13	$C_6H_2(OMe)_3$	Me	50:50	0.000	9b

utilization. As part of an evaluation of the use of force field calculations as a modeling tool, an attempt was made to apply molecular mechanics to the resolution of some of the factors, the stereochemistry of the aldol condensation, with the hope of developing a quantitative predictive model. To initiate the investigation, the kinetic deprotonation of carbonyl compounds to stereoselectivity generate an enolate has been addressed.

Background and Design. Enolate stereochemistry has been studied by a number of groups,[4] in the context of the aldol condensation,[5] the Claisen rearrangement,[6] and alkylation reactions,[7] and a number of parameters have been identified which the chemist can, in principle, vary in order to obtain the desired stereochemical outcome. Cis:trans[8] isomer ratios are influenced by the base,[9] the countercation,[7,9c,10] the solvent,[6,9a,11] and the nature of R_1 and R_2.[5,6,10a] The existing data allow several generalizations to be made: formation of the trans isomer is favored under kinetic conditions, by use of coordinating countercations, nonbulky groups at R_1 and R_2, bulky bases, and nonpolar solvents which would favor an organized transition state. The cis isomer tends to be formed under thermodynamic conditions,[7,11] or under kinetic conditions with bulky groups at R_1 and R_2 and with the use of sterically small bases, noncomplexing countercations, and solvents which can effectively solvate the cation.

In kinetic deprotonation, the product ratio is, of course, determined by the relative energies of the transition states leading to the two isomers, and several transition-state models have been proposed to accommodate the experimental observations. These proposals differ primarily in the particular roles assigned to the base, counterion, and solvent and can be summarized in terms of the partial structures presented in Figure 1. These structures represent the carbonyl portion of the transition state, in which the C–H bond is partially broken and a partial negative charge has formed on the oxygen. Due to stereoelectronic considerations, the bond to the hydrogen being removed by the base would be expected to be perpendicular to the carbonyl C–O bond.[12] The
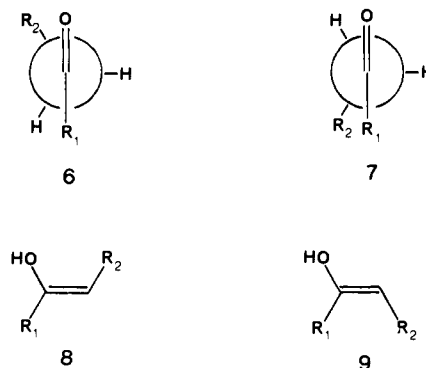
transition states corresponding to structures **4** and **5** would lead to the cis and trans enolates, respectively. It is generally felt[6,10] that when the counterion can complex the carbonyl oxygen, the oxygen is, in effect, made larger, destabilizing the transition state leading to the cis isomer (**4**) by increasing the R_2–O interaction. On the other hand, as R_1 and R_2 become bulkier, the transition state **5**, leading to the trans enolate, is destabilized. The isomer ratio is determined by the balancing of these two effects.

If it can be assumed that, under a given set of kinetic conditions, the influence of solvent, base, and counterion on the transition-state energies remains more or less constant, then differences in product ratios over a series of compounds would be determined primarily by intramolecular interactions. If the interactions of R_2 with R_1 and with the developing oxyanion in the structures shown in Figure 1 could be evaluated, it should be possible to estimate the relative stabilities of the transition states. Furthermore, if these interactions actually are playing the major role in determining the transition-state energies, there should be a relationship between the magnitudes of the interactions in the isomeric transition states and the observed isomer ratios.

On the basis of this analysis, no appropriate means was sought by which to evaluate these intramolecular interactions. First, a suitable molecular framework is necessary which would place the groups in spatial relationships similar to those in the transition states, and secondly, a calculational method of sufficient reliability must be employed to evaluate the magnitude of the interaction between the groups. Ideally, the actual transition-state geometries would be used and the actual transition-state energies would be evaluated. However, in the absence of detailed knowledge of the geometries, and since the calculations necessary to evaluate the actual transition states accurately can be extremely time-consuming and unwieldy,[13] other models are necessary. Two model geometries were primarily employed in this work. The first model used conformations of the starting carbonyl compound having one

(1) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(2) (a) Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press, Inc.; New York, 1983; Vol. 2, Chapter 2. (b) Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1983; Vol. 2.

(3) Evans, D. A.; Nelson, J. V.; Taber, T. R. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, p 1.

(4) For general reviews, see: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. d'Engelo, J. *Tetrahedron* **1976**, *32*, 2979.

(5) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066; (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(6) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(7) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.

(8) The terms cis and trans will be used to refer to the disposition of the α-substituent, R_2, and the carbonyl oxygen.

(9) (a) Kleschick, W. A. Ph.D. Dissertation, The University of California, Berkeley, CA, 1977. (b) Buse, C. T. Ph.D. Dissertation, The University of California, Berkeley, CA, 1978. (c) Sohn, J. E. Ph.D. Dissertation, The University of California, Berkeley, CA, 1981.

(10) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.

(11) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

(12) See discussion: Kirk, D. N.; Hartshorn, M. P. "Steroid Reaction Mechanisms"; Elsevier: New York, 1968; p 158 ff.

(13) See discussion: Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1.

Table II. Structural Characteristics Used To Calibrate the π-System Adjustments

compound	exptl value	before adjust-ment	after adjust-ment	ref
	Bond Lengths (Angstroms)			
benzene	1.397	1.401	1.396	18
tran-butadiene				
σ	1.466	1.473	1.467	18
π	1.343	1.348	1.343	
	Torsional Angles (Degrees)			
biphenyl	42–45	35	41	19
cis-stilbene				
σ	43	35	38	20
π	?	11	11	
trans-stilbene				
σ	ca. 30	0	20	21
π	?	180	180	

Table III. Torsional Parameters Used in the Modified MM2 Force Field

torsional angle	V_1	V_2	V_3	note
$Csp^2-Csp^2-Osp^3-H$	0.0	0.0	0.0	a
$Osp^3-Csp^2-Csp^2(carbonyl)$	0.0	16.250	0.0	b
$Csp^2-Csp^2-Csp^2(carbonyl)-Osp^2$	0.0	13.029	0.303	
$Csp^2-Csp^2-Csp^2(carbonyl)-Csp^3$	0.150	13.029	0.0	
$Csp^2-Csp^2-Csp^2(carbonyl)-H$	−0.300	13.029	0.0	

^{a} Same as $Osp^2-Csp^2(carbonyl)-Osp^3-H$. ^{b} Same as $Csp^2-Csp^2-Csp^2-Osp^3$.

of the α-C–H bonds perpendicular to the carbonyl–oxygenbond, as shown in structures **6** and **7** in Figure 2. These geometries were chosen to mimic the expected transition-state geometries shown in Figure 1. The second model employed the enol forms **8** and **9**, which correspond to the product enolates **2** and **3**. While neither of these models could be expected to have the same geometry as the transition state, both contain interactions between the grous which are expected to determine the relative transition-state energies, so both should provide some measure of how those interactions vary with the nature of the groups.

The difference in the calculated enthalpies of the model geometries (subsequently referred to as ΔH_m) can be used to indicate the relative severities of the intramolecular interactions in the isomeric model transition states. If the assumptions made in designing the model are valid, then a regression analysis between the values of ΔH_m and the corresponding experimental ratios would establish whether the enolate ratios are indeed primarily determined by the intramolecular interactions under consideration.

Experimental Section

Experimental Enolate Ratios. The experimentally determined ratios for the formation of ketone and ester enolates with LDA at −70 °C were obtained from the literature. The data for the 13 ketone and esters used in this study are compiled in Table I. Although experimental data are also available for the formation of a number of amide, aryl ester, thio ester, and silyl ester enolates, we have not yet obtained the force field parameters required to calculate these functional groups. Unfortunately, this limits the amount of usable data, particularly for the preferential formation of the cis enolate. To establish this end of the scale, ratios of 99% cis:1% trans were used to represent the approximate ratios reported for adamantyl ethyl ketone (entry 8) 2,2-dimethyl 3-pentanone (entry 9), and propiophenone (entry 12).

Some conflicting experimental data exist for the deprotonation of propiophenone (entry 12) with LDA in THF at −70 °C. A ratio of 90% cis:10% trans has also been reported under these conditions, as opposed to the nearly exclusive formation of the cis isomer as listed in the table.[14] Both values will be considered in the discussion.

Methods. Since the models used in this work are uncharged, ground-state molecules, their energies can, in principle, be evaluated by a number of calculational methods. Energy and geometry optimizations were carried out with Allinger's MM2 force field program (1980 parameter set),[15] which was obtained from QCPE[16] and modified extensively for interactive use[17] ona PRIME 750 minicomputer.[18] The calculated energies are reported to two decimal places throughout this work. For calculations on compounds containing conjugated π systems, the

VESCF/PI subroutines from MMPI[19] were inserted into the MM2 program. These routines adjust the force field parametersfor bond lengths and torsional angles in the conjugated portion of the molecule according to the bond orders determined by the VESCF calculation. The program resulting from the inclusion of these routines systematically overestimated bond lengths and underestimated torsional angles in conjugated systems, indicating a difference in the adjustments required by the MM1 and MM2 force fields. To compensate for this difference, the adjustment factors in subroutine PICON were altered so bond lengths and torsional angles were reproduced more accurately, as listed in Table II. The existing adjustments for the bond-stretching parameters were multiplied by a factor of 0.996, to reproduce the bond lengths in butadiene[19a] and benzene.[19a] The torsional adjustment was multiplied by a factor of 0.767, to approximate the gas-phase geometries of biphenyl[20] and cis-[21] and trans-stilbene.[22] While these adjustments appear to give satisfactory results for conjugated polyene systems,[23] they result in large errors in the rotational barriers for benzaldehyde and acetophenone. The V_2 torsional parameters for α,β-unsaturated aldehydes and ketones were therefore adjusted to reproduce these experimental values (benzaldehyde: calcd 4.89 kcal mol⁻¹, obsd[24,25] 4.90–4.92 kcal mol⁻¹; acetophenone: calcd 3.13 kcal mol⁻¹, obsd[25] 3.1 kcal mol⁻¹).[26] The parameters used are listed in Table III. Also included in this table are the torsional parameters added to permit the calculation of enols and β-alkoxy α,β-unsaturated carbonyl compounds. All adjustments to the program were made to compensate for obvious deviations from experimental data arising from the inclusion of the π-calculation routines. No attempt has been made to fully optimize either the adjustments to the π calculation or the parameter adjustments.

Least-squares regression analyses were performed on a PDP-11 minicomputer[27] with ISP ("Interactive Statistical Package"), a package of general statistics programs maintained by the University of California, Berkeley Statistics Department (Release 3.0d), and run under the UNIX[28] operating system.

Results

The Carbonyl Model. The model conformations **6** and **7** were evaluated for the 13 examples in the data set. The dihedral angle between the carbonyl and one of the α-C–H bonds in both model conformations was maintained at 90° with the program's dihedral angle driver, while the remaining structural parameters were allowed to optimize.

The effect of rotation about the bond between the carbonyl carbon and R_1 on the energy of model geometries **6** and **7** was examined with MM2. Both the methyl and *tert*-butyl esters (entries 4,5,10 and 11 and entries 2 and 3, resp.) have two rotational minima, with the ester alkyl group either syn (**10**) or nearly anti (**11**) to the carbonyl oxygen. The syn orientation of the methyl esters was calculated to be at least 4.9 kcal mol⁻¹ more stable than the anti conformation. This is in accord with microwave studies of methyl formate, which suggest that the syn

(14) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Allinger, N. L.; Hindman, D.; Hönig, H. *J. Am. Chem. Soc.* **1977**, *99*, 3282. (c) Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.

(15) Noyori, R., personal communication to C. H. Heathcock.

(16) Program No. 395, Quantum Chemical Program Exchange, Chem. 204, University of Indiana, Bloomington, Indiana, 47405.

(17) Many of these modifications have been adapted to MMP2 and are available through Molecular Design Limited, 1122 B St., Hayward, CA 94541.

(18) The system is owned and operated by Molecular Design Limited.

(19) (a) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1973**, *95*, 3893. (b) Program No. 318, Quantum Chemical Program Exchange.

(20) Dannenberg, J. J.; Blackwood, A. L. *J. Am. Chem. Soc.* **1975**, *97*, 4753 and references cited therein.

(21) Traetteberg, M.; Fransten, E. B. *J. Mol. Struct.* **1975**, *26*, 69.

(22) Traetteberg, M.; Fransten, E. B.; Mijhoff, F. C.; Hoekstra, A. *J. Mol. Struct.* **1975**, *26*, 57.

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(24) Kakar, R. K.; Rinehart, E. A.; Quade, C. R.; Kojima, T. *J. Chem. Phys.* **1970**, *52*, 3803.

(25) Miller, F. A.; Fateley, W. G.; Witkowsky, R. E. *Spectrochim. Acta* **1967**, *23A*, 891.

(26) For results obtained with MMPI, see: Liljefors, T.; Allinger, N. L. *J. Am. Chem. Soc.* **1976**, *98*, 2745.

(27) The system is owned and operated by University of California, Berkeley, Computer Facilities and Operations.

(28) UNIX is a trademark of Bell Laboratories.
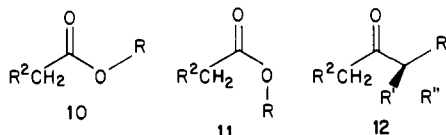
orientation is exclusively populated in the gas phase.[29] The syn conformation of the *tert*-butyl esters was calculated to be at least 8.5 kcal mol⁻¹ more stable than the anti conformation. Due to the consistently high energies of the anti conformations, only the syn conformations were used in determining the model energies for the esters. When R_1 is ethyl (entry 6) or isopropyl (entry 7), three orientations of R_1 (with R, R′, or R″ eclipsing the carbonyl in structure 12) are possible in both models 6 and 7. Since the different orientations were calculated to be of similar energies, the energies of models 6 and 7 were weighted according to Boltzmann statistics and adjusted for entropy of mixing.[30]

It is well established that the favored conformation of simple, saturated aliphatic aldehydes and ketones is that having the carbonyl eclipsed with an α-alkyl substituent.[31] A detailed examination of a number of simple aldehydes and ketones[32] has indicated that the MM2 program reproduces this characteristic quite well. Conformations of esters are less thoroughly studied, but propionic and butyric acids have been shown to favor the conformation having the α-alkyl group eclipsed with the carbonyl in the crystal,[33] and ab initio calculations at the STO-3G level[34] suggest that this conformation is also favored in the gas phase. Examination of a number of esters with the MM2 force field indicated that the conformation having the carbonyl eclipsed with the α-alkyl substituent is favored when R_2 is methyl, ethyl, and *tert*-butyl.[32] The tendency of α-alkyl substituents to eclipse the carbonyl is reflected in the data for the carbonyl model, in that the state model 6, being more nearly eclipsed, is more stable that model 7 in all cases but one (see discussion, below). The differences between the calculaed enthalpies of the model geometries 6 and 7 (ΔH_m) are compiled in Table IV.

A regression analysis between the calculated carbonyl model energy differences and the logs of the observed isomer ratios from Table I produced the relationship

$$\ln (t/c) = -2.79\Delta H_m + 3.88 \qquad (1)$$

$$n = 9;\ s = 0.52;\ r^2 = 0.975\ (99.9);\ F = 278\ (99.9)$$

where $\ln (t/c)$ is the natural log of the experimental trans to cis ratio, and ΔH_m is the difference in the energies calculated for the model geometries 6 and 7. The regression coefficient r and the F value indicate a reasonably strong correlation[35] for nine data points, with a standard deviation of 0.52. Four data points were not included in the correlation. Entries 10–13 deviate from the correlation either because of a limitation of the calculational method or because of an additional factor in the transition state (see discussion on outlying points, below) and, as shown in Figure 3, lie substantially away from the correlation line. Each of these points can be excluded from the correlation on the basis of a t-test analysis at the 95% confidence level. Entry 11 is not included in Figure 3 due to its large deviation.

The Enol Model. The use of this model was restricted to the examination of the formation of ketone enolates, since force field

Table IV. The Differences in Calculated Energies for the Model Transition States (ΔH_m) (kcal mol⁻¹)

entry	R_1	R_2	carbonyl model (7–6)	enol model (9–8)
1	mesityl	Me	0.04	0.51
2	O-*t*-Bu	Et	0.49	
3	O-*t*-Bu	Me	0.47	
4	OMe	Me	0.58	
5	OMe	Et	0.60	
6	Et	Me	0.88	2.34
7	*i*-Pr	Me	1.24	2.67
8	adamantyl	Me	3.05	4.65
9	*t*-Bu	Me	3.07	4.64
10	OMe	*t*-Bu	1.05	
11	OMe	Ph	−0.43	
12	Ph	Me	1.51	4.40
13	$C_6H_5(OMe)_3$	Me	0.53	2.85
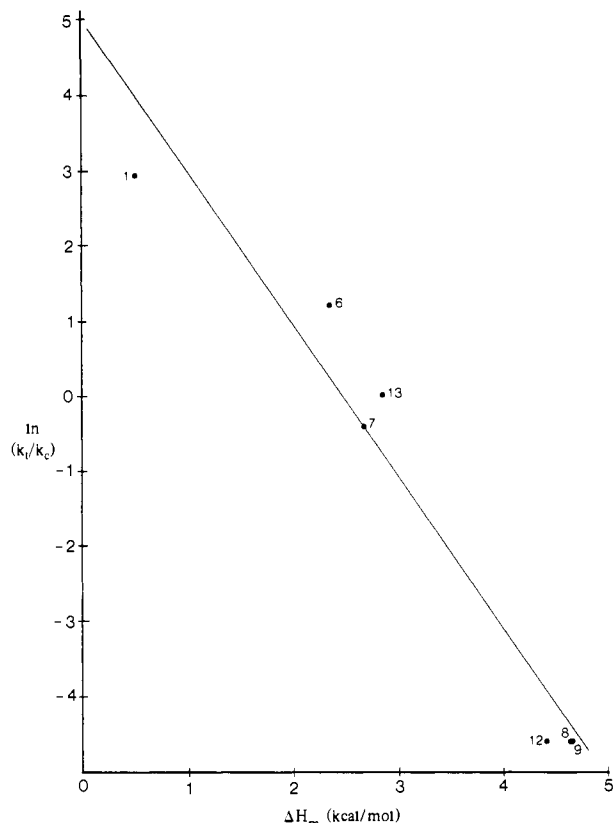
Figure 3. Scatter plot of ln (k_t/k_c) vs. ΔH_m for the carbonyl model, with eq 1 superimposed. Outlying points are marked by ▲. Entry numbers correspond to Tables I and IV.

parameterss were lacking for the ketone acetal functionality of the ester enol models. The energies of the model geometries 8 and 9 were determined for the seven remaining cases, and the resulting values of ΔH_m are compiled in Table IV. The calculated energies were adjusted according to Boltzmann statistics for the rotamers of the hydroxyl group and, when R_1 was ethyl or isopropyl, for rotamers of R_1. The cis enol is calculated to be more stable than the trans isomer in all cases, due to the small steric bulk of the hydroxyl relative to the R_1 group. This is in qualitative agreement with the experimental observation that the cis enolate is generally favored in equilibria.[7b] However, in the enolate, the oxyanion is effectively larger than a hydroxyl group because of the proximity of the counterion and the species coordinated with it. The increase that this causes in the interaction between the oxyanion and R_2 in the cis enolate tends to destabilize that isomer, so the difference in the energies of the cis and trans enolate isomers is less than that between the corresponding enol isomers. Thus, while the enthalpies calculated for the enols can be used in the correlative analysis, they cannot be used to quantitatively predict

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(31) See, for example: Karabotsos, G. J.; Feniglio, D. J. In "Topics in Stereochemistry"; Allinger, N. L., Eleil, E. L., Ed.; Wiley: New York, 1970; Vol. 5, p 167.

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(35) The values in parentheses are the confidence levels (in percent) indicated by the r and F statistics. See: (a) Bevington, P. R. "Data Reduction and Error Analysis for the Physical Sciences"; McGraw-Hill: San Fransisco, 1969. (b) Keppel, G. "Design and Analysis. A Researcher's Handbook"; 2nd ed.; Prentice-Hall: Englewood Cliffs, NJ, 1982.
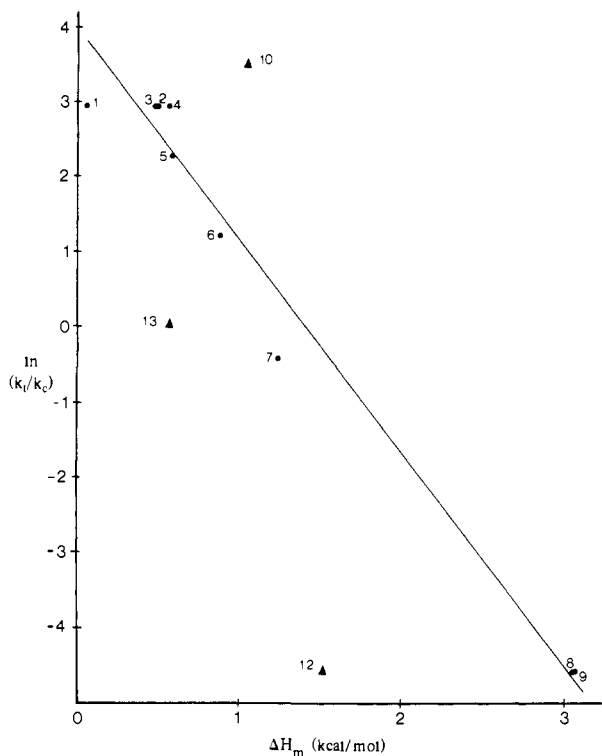
Figure 4. Scatter plot of ln (k_t/k_c) vs. ΔH_m for the enol model, with eq 2 superimposed. Entry numbers correspond to those given in Tables I and IV.

the thermodynamic stabilities of the isomers.[36]

A regression analysis between the energy differences calculated for the enol model and the logs of the experimental ratios from Table I produced the relationship

$$\ln (t/c) = -2.01\Delta H_m + 4.89 \tag{2}$$

$$n = 7; \ s = 0.75; \ r^2 = 0.950 \ (99.9); \ F = 94.8 \ (99.9)$$

The correlation between the log of the trans-to-cis ratio and the enthalpy difference between the isomeric enols is not as strong as with the ketone model, though it is still fairly good (see Figure 4). The standard deviation is somewhat larger than in the carbonyl model correlation, probably due to the smaller data set.

Discussion

The examination of transition-state models with the combination of force field calculations and correlative techniques has several facets. The force field calculations give detailed information about structural and energetic aspects of the molecules being used as models. The correlations then relate this information to the behavior of the reaction and allow inferences to be made regarding the transition-state geometry. If the experimental data used are the true kinetic ratios, then the correlation provides a statistical base line of how the kinetic reaction behaves on simple molecules in the absence of unusual solvation or complexation effects. Examination of the correlation and the compounds which follow the correlation can allow generalizations to be made regarding the relationship between structure and the course of the reaction. Analysis of those cases which do not follow the correlation can give added information about either the model or the transition state. The deviation of a data point from the correlation would suggest one of the following conditions (1) the calculation of the model enthalpy difference is in error, (2) the experimental value is not a true kinetic ratio but is the result of partial or complete equilibration, or (3) there is an added factor in the transition state which is not accounted for in the model and which alters the

behavior of the kinetic reaction.

Interpretation of the Correlations. The presence of significant correlations between the model transition-state energies and the observed isomer ratios supports the contention that the roles of the base, counterion, and solvent are relatively constant and that variations in the enolate ratios across the series are primarily due to intramolecular interactions. More importantly, a number of inferences can be made regarding the mechanism of the kinetic deprotonation of simple ketones and esters and the nature of the transition state. In establishing the model, it was assumed that the relative rates for the formation of the isomeric enolates are proportional to the difference in free energy $(\Delta G^\ddagger)$ between the two transition states. According to the Curtin–Hammett principle, equilibrium between the conformations leading to the transition states must be rapid relative to the rate of reaction in order for this to be true.[37] Since the rotational barrier between the two productive conformations of the starting carbonyl compound should be less than 2.0 kcal mol^{-1}, the rate constant for their interconversion should be on the order of 10^{10} s^{-1}. If deprotonation is diffusion controlled, then at -70 °C the rate of the reaction would be approximately 10^8 L mol^{-1} s^{-1}.[38] Thus, equilibration should occur at least two orders of magnitude faster than deprotonation, and the classical Curtin–Hammett conditions are satisfied. The relative reaction rates are, then, related to the difference in free energies of activation by the Eyring equation in ratio form,[39]

$$\ln \left(\frac{k_t}{k_c} \right) = \frac{-1}{RT}(\Delta G_t^\ddagger - \Delta G_c^\ddagger) = \frac{-1}{RT}\Delta G^\ddagger \tag{3}$$

where $\Delta G_t^\ddagger$ and $\Delta G_c^\ddagger$ are the free energies of the transition states leading to the cis and trans enolates, respectively. This can also be expressed as

$$\ln \left(\frac{k_t}{k_c} \right) = \frac{-1}{RT}\Delta H^\ddagger + \frac{\Delta S^\ddagger}{R} \tag{4}$$

In the model used, it has been assumed that the geometric relationship between the base, the counterion, the solvent molecules, and the carbonyl substrate remains more or less constant as R_1 and R_2 are varied. Thus, the degree of organization should be approximately the same for each transition state, and the entropy of activation for each should be constant. This being the case, $\Delta S^\ddagger$ should also be a constant, and a plot of ln (k_t/k_c) va. $\Delta H^\ddagger$ would have a slope of $-1/RT$ and an intercept of $\Delta S^\ddagger/R$.

The regression analyses presented in this work yield linear relationships of the form

$$\ln (k_t/k_c) = m\Delta H_m + C \tag{5}$$

where m is the slope of the line, ΔH_m is the difference in the calculated enthalpies of the model geometries, and C is the intercept on the ln (k_t/k_c) axis. Since this is similar in form to the Eyring equation, a comparison of the two correlations with the theoretical relationship can suggest much about the nature of the transition state.

The current hypothesis is that the enthalpy difference between the cis and trans models is proportional to the difference in activation enthalpies between the isomeric transition states. Thus, the relationship

$$\Delta H^\ddagger = a\Delta H_m \tag{6}$$

should hold, where ΔH_m is the difference in the calculated enthalpies of the two model transition states, $\Delta H^\ddagger$ is the actual

(36) A tentative parameter set has been developed for MM2 for a more accurate calculation of the thermodynamic behavior of enolate anions. See: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *23*, 3981.

(37) For a detailed review of the Curtin–Hammett principle, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(38) This should represent the maximum possible rate of the reaction. It is quite likely that deprotonation actally occurs at a much slower rate. The diffusion-controlled rate was estimated by using the viscosity of diethyl ether (222 P) and the formula given by Gordon and Ford Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; p 137.

(39) Both the Eyring and the Arrhenius equations can be used in this analysis with similar results. The former was chosen because it permits explicit treatment of $\Delta H^\ddagger$ and $\Delta S^\ddagger$.
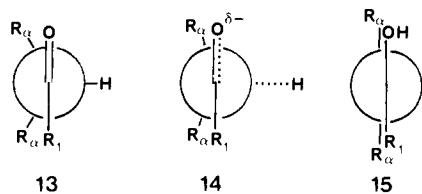
13   **14**   **15**

Figure 5. Comparison of the model and the transition-state geometries.

difference in activation enthalpies, and a is a proportionality constant relating the two. Since ΔH_m is determined solely by intramolecular interactions as discussed previously, the constant a should provide a measure of the amount by which these interactions differ from those in the actual transition state.

Multiplication of both sides of eq 6 by $-1/RT$ results in the relationship

$$\frac{-1}{RT}\Delta H^{\ddagger} = \frac{-1}{RT}a\Delta H_m \qquad (7)$$

and it is possible to define the slope of the correlations to be $(-1/RT)a$. The value of a can then be determined for each correlation by dividing the observed slope by $-1/RT$. A value of a greater than 1.0 would indicate that ΔH_m is less than $\Delta H^{\ddagger}$, and a value less than 1.0 would indicate that ΔH_m is larger than $\Delta H^{\ddagger}$. At -70 °C, the value of $-1/RT$ is -2.48 mol kcal^{-1}. This gives an a for the carbonyl model of 1.12, indicating Δh_m to be *less* than $\Delta H^{\ddagger}$. On the other hand, a value of 0.81 is obtained for the enol model, indicating that ΔH_m, in this case, is *greater* than $\Delta H^{\ddagger}$. The order ΔH(carbonyl model) $< \Delta H^{\ddagger} < \Delta H$(enol model) is as one would expect on examination of the structures in Figure 5. Structure **13** corresponds to the carbonyl model, with the α-carbon fully sp^3 hybridized. Structure **14** represents the carbonyl portion of the actual transition state, in which the α-carbon has partially rehybridized, moving the substituents R_a closer to the developing oxyanion and R_1. This would increase the severity of the interactions of the α-substituents with R_1 and the oxygen in the transition states leading to both the cis and the trans enolates. Since R_1 is larger than the developing oxyanion, the enthalpy of the transition state leading to the trans isomer would be increased more than that leading to the cis isomer, so $\Delta H^{\ddagger}$ should be larger than the enthalpy difference between the two carbonyl conformations.

In the enol model **15**, the α-carbon is fully rehybridized to sp^2, and the α-substituents lie in the same plane as the oxygen and R_1. The interactions between the groups should be more severe than in the actual transition state, so the ΔH_m for this model should be larger than $\Delta H^{\ddagger}$, as is observed. The value of a of 0.81 obtained for the enol model indicates that these interactions are some 23% greater than those in the transition state. In contrast, the interactions in the carbonyl model differ from those in the transition state by only 11%. On the basis of these figures, it is reasonnable to infer that the transition state more closely resembles the carbonyl model, so it is reactant-like.

Further inferences can be made on examination of the intercepts of the correlation lines (eq 1 and 2). As previously noted, the model transition state leading to the cis isomer was calculated to be more stable in nearly all cases for both the ketone and the enol models, even when the trans enolate is formed predominantly. Consequently, neither correlation passes through the origin, as would be expected if the product ratios were determined solely by the enthalpy term. Two possible interpretations of this nonzero intercept are presented here.

The first inclination is to view the intercept as an entropy term, as would be suggested by the Eyring equation. The Eyring equation (eq 4) and the correlations (eq 5) would then be related to

$$\frac{-1}{RT}\Delta H^{\ddagger} + \frac{\Delta S^{\ddagger}}{R} = m\Delta H_m + C \qquad (8)$$

If the original hypothesis that ΔH_m and $\Delta H^{\ddagger}$ are directly proportional (eq 6) is correct, it can be seen that the intercepts for

both correlations and for the Eyring equation should be the same when ΔH_m is zero:

$$\Delta S^{\ddagger}/R = C \qquad (9)$$

Due to the large standard deviation in the enol model correlation, the intercepts for the two correlations (eq 1 and 2) can be considered to be quite similar, and an estimate of $\Delta S^{\ddagger}$ can be obtained by multiplying either intercept by the gas constant R. The resulting value of $\Delta S^{\ddagger}$ indicates that the entropy of activation is 7.7 to 9.7 cal mol^{-1} K^{-1} more positive in the trans transition state than in the cis. Such a value indicates a substantial difference in the degree of organization between the transition states leading to the two isomers, with the cis transition state being more ordered. Presumably this difference would be in the degree of organization of the solvent, the base, and the countercation. A difference in the degree of organization of the transition states is not inconsistent with the original assumptions of this work, providing that this differnce is constant. However, the suggestion that the transition state leading to the trans enolate is the lesser organized is difficult to reconcile. One might reasonably expect the α-substituent in the transition state leading to the cis isomer to be an a position to influence the solvation about the carbonyl oxygen or to alter the location of the complexing counterion, but this would result in a negative $\Delta G^{\ddagger}$. There is no apparent factor of this type which would cause the trans transition state to be less organized, so this interpretation of the intercept is somewhat inconsistent with the expected behavior of the reaction.

A second interpretation assumes that the degree of organization of each of the transition states is similar, so the $\Delta S^{\ddagger}$ term should be very small and can be approximated as zero. If this is so, than a nonzero intercept would have to be part of the enthalpy term and would represent a constant difference between the enthalpies of the two transition states in addition to the difference calculated. The intercept C can be expressed as

$$C = m\Delta H_b \qquad (10)$$

where m is the slope of the correlation and ΔH_b is the constant enthalpy term. Equation 5 can then be rewritten as

$$\ln (k_t/k_c) = m(\Delta H_m + \Delta H_b) \qquad (11)$$

where both ΔH_m, the enthalpy difference calculated between the models, and ΔH_b, the additional constant enthalpy value, have been collected into the same term.[40]

For comparison purposes, $\Delta H^{\ddagger}$ can be divided into two terms, $\Delta H^{\ddagger}_a$ and $\Delta H^{\ddagger}_b$

$$\Delta H^{\ddagger} = \Delta H^{\ddagger}_a + \Delta H^{\ddagger}_b \qquad (12)$$

where $\Delta H^{\ddagger}_a$ is proportional to ΔH_m and includes all contributions to the enthalpy from intramolecular interactions, and $\Delta H^{\ddagger}_b$ is proportional to ΔH_b and includes all other enthalpy contributions. The Eyring equation (eq 4) can then be expressed as

$$\ln \left(\frac{k_t}{k_x}\right) = \frac{-1}{RT}(\Delta H^{\ddagger}_a + \Delta H^{\ddagger}_b) + \frac{\Delta S^{\ddagger}}{R} \qquad (13)$$

or, since $\Delta S^{\ddagger}$ is expeced to be zero,

$$\ln \left(\frac{k_t}{k_c}\right) = \frac{-1}{RT}(\Delta H^{\ddagger}_a + \Delta H^{\ddagger}_b) \qquad (14)$$

Equations 11 and 14 can be equated as

$$\ln \left(\frac{k_t}{k_c}\right) = m(\Delta H_m + \Delta H_b) = \frac{-1}{RT}(\Delta H^{\ddagger}_a + \Delta H^{\ddagger}_b) \qquad (15)$$

and, since ΔH_m and $\Delta H^{\ddagger}_a$ are directly proportional, the intercepts of the equations should be the same

$$m\Delta H_b = \frac{-1}{RT}\Delta H^{\ddagger}_b \qquad (16)$$

(40) See: Leffier, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions as Treated by Statistical, Thermodynamic, and Extrathermodynamic Methods", Wiley: New York, 1963; Chapter 6.

A value for $\Delta H^{\ddagger}{}_b$ can be obtained by multiplying the intercepts of the correlations by $-RT$ (-0.4 kcal mol^{-1} K at 203 K). Since $\Delta H^{\ddagger}{}_b = H^{\ddagger}{}_{b(trans)} - H^{\ddagger}{}_{b(cis)}$, a positive value would indicate a factor which causes the cis transition state to be systematically favored over the trans transition state. The value obtained is -1.6 to -2.0 kcal mol^{-1}, indicating either that the trans transition state is being preferentially stabilized or that the cis transition state is being preferentially destabilized. Since the calculated ΔH_m should include all contributions to the enthalpy from intramolecular interactions, the additional term must be due to intermolecular interactions with the countercation, the base, and/or the solvent. Furthermore, since it has been assumed that the relative locations of the species present in the transition states are fairly constant, the term must be caused by the difference in the location of R_2 between the two transition states. It is difficult to conceive of a factor based on the position of R_2 which would stabilize the trans transition states. However, the cis transition state would tend to be destabilized if the carbonyl oxygen was effectively made larger by association with the other reagents in the reaction, as originally proposed by Ireland.[6] This would introduce an interaction between R_2 and the coordinated oxygen which would only be present in the cis transition state. Since all of the compounds in the correlation have the sterically similar[41] methyl and ethyl groups for R_2, such an interaction would be essentially the same in all cases. Thus, this interpretation of the intercept is quite consistent with experimental observations.

The Outlying Points. Four data points deviate significantly from the carbonyl model correlation. While the data set is not large enough to permit firm conclusions to be drawn, each of these points can be suggestive of some characteristic of the mechanism, the calculational method, the model, or the experimental result.

The deprotonation of methyl 3,3-dimethyl butanoate, entry 10 in Tables I and IV, results in considerably more trans isomer than would be expected on the basis of the correlation (eq (1)), as indicated by the location of the point above the correlation line in Figure 3. On the basis of the correlation, the ΔH_m of 1.05 kcal mol^{-1} for this molecule would indicate a 47% cis to 53% trans mixture for the deprotonation, rather than the almost exclusive formation of the trans isomer observed. While it is impossible to rule out experimental or computational error on the basis of a single data point, the deviation of this point is consistent with the foregoing interpretation of the intercepts. The interaction of the bulky *tert*-butyl group at R_2 with the other reactants would be much more severe than when R_2 is methyl or ethyl, so the destabilization of the transition state leading to the cis isomer would be greater. If this interpretation of the deviation of this point can be accepted on a tentative basis, then it is possible to include the effect of the size of R_2 in the correlation. When the steric parameter ν^{42} was included for the R_2 substituents (Me = 0.52, Et = 0.56, *t*-Bu = 1.24), the relationship

$$\ln (t/c) = -2.77\Delta H_m + 3.59\nu_{R_2} + 1.95 \qquad (17)$$

$n = 10$; $s = 0.51$; $r^2 = 0.979$ (99.9); $F = 164$ (99.9);
$$F_X = 15.9 \ (99.0)$$

was obtained.[43] This correlation would be consistent with the presence of a repulsive steric interaction involving R_2 which destabilizes the cis transition state. While the r and F statistics indicate a fairly strong correlation, a broader sampling of R_2 groups would be required to fully substantiate this interpretation.

Methyl 2-phenylacetate (entry 11) is the only case in which model geometry **7** is calculated to be more stable than geometry **6**. On this basis, exclusive formation of the trans isomer would be predicted, rather than the 71% cis:29% trans mixture actually observed. The behavior of this point is probably due to the inability
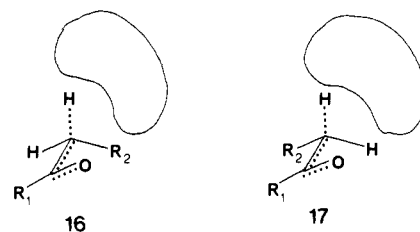

Figure 6. Regions occupied by the base and countercation in the cyclic transtion states leading to the cis and trans enolates.
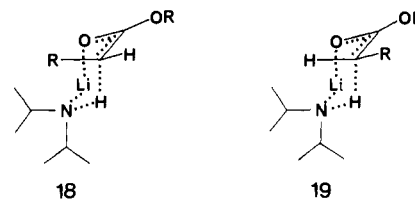

Figure 7. The cyclic transition-state geometries proposed by Ireland.

of the model to evaluate the overlap of the developing anion with the π system of the phenyl ring. One would expect this overlap to increase the barrier for the rotation of the phenyl ring, so the energies of the transition states are not accurately reflected in the current model.

The remaining two outliers are the aryl ketones propiophenone (entry 12) and (2,4,6-trimethoxyphenyl) ethyl ketone (entry 13). While the MM2 program was parameterized to reproduce the rotational barriers of aryl ketones and aldehydes in the gas phase, rotational barriers for these classes of compounds are considerably larger in solution, particularly with polar solvents.[44] Thus, the use of the gas-phase calculation in these particular cases introduces a significant error in the energies obtained.[32]

Implications about the Trnsition-State Geometry. A general picture of the transition-state geometry of the deprotonation of simple ketones and esters can be constructed on the basis of the preceding analysis. From the slopes of correlations 1 and 2, it was concluded that the transition state is reactant-like, as would be expected for an exothermic reaction according to the Hammond postulate.[45] While the existence of the correlations tends to support the premise that, for simple carbonyl compounds, the role of the base, countercation, and solvent remains relatively constant, it appears from the intercepts of the correlations that there is an important steric interaction between these species and R_2 in the cis transition state.

The selective destabilization of one transition state by an intermolecular interaction strongly implicates an organized, cyclic transition state. In an acyclic transition state, stereoelectronic considerations should favor the approach of the base or base aggregate along the axis of the α-C–H bond. This approach would place the base in the plane defined by the carbonyl carbon, the α-carbon, and the proton being removed. In this position, the interaction of the base with R_2 is no worse in the cis transition state than it is in the trans transition state, so in itself, the approach of the base could not selectively destabilize either one. It is unlikely that the dipole–dipole interaction between the carbonyl and the weakly polar THF would cause sufficiently heavy solution about the oxygen to introduce the observed interaction. Furthermore, even if the countercation were to complex to the carbonyl oxygen rather than the more basic amide anion, it would still be free to shift about the oxygen so as to relieve any steric interactions with R_2. Thus, the existence of the intermolecular interaction suggests

(41) The similarity of the steric bulk of these groups can be illustrated by comparing their conformational free energies: methyl, 1.70 kcal mol^{-1} and ethyl 1.75 kcal mol^{-1}. See: Hirsch, J. A. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1963; Vol. 1, p 199.

(42) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.

(43) F_X is a measure of the improvement of the correlation on inclusion of both ΔH_m and ν_{R_2} over that containing just ΔH_m for the same data set. See ref 35a, p 200.

(44) (a) Campagnaro, G. E.; Wood, J. L. *J. Mol. Struct.* **1970**, *6*, 117. (b) Doddrel, D. M.; Bendall, M. R.; Barron, P. F.; Pegg, D. J. *J. Chem. Soc., Chem. Commun.* **1979**, 77. (c) Lunazzi, L. *Tetrahedron Lett.* **1975**, 1205. (d) Drakenberg, T.; Jost, R.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1974**, 1011. (e) Drakenberg, T.; Sommers, J.; Jost, R. *Org. Magn. Reson.* **1976**, *8*, 579. (f) Grindley, T. B.; Katritsky, A. R. *Tetrahedron Lett.* **1972**, 2643.

(45) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: San Fransisco, 1976; p 102.

**Table V.** Data for Deprotonations with LDA in 77% THF:23% HMPA Solvent Mixtures

entry	R_1	R_2	cis:trans ratio	ln (ratio)	ref
1	mesityl	Me	58:42	−0.323	9a
2	O-t-Bu	Et	77:23	−1.208	6
3	O-t-Bu	Me	84:16	−1.658	6
4	OMe	t-Bu	91:9	−2.314	6
5	OMe	Ph	95:5	−2.944	6
6	Et	Me	95:5	−2.944	6

that the base and counterion are constrined to the region about the carbonyl compound depicted in Figure 6. The base and countercation cannot be precisely located on the basis of the current data, but only a transition state in which the counterion bridges the space between the carbonyl and the base is consistent with this analysis.

The cyclic transition states **18** and **19** (Figure 7) were originally proposed by Ireland[6] for the deprotonation of esters with LDA in THF. The transition state leading to the cis isomer **18** would be destabilized by an intermolecular interaction between R_2 and the carbonyl oxygen, which has been, in effect, made larger by complexation with the base and counterion. While transition states such as these would seem to be supported by the current work, objections have been raised regarding their apparent violation of the stereoelectronic requirements for deprotonation. These objectives can be met by considering that the lithium amide base is likely to be in tetrameric or dimeric form.[46] Thus, the α-carbon, hydrogen, and base can be collinear, in accord with stereoelectronic considerations, while substituents elsewhere in the aggregate are situated to interact with R_2 in the transition state leading to formation of the cis isomer. Thus, as the bulk of the substituent on the amide increases, more of the trans isomer should be formed, as is observed.[5a,9c] The lower reactivity on lithium pyrrolide[9c] might be explained by a tighter aggregation of the base, which would be permitted by the small bulk of the substituents on the nitrogen. The irregular behavior[5a] of lithium hexamethyl disilazide (LHMDS) might be explained by its monomeric nature in THF solution.[47] Being monomeric, LHMDS would react through a different transition-state geometry than LDA or lithium tetramethyl piperidide (LTMP), so it would not necessarily behave in the same manner as the sterically similar LTMP.

Ireland proposed the cyclic transition-state geometry on the basis of the observation that the use of polar solvent mixtures (THF:HMPA 77:23 (v/v)) resulted in the production of much higher proportions of the cis enolate. He reasoned that the polar solvent should give better solvation of the lithium cation, so it would be less tightly coordinated to the carbonyl oxygen. This would effectively make the carbonyl oxygen smaller than in the absence of HMPA, so its interaction with R_2 in the transition state leading to the cis isomer would be diminished.

The proposal that the transition states are different between the two media can be tested by correlating the model energies with the isomer ratios reported for deprotonations in THF–HMPA mixtures. If the transition states in these solvent mixtures were acyclic, then there should be no aded enthalpy term due to a difference in intermolecular interactions, and the correlations should pass through the origin. If the transition states are cyclic, but less tightly organized than in the absence of HMPA, then the interaction of R_2 with the base and counterion should be diminished and the intercept of the correlation would be nonzero, but lower than in the correlation using the THF data. The data for the deprotonation of a number of ketones and esters with LDA
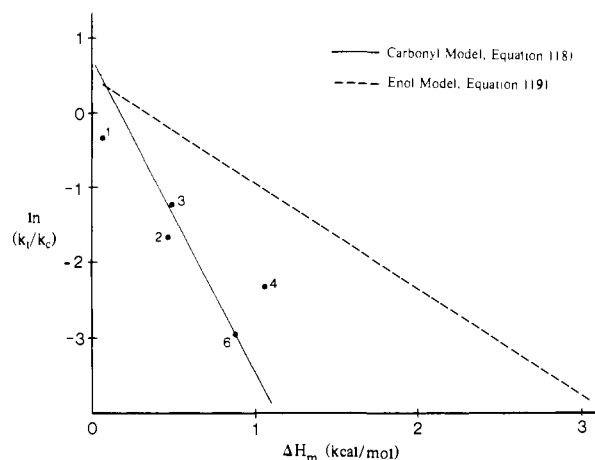
Figure 8. Scatter diagram of ln (k_t/k_c) vs. ΔH_m for the THF:HMPA data and the correlation lines for the carbonyl and enol models. Entry numbers correspond to those given in Table V.
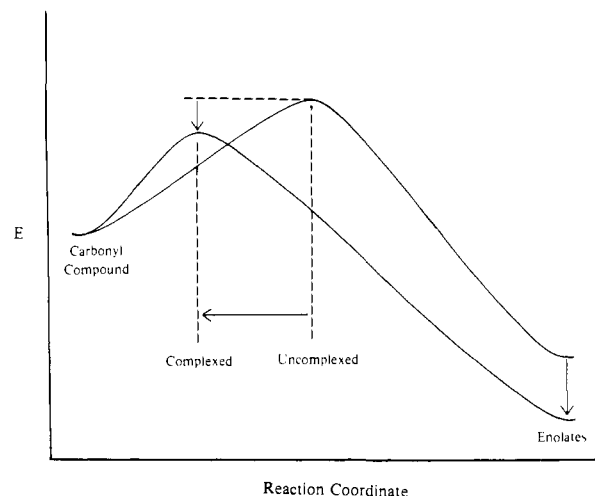
Figure 9. The effect of a coordinating countercation on the position of the transition state.

in THF containing 23 vol % HMPA are compiled in Table V. Correlation of these ratios with the appropriate carbonyl model energies from Table I resulted in the relationship

$$\ln (t/c) = -4.22\Delta H_m + 0.71 \qquad (18)$$

$$n = 4;\ s = 0.30;\ r^2 = 0.948\ (95.0);\ F = 36.8\ (95.0)$$

with entries 4 (R_2 = *tert*-butyl) and 5 (R_2 = Ph) as outlying points. A scatter diagram of the data is presented in Figure 8. Unfortunately, only rough estimates of the slope and intercept are possible for the enol model, since only two model enthalpies are available, but the relationship

$$\ln (t/c) = -1.4\Delta H_m + 0.4 \qquad (19)$$

is suggested.

Following the reasoning previously developed, it is apparent from the slopes of relationships 18 and 19 that the transition state of the reaction run in the presence of HMPA is much more advanced that that for the reaction run without HMPA. Such a shift between the transition states in the two media would be expected. In the cyclic transition state in THF, the metal cation is tightly coordinated to the carbonyl oxygen, increasing the polarization of the carbonyl group and increasing the partial positive charge on the carbonyl carbon. This carbon can be viewed as an electron-withdrawing substituent on the α-carbon, which would remove electron density from the α-C–H bond and make it easier to extend and break.[48] Thus, the transition state would be shifted

(46) LTMP has been reported to be tetrameric in crystalline form: Atwood, J. L.; Lappert, M. F.; Shakir, R.; Slade, M. J. cited in: Cetinkaga, B.; Grümrükçu, I.; Lappert, M. F.; Atwood, J. L.; Shakir, R. *J. Am. Chem. Soc.* **1980**, *102*, 2086, footnote 12. Lithium alkyls and lithium alkoxides are typically dimeric or tetrameric in ether solvents, and similar levels of aggregation might be expected for lithium amides. See: West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 633. Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177.

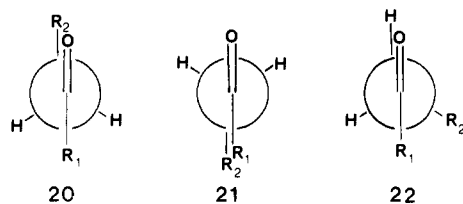(47) Kimura, B. Y.; Brown, T. L. *J. Organomet. Chem.* **1971**, *26*, 57.

Figure 10. Carbonyl conformations used as alternate model geometries.

toward the left (Figure 9). In an acyclic or expanded transition state, the metal is, at most, weakly complexed to the carbonyl, to the carbonyl carbon is less electropositive. The α-C–H bond becomes more difficult t extend and break, so the transition state is more product-like.

While the relationships in eq 18 and 19 pass much closer to the origin than those for the THF data, the intercepts are still nonzero. With the carbonyl model, the intercept is statistically significant, so it appears that the transition state leading to the cis enolate is still being destabilized by a small (0.2–0.3 kcal mol^{-1}) intermolecular interaction. The behavior of methyl 3,3-dimethylbutanoate (entry 4, Table V), which has a *tert*-butyl group at R_2, is consistent with this interpretation. As with the correlation using the data obtined with no HMPA, the deviation of this point suggests that the cis transition state is being destabilized more than in those cases having only methyl or ethyl at R_2. Inclusion of the steric parameter ν resulted in the correlation

$$\ln{(t/c)} = -4.22\Delta H_m + 1.99\nu_{R_2} - 0.35 \qquad (20)$$

$n = 5;\ s = 0.29;\ r^2 = 0.959\ (99.0);\ F = 23.5\ (95.0);$
$$F_X = 9.0\ (90.0)$$

While the small data set allows only a tentative conclusion to be drawn, the correlation is, nevertheless, consistent with the presence of a repulsive steric interaction between the base and R_2 which destabilizes the transition state leading to the cis isomer. Further evidence for such an interaction is the formation of only 48% of the cis isomer when LTMP is used to deprotonate 3-pentanone,[11] compared with the 95% of this isomer obtained with the sterically smaller LDA.[6] Increasing the steric bulk of the base would worsen the interaction as effectively as adding bulk at R_2. It thus appears that, even in the presence of HMPA, deprotonation with LDA proceeds through a cyclic transition state, though it is less tightly organized than that found in THF. A noncomplexing counterion, such as the *tetra*-n-butylammonium ion,[10b] may be required if the transition state is to be truly acyclic.

To summarize, the assumption that the roles of the base, countercation, and solvent remain more or less constant appears to be valid, and a quantitative relationship exists between the severity of intramolecular interactions and the change in product ratios across the series of compounds studied. Although the locations of the base and countercation cannot be precisely determined, their roles in the transition state are clear, and the following conclusions can be drawn: In THF, the transition states are reatant-like, cyclic and contain a steric interaction between the α-substituent and the base and/or countercation which disfovors formation of the cis isomer. The transition states in THF–HMPA mixtures are still cyclic but are expanded by comparison and are less reatant-like. The interaction which destabilizes the transition state leading to the cis geometry is diminished, and the inherent stability of the eclipsed orientation of α-alkyl ketones and esters results in the preferred formation of the cis isomer.

Alternate Carbonyl Model Geometries. While the carbonyl geometries **6** and **7** were chosen to mimic the expected geometries of the actual transition states, other geometries can, in principal, be used. Two alternate geometries were briefly examined to test the sensitivity of the correlations to variations in the model geometry.

The first of the alternate models employed the carbonyl compound conformations **20** and **21** (Figure 10), in which R_2 is eclipsed with the carbonyl oxygen and R_1, respectively. A regression

analysis using entries 1–9 of Table I and the corresponding values of ΔH_m from this model produced the correlation

$$\ln{(t/c)} = -1.32\Delta H_m + 4.3m \qquad (21)$$

$$n = 9;\ s = 0.65;\ r^3 = 0.962\ (99.9);\ F = 176\ (99.9)$$

which is comparable in strength to the correlation obtained with the original model geometries (eq 1).

The second alternate model simply employed the minimum energy conformations of the carbonyl compounds. The molecular geometries in this model were allowed to optimize with no constraints into their natural minima, so the actual geometries varied somewhat with different R_1 and R_2 groups. ΔH_m was determined by taking the difference in energy between that conformation having R_2 most nearly eclipsed with the carbonyl oxygen (as in structure **20**) and that having R_2 rotated about 120° from the oxygen (as in structure **22**). A regression analysis using entries 1–9 of Table I and the corresponding values of ΔH_m from this model gave the correlation

$$\ln{(t/c)} = -3.40\Delta H_m + 5.05 \qquad (22)$$

$$n = 9;\ s = 1.00;\ r^2 = 0.911\ (99.9);\ F = 71.2\ (99.9)$$

Although this correlation is acceptably strong, the standard deviation is nearly twice that of the original correlation (eq 1), probably because of the somewhat variable geometries of the unconstrained models.

Both of these models give reasonable results on the basis of the interpretation of the correlations presented above. The relative magnitudes of ΔH_m, as indicated by the slopes of the correlations, are consistent with the model geometries, and the intercepts give values of 1.8 and 20 kcal mol^{-1} for the interaction of R_2 with the base, in good agreement with the values obtained from the original models.

The strength of these correlations clearly indicates that model geometries can be used which do not closely mimic the expected transition-state geometries. However, while any of a number of model geometries can be used, the higher standard deviation of the unconstrained model (eq 22) suggests that a model with geometric constraints be used. This is not an unreasonable condition for the model, since the stereoselective requirements of the deprotonation are likely to impose geoemetric constraints on the actual transition state.

Some characteristics of the correlation models as applied to enolate formation are underscored by considering these alternate model geometries. Neither of the alternate models has a proton in the proper geometry with respect to the carbonyl for deprotonation, and it is not clear how to relate the geometries in the unconstrained model to the expected geometry of the transition state. It must be emphasized that the method only allows a comparison to be made between the energies of a set of model geometries and the energies of the transition state. The correlations give no information regarding changes in bond lengths, the degree of rehybridization of the α-carbon, or the orientation of the α-C–H bond in the transition state.

The Prediction of Enolate Ratios. In addition to providing a method for the investigation of transition-state geometries, the combinatino of force field modeling with multiple linear regression analysis has considerable potential as a predictive tool. The correlations offer the possibility of estimating the enolate ratio for the deprotonation of a projected intermediate in a synthetic route, thus aiding in the evaluation of a proposed synthesis. One can envision a series of correlations, each for a different set of reaction conditions. Thus, a single determination of ΔH_m for the compound of interest would permit the rapid screening of a number of reaction conditions to select those best suited for the desired application.

Either the carbonyl model or the enol model could be used for this purpose, depending on the availability of parameters for the program and the nature of the compound (e.g., the enol model must be used for aryl ketones while the carbonyl model must be used for esters). To obtain an esimate of the isomer ratio for a new compound, one need only to calculate the energies of the two

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model transition states (**6** and **7** for the carbonyl model or **8** and **9** for the enol model) for the compound of interest and enter the difference into the appropriate equation. For deprotonation with LDA in THF at –70 °C, eq 1 would be used for the carbonyl model and eq 2 would be used for the enol model. Equations 18 and 19 would be used for the carbonyl and enol models, respectively, for deprotonation with LDA in a 77:23 (v/v) THF:HMPA solvent mixture at –70 °C. If the group at R_2 is something other than methyl or ethyl, the carbonyl model would be used with the equations which include the steric parameter ν (eq 17 for LDA in THF and eq 20 for LDA in THF/HMPA).

The standard deviation of the correlations reflects both the uncertainty in the calculated energies and the variability in the observed enolate ratios due to minor differences in experimental technique. With the correlations in this work, predictions made using the carbonyl model should be accurae to within about 20% at the 95% confidence level. For the enol model, there can be no estimation of the error for eq 19, but predictions made with eq 2 would have an accuracy of about 20% at the 68% confidence level. It is anticipated that, as more data become available, both by experimentation and as more force field parameters are obtained, the correlations will gain strength and the uncertainty in the predictions will decrease.

The effect of cation-coordinating groups at R_1 and R_2 and the behavior of compounds with disubstitution at the acidic center have not been addressed in this work. One strength of the correlative approach is that new data can be incorporated into the model, and it is anticipated that the correlations can be adapted to accommodate these types of functionality as data permits.

Conclusion. The combination of force field modeling and regression analysis has proven to be a powerful probe into transition-state geometry which can potentially be applied to a wide variety of reactions. While the energies in this work were calculated exclusively with the MM2 program, the model energies can, in principle, be calculated by any method of comparable accuracy. The force field calculations give detailed structural and thermodynamic information about the molecules being used as the transition-state models. Regression analysis then relates this information to the behavior of the reaction, and the resulting correlations have a number of uses. By comparison of the correlation equations with the theoretical behavior, the position of the transition state on the reaction coordinate and the presence of general factors not included in the model can be deduced. Examination of the points which do not follow the correlation can identify anomalous behavior due to unusual steric or electronic substituent effects, partial or complete equilibration, or errors in the computational method. The use of two models can minimize errors due to the latter. Finally, the correlations can be used as a predictive tool, with the standard deviation providing a measure of the reliability of the prediction.

The methods presented in this paper represent a fairly general approach to the investigation of regio- and stereoselective reactions. Preliminary efforst with transition-state models for the aldol condensation have been successful, suggesting that the quantitative prediction of erythro:threo ratios is possible.[49]

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Energies of Non-Kekulé Molecular States. Calculation by a Predictively Useful Semiempirical Method

Paul M. Lahti,[†] **Angelo R. Rossi,**[*‡] **and Jerome A. Berson**[*†]

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511, and the University of Connecticut, Storrs, Connecticut 06268. Received September 26, 1984

Abstract: The order and spacing of the lowest energy states of non-Kekulé molecules are reproduced by INDO/S-CI calculations. The results agree with those obtained from high-level ab initio calculations and with available experimental findings. State energy orders for a number of unknown non-Kekulé species are predicted. Hund's rule appears to be obeyed for large π-electron systems, although violations may occur for smaller molecules belonging to or closely related to the disjoint class. Good agreement also is found between the observed and INDO/S-CI calculated electron configurations (π vs. σ) of some doublet radicals. The method should be useful as a qualitative predictive tool.

The chemical and magnetic properties of non-Kekulé molecules are determined by the order and spacing of the lowest energy states. Attempts to predict the most stable spin and occupation pattern for the two (or more) frontier electrons require a decision on whether to invoke Hund's first rule, since the one-electron frontier orbitals are degenerate or nearly so.[1] This problem, adumbrated early in the history of molecular quantum mechanics,[2] has been brought into sharp focus recently by corollaries of approximate molecular orbital[3] and valence bond[4] arguments, which predict the possibility or even likelihood of violations of Hund's rule in disjoint non-Kekulé systems. The experimental observation that such a violation does not occur in a specially constructed disjoint test system[5d] provided one of the motivations for the present study, which aims to develop a more general basis for the prediction of the energies of non-Kekulé molecular states.

†Yale University.
‡University of Connecticut.

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