

“Transition-State Modeling” Does Not Always Model Transition States

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Received July 5, 1988

Abstract: “Transition state modeling” methodology has been applied to a series of five ketoalkoxides whose energy barriers for degenerate intramolecular hydride transfer are known from dynamic NMR studies. The parameter sets derived from 3-21 and 6-31G ab initio calculations on conventional transition states resulted in an unsatisfactory agreement between calculated and observed energy barriers. Such was not the case with alternative transition-state models including a diketone, a distorted ketoalkoxide, and a bridged hydrocarbon (all of which are ground-state systems). For example, viewing the transition state as a ketoalkoxide with a C/H distance of 1.77 Å gave a correlation coefficient of unity (allowing prediction of energy barriers to less than 1 kcal/mol). The data show that it is not necessary here to invoke transition states to achieve high predictive power. Far better correlations were obtained with ground-state structures having all their bonds intact. Thus, it appears that the ability of “transition-state modeling” to predict rates in solution does not depend on the accuracy, or even the existence, of a transition state but rather on how closely the associated parameters coincide with one of many parameter sets that happen to provide a high correlation. With the hydride transfers, at least three different ground-state systems produce appropriate parameters sets. Distortions remote from the reaction center must dominate the relative rate sequence.

“Transition-state modeling”, developed largely by Houk and co-workers,¹ has been applied widely to problems in organic chemistry—particularly the correlation of reactivity with structure. Recently, our attention was captured by two “transition state modeling” articles concluding that *reactivity and distance are unrelated*.^{2,3} Since this generalization controverts our published views of reactivity,^{4,5} we felt it prudent to examine further our own tenets⁶ as well as the basis of “transition-state modeling” from which the disagreement emerged. With regard to the latter, we asked whether the procedure accurately depicts transition structures and, more to the point, whether accurate transition structures are even required for satisfactory reactivity–structure correlations. Our objective in addressing these questions is not to cavil and confute but to consider and weigh a methodology receiving major attention.

“Transition-state modeling” was applied, in typical fashion,¹ to the degenerate hydride transfer ($\text{CHO}^-/\text{C}=\text{O} \rightarrow \text{C}=\text{O}/\text{CHO}^-$) in hydroxy ketones 1–5 (Figure 1). This set of reactions was selected because (a) the energy barriers are known from dynamic NMR experiments^{7,8} and (b) symmetrical transition states and the absence of intermediates both simplify the analysis. Simplicity, always a virtue, is particularly desirable here where we seek to assess an assumption-laden⁵ technique.

Computational Methods

All computations were performed on either a DEC VAX 11/780 or a DEC MicroVAX II computer using a slightly modified MODEL program of Still for molecular mechanics calculations, AMPAC with the AM1 Hamiltonian of Dewar for semiempirical molecular orbital calculations, and the Gaussian 82 programs of Pople for ab initio calculations.

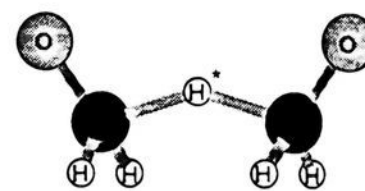
Our general approach consisted of three steps (the first two of which provided the parameters necessary for molecular mechanics calculations on the ground and transition states of the five

Table I. Geometric and Dipole Parameters for Acetone and Isopropoxide Calculated by Several Methods^a

	AMPAC	STO-3G	3-21G	6-31
Acetone				
C–O bond length, Å	1.235	1.219	1.211	1.2119
partial charge on O	–0.292	–0.226	–0.543	–0.532
Isopropoxide ^b				
C–O bond length, Å	1.317	1.336	1.344	1.368
partial charge on O	–0.745	–0.614	–0.862	–0.936
C–H bond length, Å	1.154	1.133	1.125	1.117
partial charge on H	–0.093	–0.089	0.007	–0.015
C–C–O bond angle, deg	113.7	115.7	113.0	111.8
C–C–H bond angle, deg	104.4	101.3	103.2	105.0
O–C–H bond angle, deg	113.1	117.1	116.8	113.8

^aAll other parameters remained at their standard MODEL values. ^bH refers to methine hydrogen.

Table II. Geometric and Dipole Parameters for the C_{2v} Transition State for the Transfer of Hydride from Methoxide to Formaldehyde Calculated by Several Methods



	AMPAC (AM1)	STO-3G	3-21G ^a	6-31G
C–O bond length, Å	1.267	1.273	1.261	1.273
partial charge on O	–0.560	–0.440	–0.711	–0.742
C–H* bond length, Å	1.379	1.375	1.463	1.422
partial charge on H*	–0.162	–0.068	–0.077	–0.048
H–C–O bond angle, deg	118.98	120.07	120.59	119.32
H–C–H* bond angle, deg	95.38	94.42	90.47	92.53
O–C–H* bond angle, deg	111.18	114.86	118.16	116.38
C–H*–C bond angle, deg	146.73	165.02	151.41	148.47

^aThis calculation is similar to that described in Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* 1987, 109, 906. Good agreement was achieved.

substrates): (a) We initially performed AMPAC and ab initio calculations at the STO-3G, 3-21G, and 6-31G levels on isopropoxide and acetone to secure ground-state parameters (Table I). Parameters required but not listed in the table were used as given in the MODEL program. (b) We then developed (again using four different computational modes) corresponding parameters sets for the symmetrical “ C_{2v} ” transition state in the hydride

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(2) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* 1987, 109, 3698.

(3) Dorigo, A. E.; Houk, K. N. *Adv. Mol. Model.* 1988, 1, 135.

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(6) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* 1988, 110, 6794.

(7) Craze, G.; Watt, I. *J. Chem. Soc., Perkin Trans. 2* 1981, 175.

(8) Cernik, R.; Craze, G.; Mills, O. S.; Watt, I. *J. Chem. Soc., Perkin Trans. 2* 1982, 361.

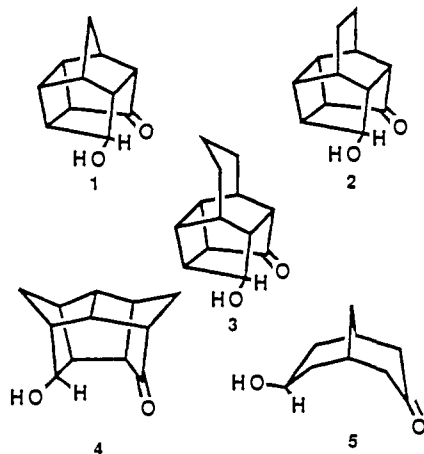


Figure 1. Hydroxy ketone substrates.

Table III. MODEL-Derived Steric Energies for Ground and Transition States of Compounds 1-5 Using Four Different Parameterization Sets

	1	2	3	4	5
Ground State					
AMPAC	70.0	71.3	80.3	68.8	19.7
STO-3G	69.7	71.0	80.1	68.8	19.6
3-21G	72.6	74.0	83.3	71.3	21.5
6-31G	72.5	73.9	83.1	70.9	21.2
Transition State					
AMPAC	70.0	68.6	75.6	59.7	19.8
STO-3G	73.4	72.3	79.6	62.7	21.3
3-21G	73.0	72.5	80.4	65.6	23.3
6-31G	74.2	73.3	80.9	65.7	24.3

transfer from methoxide to formaldehyde (Table II). (c) Finally, with the necessary parameterizations in hand, we calculated via MODEL molecular mechanics the steric energies of the ground and transition states for compounds 1-5. These are presented in Table III. Note that since MODEL does not contain a complete parameter set for alkoxides, we had to assume that the force constant for C-O⁻ is identical with that of the corresponding C-OH. No further assumptions were needed with regard to alkoxide radius and VDW parameters, as these had already been defined (with an unknown reliability) by the MODEL force field. Partial bonds in the transition states were treated exactly as prescribed by Houk in his "transition-state modeling": they were assigned one-half the normal bending and stretching constants. Partially negative oxygens retained their alkoxide-type VDW parameters. The C...H...C angle was given an arbitrarily weak bending constant of 0.2, while a small torsional potential ($V_2 = 0.2$) was applied to the mobile hydrogen to keep it in the plane of the transition-state carbonyls. Although our assumptions are multifold and a reasonable sense of doubt is recommended, it must be stated that the uncertainties are far less than in previous "transition-state modeling", such as performed on lactonizations,² where charged tetrahedral intermediates are involved and where even the nature of the rate-determining step is unclear.⁵ Thus, our simple and degenerate hydride transfer systems, unencumbered by conformational ambiguities, should provide every fair chance for "transition-state modeling" to shine.⁹

Results and Discussion

Any pair of ground state and transition state energies in Table III can be used to calculate activation energies for the five hydride transfers, but for brevity we will focus on the 3-21G-based data since this computational level has been favored in past "transition-state modeling".^{1,2} Thus, the 3-21G values have been abstracted from Table III and listed in Table IV along with

Table IV. "Transition-State Modeling" of Compounds 1-5 Based on 3-21G Parameterization^a

compd	steric energy, ketoalkoxide	steric energy, transition state	$E_a(\text{calcd})^b$	$E_a(\text{obsd})$
1	72.6	73.0	0.45	21.7
2	74.0	72.5	-1.54	19.0
3	83.3	80.4	-2.93	17.3
4	71.3	65.6	-5.75	13.7
5	21.5	23.3	1.81	19.4

^aAll energy in kilocalories/mole. ^bCalculated from the difference between the two preceding steric energies in the table.

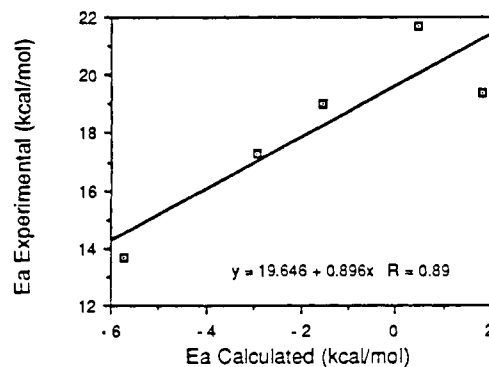


Figure 2. Correlation between experimental and calculated activation energies for compounds 1-5 using "transition-state modeling", 3-21G-based parameterization, and conventional transition states with partial bonds.

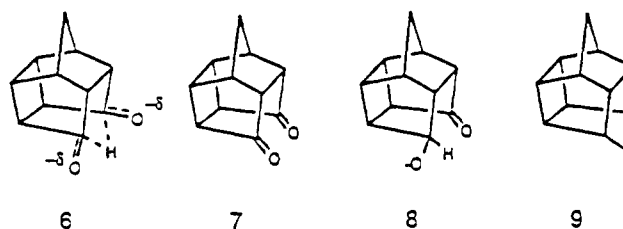


Figure 3. Transition-state models for compound 1. Model 6 is a symmetric conventional transition state, while the other three are ground states with all their covalent bond intact. Model 8 is the ketoalkoxide that has been compressed to a H/C(=O) distance of 1.77 Å.

calculated and observed activation energies.

Two points about Table IV are noteworthy. (a) Calculated and observed energy barriers differ by about 20 kcal/mol. Changes in steric energies, although termed "calculated activation energies" by Houk,¹ cannot of course be expected to equal the actual values. Moreover, solvation (among other factors) contributes heavily to energy barriers in solution.^{4,5} Thus, "transition-state modeling" focuses exclusively on relative trends rather than on absolute numbers. (b) More seriously, the correlation coefficient between observed and calculated energy barriers is only 0.89 (Figure 2). Stated in another way, rate constants predicted from an $E_a(\text{obsd})$ vs $E_a(\text{calcd})$ plot have a 10^3 -fold uncertainty. Matters would not improve if data from Table III based on 6-31G (our most sophisticated basis set) had been used. Since the chief merit of "transition-state modeling" lies in its predictive power and since our success in this regard was only modest, we next examined how alternative modeling would affect the correlations.

Four transition state "models" (Figure 3) were compared: (a) the conventional transition state 6 replete with partial bonds and already discussed; (b) a diketone *ground state*, 7; (c) an alkoxy ketone in which a 1.77 ± 0.01 Å H/C(=O) distance was imposed upon the molecule, 8; (d) a bridged *ground state*, 9. The latter three ground states differ from the conventional transition state in having all their covalent bonds intact.

It may seem strange at first that ground states 7-9 were employed as "substitutes" for the conventional transition state 6. But herein lies the essence of our work. If the standard partially bonded transition state provides better correlations and predictive

(9) For previous calculations on hydride transfers, see: Field, M. J.; Hillier, I. H.; Smith, S.; Vincent, M. A.; Mason, S. C.; Whittleton, S. N.; Watt, C. F.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* 1987, 84.

Table V. Correlation Coefficients for $E_a(\text{obsd})$ vs $E_a(\text{calcd})$ Using Various Transition-State Models

model ^a	C/C distance, ^b Å	C/H distance, ^b Å	corr coeff ^c
6 (3-21G)	2.63	1.46	0.89
6 (6-31G)	2.56	1.43	0.89
7 (MODEL)	2.63		0.97
8 (AMPAC)	2.43	1.76	0.99
8 (3-21G)	2.43	1.77	1.00
8 (6-31G)	2.42	1.78	1.00
9 (MODEL)	2.24		0.99

^aSee Figure 3 for structures of 6–9; the source of the force field is given in parentheses. ^bC/C and C/H represent the optimized hydroxy carbon/carbonyl carbon and carbonyl carbon/hydrogen distances for compound 1, respectively. ^cEncompass substrates 1–5. A correlation coefficient of unity reflects a value >0.995.

power than the ground-state representations, then obviously one benefits from invoking the transition state, mental construct though it may be. If, on the other hand, the ground-state representations yield the better correlations, then one can conclude either that (a) bond breakage–formation is peripheral to distortion of the supporting carbon framework as found in the ground-state systems or (b) transition-state modeling introduces artifacts that are readily alleviated by ignoring the transition state altogether and by focusing on more computationally accessible ground states.

The ground-state models of the transition states were treated exactly as described in detail for the conventional transition states. Thus, apparent activation energies were obtained by subtracting the 3-21G-based ground-state energies of compounds 1–5 from energies of “transition-state models” (i.e. 7–9 for compound 1), embodying one of the three ground-state types. These apparent activation energies were then compared to experimental values to give the correlation coefficients in Table V. For example, conventional transition state 6 with 3-21G or 6-31G parameterization gave, as already mentioned, a coefficient of only 0.89. In contrast, all the ground-state models of the transition state yielded vastly improved correlations. For example, MODEL calculations performed on the five substrates when the transition states were bridged (as in 9 for compound 1) gave a correlation coefficient of 0.99, and by viewing the transition state as a strained ground state with a C/H distance of 1.77 Å (as in 8 for compound 1) it was possible via 3-21G or 6-31G to achieve a correlation coefficient of *unity*. Figure 4 represents one of the plots from which the correlation coefficients were derived. Seemingly fictitious transition states allow prediction of energy barriers to less than 1 kcal/mol!

One might surmise a priori that the ground-state systems *should* indeed give good correlations because they “resemble” the transition state. Two considerations belie such a thought. (a) As seen from the C/C and C/H distance data for compound 1 in Table V (selected arbitrarily from a vast amount of geometric output that has been omitted for brevity), the conventional transition state 6 and its ground state model 8 are structurally dissimilar. (b) Since the correlation with the ground-state models *exceeds* that of the conventional model, it makes little sense to claim that the ground-state models achieve their success by resembling the transition state. The *reverse*, of course, could be true. Thus, the ability of “transition-state modeling” to predict does not depend on the accuracy or even the existence of a transition state but rather on how closely the associated parameters coincide with one of many parameter sets that happen to provide a good correlation. With the hydride transfers, at least three different

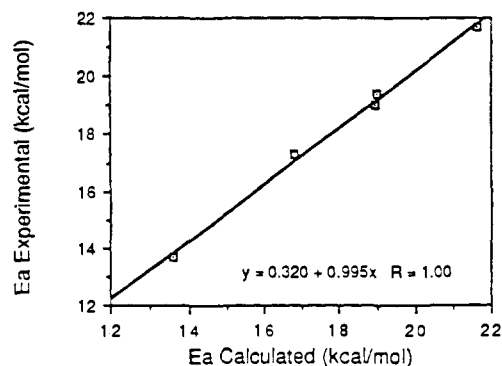


Figure 4. Correlation between experimental and calculated activation energies for compounds 1–5 using “transition-state modeling” and ground state 8 as the transition state for 1 and corresponding transition states for the other four substrates.

ground-state systems produce appropriate parameters sets.

We cannot, naturally, eliminate the possibility that our standard “transition-state modeling” involves assumptions and uncertainties that impair its predictive value relative to the ground-state alternatives. Two points must be made with regard to this possibility: (a) If a harmful artifact existed with our simple hydride transfer, then the general utility of “transition-state modeling” with more complicated and colorful reactions would be called into question. This is particularly true since a fairly sophisticated basis set, 6-31G, failed to give high correlations with the conventional partially bonded transition-state model. (b) Even if an artifact existed with the conventional transition state, and it were somehow eliminated, the resulting correlation coefficients could hardly exceed those secured by using the ground-state models (i.e. unity). And given a choice, Bishop Occam would no doubt bless the latter.

The final question to consider is why the ground-state models of the transition state so effectively predict the experimental observations. To answer this question, at least in a qualitative manner, we must refer to the previously published notion that reactions in solution are strongly dependent on distance.^{4,5} Fast intramolecular and enzymatic processes have been, accordingly, ascribed to enforced residency at contact distances. In support of this construct, we have developed an equation relating rate and distance⁵ and have synthesized molecules in which properly juxtaposed functionalities lead to astounding rate increases (e.g. hydrolysis of unstrained, aliphatic amides at pH = 7 and 22 °C).⁶ Thus, we are not surprised that our hydride-transfer calculations have less to do with partial bonds in a transition state than with bent covalent bonds in the ground state. *Once the proper contact distances are achieved between hydrogen and carbonyl carbon, bond formation–breakage becomes peripheral to the rate changes within the series.*¹⁰

It is not the intention of this paper to denigrate the predictive value of “transition-state modeling”. We do, however, think it advisable not to overinterpret correlations by concluding, for example, that a transition-state model represents reality or that reactivity and distance are unrelated.^{2,3}

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health.

(10) In many intermolecular systems, activation energies reflect mainly the desolvation of approaching functional groups rather than distortion of carbon frameworks. Glew, D. N.; Moelwyn-Hughes, E. A. *Proc. R. Soc. London, Ser. A* 1952, 211, 254.