Direct Evidence of Limitations in the Applicability of the Kinetic Method of Conformational Analysis

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IN a previous Paper[1] it has been demonstrated that serious doubts must be raised concerning the validity of conformational energies computed by means of the kinetic method of Winstein[2] and Eliel[3] and their co-workers. These doubts were founded on both theoretical arguments as well as on expositions of experimental inconsistencies in published results. Since then others[4] have presented evidence which can be construed as supporting our basic thesis[1] that the transition state of 4-t-butylcyclohexyl derivatives (undergoing reaction at position 1) could only be fortuitously comparable, either structurally or energetically, to the corresponding conformers of the unsubstituted cyclohexane compound (which is the essence of the kinetic method of conformational analysis).

Previous arguments[1] advanced against the kinetic method have nonetheless accepted the basic (but unsupported) premises of the method; namely, the unsubstituted cyclohexyl substrate reacts *via* two distinct transition states corresponding to the axial and equatorial conformers that populate the

TABLE

Temperature dependence of A *as determined from rates*[a] *of solvolysis of cyclohexyl tosylates in acetic acid.*

Temp. (°c)	k, sec.$^{-1}$ (10)^5 *trans*-4-t-Butyl	k, sec.$^{-1}$ (10^5) Unsubstituted	k, sec.$^{-1}$ (10^5) *cis*-4-t-Butyl	*A* (Calc.)
50	0·17	0·19	0·30	1·15
70	2·11	2·36	4·61	1·47
90	22·1	23·9	47·1	1·87
116	342	369	708	2·05
102·5	568	568	1020[b]	——
122·8	631	622	1280[b]	——
124·8	726	683	1600[b]	——

[a] All rate constants have been determined as the average of at least three determinations with an average deviation of ± 1% or better.

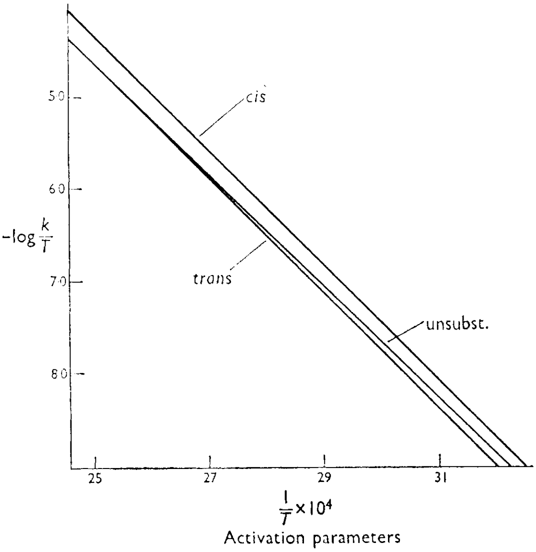
[b] Calculated by extrapolation of the log k against $1/T$ line. All other rate constants listed in this Table have been calculated from direct experimental data.

ground state; the 4-t-butyl epimers react through distinctly unrelated transition states, each corresponding energetically and structurally to the pure axial or equatorial ground states from which they respectively arise. The data to be presented here, however, may be construed to indicate a serious error in the premise of a multiplicity of transition states through which unsubstituted cyclohexyl substrates have been presumed to react.

The solvolysis rates determined for the three pertinent cyclohexyl tosylates in acetic acid over a temperature range of roughly 75°, as listed in the Table have been plotted in the Figure in accordance with the functional variables of the absolute rate theory[5] equation in the form $\log k/t = a + b/T$.

Clearly, the activation parameters of *cis*- and *trans*-4-t-butyl substrates are entirely parallel over the temperature range investigated, and this must be deemed as exceedingly strong evidence of constantly maintained differenecs in transition-state structure of the two substrate reactions as the temperature is changed. Furthermore, these differences are apparently due to disparities in entropy content reflecting dissimilarities in transition-state structure, rather than (directly) in enthalpy of bond breaking. Thus, if the unsubstituted compound, as demanded by the kinetic method of conformational analysis, solvolyzes *via* a mixture of the two transition states corresponding in structure to those of the *cis*- and *trans*-4-t-butyl compounds (respectively), the appropriate data should plot a line which lies both parallel to and between those of the two conformer models. The Figure in which these plots are presented conveys a convincing denial of this expectation.

It can be deduced from these data that cyclohexyl tosylate, although a mixture of ground-state conformers, solvolyzes essentially *via* a single transition state whose free-energy change is identical with the respective 4-t-butyl models at two temperatures. That is to say, at the higher of these temperatures cyclohexyl tosylate solvolyzes at the same rate as the *trans*-4-t-butyl, and at a lower it reacts at the same rate as the *cis*, contrary to the theory underlying the kinetic method.



FIGURE

Solvolysis of 4-t-butyl- and unsubstituted cyclohexyl tosylates in acetic acid.

Although reservations regarding the soundness of the three basic assumptions of the kinetic method have been expressed by Eliel and his collaborators,[6,8] the method continues to be applied.[6] It is our opinion that the kinetic method cannot be justified merely because it seems to work sometimes.[6,8] Its use can only be tentatively subscribed where the reaction centre is not on the carbocyclic ring, such as (for example) in certain reactions of carboxylic groups, and where the transition state may not involve a change in the hybridization of any ring atom. Moreover, even under these circumstances it remains to be proved that an unsubstituted cyclohexyl substrate reacts *via* a mixture of two transition states (according to the kinetic method).

(*Received, December* 13*th*, 1966; *Com.* 987.)

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[2] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

[3] E. L. Eliel and R. S. Ro, *Chem. and Ind.*, 1956, 251.

[4] V. J. Shiner and J. Jewett, *J. Amer. Chem. Soc.*, 1965, **87**, 1382; W. H. Saunders and K. T. Finley, *ibid.*, p. 1384.

[5] For details see S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes", McGraw-Hill, New York, 1941. In this form a and b are known constants and k and T are the reaction rate constant and absolute temperature respectively.

[6] E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Amer. Chem. Soc.*, 1966, **88**, 3327; E. L. Eliel and F. J. Biros, *ibid.*, p. 3334.

[7] We use here the symbol of conformational energy A originally employed by Winstein (ref. 2) as identical with $G°$ employed by Eliel (ref. 5).

[8] See for further references E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison "Conformational Analysis", Wiley, New York, 1965; E. L. Eliel, *Angew. Chem.* (*Internat. Edn.*), 1965, **4**, 761; *J. Chem. Educ.*, 1960, **37**, 126.