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KINETICS AND MECHANISM OF THE ACID-CATALYZED HYDRATION OF DIHYDRO-1,4-DIOXIN

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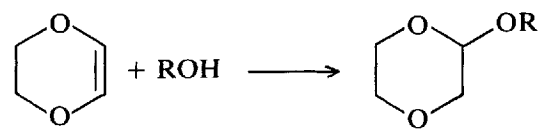
ABSTRACT

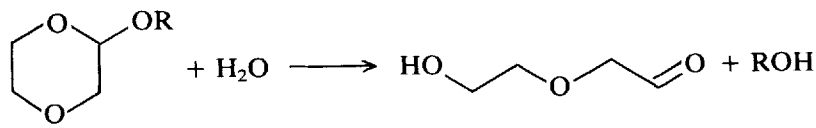
The cyclic vinyl ether dihydro-1,4-dioxin is converted to its cyclic hemiacetal hydration product, 2-hydroxy-1,4-dioxane, in aqueous solution by an acid-catalyzed reaction for which $k_{H^+} = 1{\cdot}80 \times 10^{-5}$ M^{-1} s^{-1} at 25 °C. This reactivity and the solvent isotope effect $k_{H^+}/k_{D^+} = 2{\cdot}2$ show that the reaction occurs by rate-determining proton transfer from catalyst to substrate and not by a pre-equilibrium mechanism as recently proposed.[2]

The cyclic vinyl ether dihydro-1,4-dioxin, **1**, reacts readily with alcohols in the presence of appropriate catalysts to give cyclic acetals, equation (1), which, in turn, are easily hydrolyzed



1 (1)

to regenerate the original alcohols, equation (2). This makes dihydro-1,4-dioxin a useful reagent for protecting alcohol groups, superior in some respects to the more commonly used dihydropyran.[1]



(2)

The reaction of dihydro-1,4-dioxin with alcohols is similar to its acid-catalyzed reaction with water (equation (1), R=H) for which a mechanism has recently been proposed.[2] The proposed mechanism consists of rapid pre-equilibrium protonation of the substrate on oxygen followed by rate determining bimolecular displacement on vinyl carbon, equation (3); the enol

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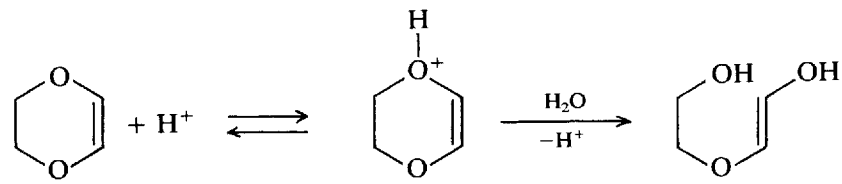
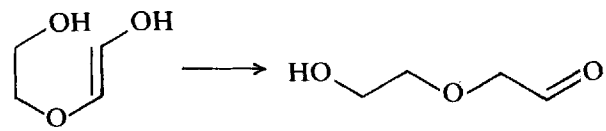


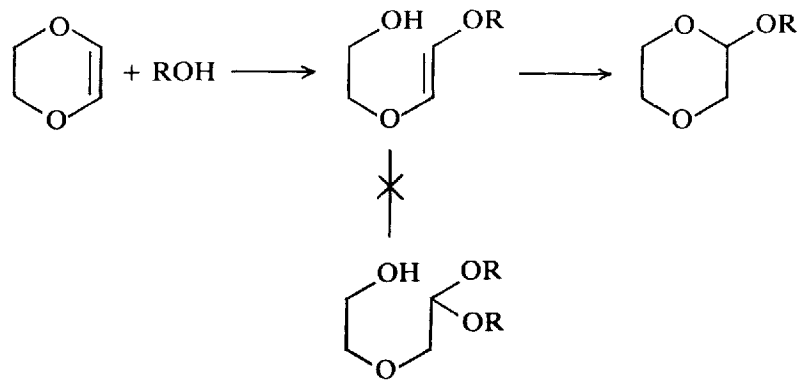
(3)

thus formed then undergoes rapid ketonization to give 5-hydroxy-3-oxapentanal, equation (4),



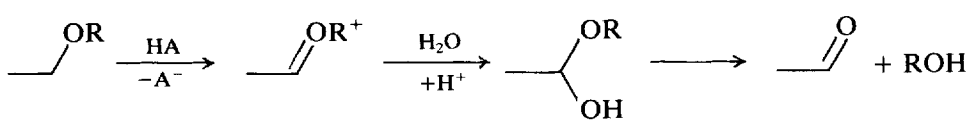
(4)

the known hydrolysis reaction product.[3] This mechanism could apply to the reaction of dihydro-1,4-dioxin with alcohols to form cyclic acetals, equation (1), provided that the intermediate acyclic vinyl ether cyclized in preference to reacting with another molecule of alcohol, equation (5). This mechanism, however, is contrary to the generally accepted reaction



(5)

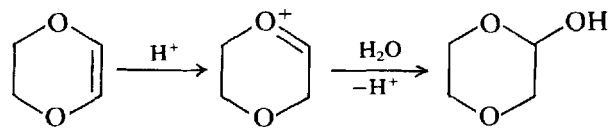
scheme for vinyl ether hydrolysis, which consists of rate-determining protonation of the substrate on carbon, followed by rapid hydration of the alkoxycarbocation thus formed and further rapid decomposition of the hemiacetal intermediate, equation (6). This vinyl ether hydrolysis mechanism is based upon a large body of evidence and appears to occur without exception.[4]



(6)

In order to investigate this apparent contradiction, we have re-examined the reaction of dihydro-1,4-dioxin with aqueous acids. We find that it does indeed occur by rate-determining proton transfer to carbon, as in the conventional vinyl ether hydrolysis mechanism (equation

(6)), but that it stops at the cyclic hemiacetal stage and gives 2-hydroxy-1,4-dioxane, **2**, as the only detectable reaction product, equation (7). This means that the position of equilibrium of



(7)

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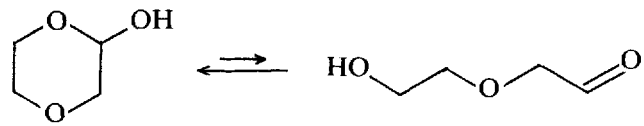
the ring-chain tautomeric process which converts this product into its open chain hydroxyaldehyde isomer, equation (8), lies strongly on the cyclic hemiacetal side, in keeping



(8)

with the results of other studies of similar systems which show that the cyclic isomer predominates in aqueous solution.[5] It also means that the reaction of dihydro-1,4-dioxin with aqueous acids examined here might more properly be called a hydration rather than a hydrolysis.

EXPERIMENTAL SECTION

Materials

Dihydro-1,4-dioxin was prepared by dehydrogenation of diethylene glycol in the presence of potassium hydrogensulfate;[6] its NMR spectrum was consistent with its structure. A sample for kinetic measurements was purified by fractional distillation (b.p., 93–95°); analytical gas chromatography showed it to be >99% pure.

All other materials were best available commercial grades. Solutions were prepared using deionized H_2O, purified further by distillation, or D_2O (Merck, Sharpe, and Dohme, >99·8 atm %D) as received.

Kinetics

Rates of reaction were determined spectroscopically, by monitoring the decrease in absorbance of dihydro-1,4-dioxin at $\lambda = 220$ nm. Measurements were made with a Cary 118 spectrometer whose cell compartment was thermostatted at 25·0 ± 0·1 °C. Reactions were usually followed for several half-lives; the data so obtained fit the first-order rate law well, and observed first-order rate constants were calculated by least-squares fitting to an exponential function. For some of the slower reactions, however, an initial rate method was employed. This involved measuring the linear decrease of absorbance over the first 1–2% reaction, using an offset scale of the spectrometer, and then converting that zero-order rate into a first-order rate constant by dividing by the initial absorbance reading. This method assumes that the reaction products have no absorbance at the wave length employed ($\lambda = 220$ nm); the fact that

rate constants determined in this way agreed well with those measured for reactions followed to completion shows that this assumption is correct.

RESULTS

A reaction of dihydro-1,4-dioxin with water conducted in D_2O solution containing 0·1 M DCl was monitored by proton NMR. The spectral changes observed indicated that the substrate was coverted smoothly into the cyclic hemiacetal 2-hydroxy-l,4-dioxane (equation (7)), and the final spectrum was consistent with that published for this substance.[7] No signal could be detected in the aldehydic proton region, and we therefore estimate that no more than 2–3% of the open chain aldehyde isomer of the cyclic acetal could have been present. This sets an upper limit of *ca.* 0·03 on the equilibrium constant for the ring-chain tautomeric reaction of equation (8).

Rates of disappearance of dihydro-1,4-dioxin were measured in moderately concentrated aqueous (H_2O) perchloric acid solutions and also in 0·10 M hydrochloric acid in H_2O and in D_2O. The data so obtained are summarized in Tables 1 and 2.

Table 1. Rates of hydration of dihydro-1,4-dioxin in concentrated aqueous (H_2O) perchloric acid solutions at 25 °C[a]

Wt. % $HClO_4$	$[H^+]$/M	X_0	$k_{obs}/10^{-2}$ s^{-1}
16·7	1·82	0·455	0·0113, 0·0112, 0·0112
23·8	2·73	0·676	0·0351, 0·0356, 0·0350
30·3	3·63	0·951	0·108, 0·108, 0·100, 0·104
33·2	4·06	1·11	0·187, 0·185
36·3	4·53	1·29	0·339, 0·339, 0·331, 0·337
39·3	5·13	1·56	0·794, 0·778, 0·810, 0·782
43·4	5·73	1·87	1·77, 1·83, 1·87, 1·83
46·6	6·32	2·19	4·01, 4·33, 4·04, 4·19, 4·06, 4·38, 3·89, 3·80, 3·82, 3·81, 3·89, 4·26
49·5	6·88	2·54	11·8, 11·5, 10·1, 9·68, 9·38, 11·3, 9·55

[a]Ionic strength = $[H^+]$.

Table 2. Rates of hydration of dihydro-1,4-dioxin in dilute aqueous acid solutions at 25 °C[a]

Acid	$[L^+]$/M	$k_{obs}/10^{-6}$ s^{-1}
HCl[b]	0·100	1·83, 1·82, 1·72
DCl[b]	0·102	0·803, 0·859, 0·801
DCl[c]	0·100	0·854

[a]Ionic strength = 0·10 M.
[b]Initial rate method; reactions monitored for first 1–2% only.
[c]Conventional method; reaction monitored for several half-lives.

Rates of reaction in perchloric acid increased with increasing acidity of the medium, but the increase was much steeper than in direct proportion to acid concentration. Such behaviour is common for acid-catalyzed reactions in concentrated acid solution, and the situation is generally handled by using an acidity function to correlate the data. The X_0 function[8] appears to be the best scale currently available for this purpose.[9]

Correlations of this kind are conventionally made using an expression of the form of equation (9), in which k_{H^+} is the bimolecular catalytic coefficient that applies in dilute solution

$$\log(k_{obs}/[H^+]) = \log k_{H^+} + m^{\ddagger}X_0 \tag{9}$$

where $X_0 = 0$ and $m^{\ddagger}$ is a slope parameter. This expression requires log $(k_{obs}/[H^+])$ to be a linear function of X_0. Figure 1 shows that this is not so over the entire range of the present data: the relationship is linear up to $X_0 \cong 1{\cdot}5$, but rate constants determined at acidities greater than this fall below a straight line drawn through the points up to $X_0 = 1{\cdot}5$, and the difference increases with increasing acidity. Such behaviour would result if, in the more acidic solutions, significant amounts of substrate were being converted rapidly into a protonated form. This form could be the oxygen-protonated intermediate of the pre-equilibrium reaction shown in equation (3); such an oxygen-protonated species could also be a by-product made in a non-productive side reaction which occurs along with the rate-determining carbon protonation scheme of equation (7). In either case, the required modification to equation (9) takes the form shown in equation (10). Here, k_{H^+} is once again the dilute solution catalytic

$$\log(k_{obs}/[H^+]) = \log k_{H^+} + m^{\ddagger}X_0 + \log\left(\frac{K_{SH^+}}{K_{SH^+} + [H^+]\,10^{mX_0}}\right) \tag{10}$$

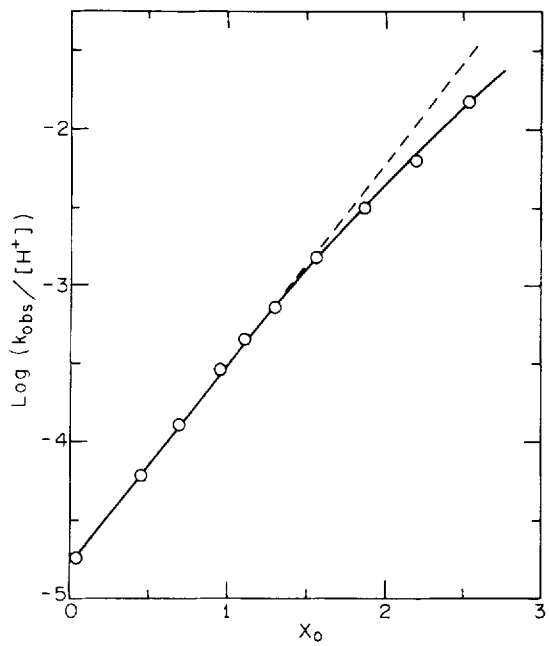


Figure 1. Relationship between rates of hydration of dihydro-1,4-dioxin in aqueous perchloric acid solution and the X_0 acidity function

coefficient and K_{SH^+} is the acidity constant of the oxygen-protonated substrate; m^+ and m are slope parameters, m^+ for the kinetic process and m for the equilibrium oxygen-protonation reaction.

Non-linear least-squares fitting of the experimental data to equation (10) gave the following parameters: $k_{H^+} = (1{\cdot}80 \pm 0{\cdot}09) \times 10^{-5}$ M^{-1} s^{-1}, $pK_{SH^+} = -2{\cdot}51 \pm 0{\cdot}45$, $m^+ = 1{\cdot}26 \pm 0{\cdot}02$, and $m = 0{\cdot}65 \pm 0{\cdot}16$. The first of these is in very good agreement with the catalytic coefficient obtained directly in 0·10 M acid, $k_{H^+} = (1{\cdot}79 \pm 0{\cdot}06) \times 10^{-5}$ M^{-1} s^{-1}, and the second is a reasonable value for the acidity constant of an oxygen-protonated aliphatic ether: for example, $pK_a = -2{\cdot}48$ and $-2{\cdot}39$ have been reported for the conjugate acids of dimethyl and diethyl ethers respectively.[10]

Combination of the rate constants determined in H_2O solution with those obtained in D_2O gives the solvent isotope effect $k_{H^+}/k_{D^+} = 2{\cdot}20 \pm 0{\cdot}06$.

DISCUSSION

Solvent isotope effects on hydronium ion catalytic coefficients provide a useful means of distinguishing pre-equilibrium proton transfer reactions, such as that of equation (3), from rate-determining proton transfers, such as that of equation (7): the isotope effects on pre-equilibrium reactions are generally inverse, $k_{H^+}/k_{D^+} < 1$, whereas those on rate-determining proton transfers are usually normal, $k_{H^+}/k_{D^+} > 1$.[11] For example, $k_{H^+}/k_{D^+} = 0{\cdot}37$ for the hydrolysis of acetaldehyde dimethyl acetal[12] and $k_{H^+}/k_{D^+} = 0{\cdot}57$ for the enolization of acetaldehyde,[13] both of which occur by pre-equilibrium proton transfer mechanisms. On the other hand, $k_{H^+}/k_{D^+} = 3{\cdot}0$ for the hydrolysis of ethyl vinyl ether[14] and $k_{H^+}/k_{D^+} = 2{\cdot}3$ for the hydrolysis of dichloroketene dimethyl acetal;[15] both of these are rate-determining proton transfer reactions. The normal isotope effect, $k_{H^+}/k_{D^+} = 2{\cdot}2$, determined here for the hydration of dihydro-1,4-dioxin therefore shows that this reaction occurs by the rate-determining proton transfer process of equation (7) and not by the pre-equilibrium proton transfer mechanism of equation (3). This isotope effect is also inconsistent with reversible carbon protonation followed by rate-determining attack of water on the alkoxycarbocation, a mechanism which is at any rate ruled out by the fact that the NMR experiment described at the beginning of the previous section showed incorporation of only one deuterium atom in the 2-hydroxy-1,4-dioxane reaction product.

Additional evidence against the pre-equilibrium oxygen protonation mechanism of equation (3) comes from a comparison of the reactivity of dihydro-1,4-dioxin with that of a saturated analog, diethyl ether. The acid-catalyzed hydrolysis of this substance doubtless takes place by such a pre-equilibrium route, equation (11). In this case, however, the slow step is bimolecular

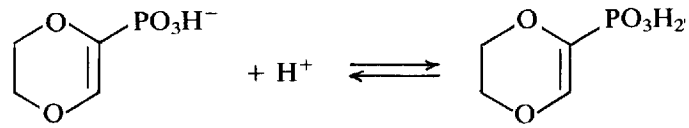
$$\mathrm{EtOEt} + \mathrm{H^+} \rightleftarrows \mathrm{Et\overset{H}{\overset{|}{O}}Et^+} \xrightarrow[-\mathrm{H^+}]{\mathrm{H_2O}} 2\mathrm{EtoH} \qquad (11)$$

displacement on saturated carbon rather than on vinyl carbon. Displacement reactions on saturated carbon are known to be more rapid than displacement reactions on vinyl carbon,[16] and that plus the expected greater basicity of saturated over vinyl ethers, and consequent higher concentration of the ether conjugate acid, leads to the prediction that diethyl ether should be more reactive than dihydro-1,4-dioxin, if both substances react by the pre-equilibrium mechanism. The data, however, show otherwise: $k_{H^+} = 2{\cdot}4 \times 10^{-13}$ M^{-1} s^{-1}

for the hydrolysis of diethyl ether[17] is many orders of magnitude less than $k_{H^+} = 1{\cdot}8 \times 10^{-5}$ M^{-1} s^{-1} determined here for the hydration of dihydro-1,4-dioxin.

This very large difference in reactivity can also be used to rule out a pre-equilibrium mechanism for dihydro-1,4-dioxin with rate determining bimolecular displacement on saturated rather than on vinyl carbon. Such a process would have an unsaturated alcohol as the leaving group, and an appropriate model might be the hydrolysis of ethyl phenyl ether, EtOPh. Since the reactivities of ethyl phenyl ether and diethyl ether are quite similar, differing by less than a factor of two,[18] reaction of dihydro-1,4-dioxin by this mechanism would also be expected to be very much slower than the rate actually observed.

The previous assignment of a pre-equilibrium mechanism for the acid-catalyzed hydration of dihydro-1,4-dioxin[2] was made on the basis of failure to detect general acid catalysis and observation of apparent saturation of catalysis by the hydrogen ion. Hydration of dihydro-1,4-dioxin, however, is a rather slow reaction, and the Brønsted exponent for this process should therefore be quite large* and general acid catalysis consequently difficult to detect.[20] The apparent saturation of hydrogen ion catalysis, moreover, could have been an artifact produced by formation of the oxygen-protonated form of the substrate in a non-production side reaction. In at least one other case it could also have been caused by a different change in the dominant form of the substrate. The substrate in this case was the phosphoric acid derivative of dihydro-1,4-dioxin, **3**. In dilute acid solutions, this substance

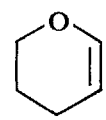


(12)

4 **3**

would exist as the phosphonate anion, **4**, but, as the hydrogen ion concentration was raised, this anion would be converted to the less reactive phosphonic acid, **3**, equation (12); the rate of dihydrodioxin hydrolysis would consequently drop, giving an effect which could easily be mistaken for saturation of hydronium ion catalysis. The inflection point in the hydrogen–ion catalytic curve in this case occurred at $[H^+] \cong 0{\cdot}3$ M,[2] which corresponds to a not unreasonable value for the ionization constant of a phosphonic acid such as **3**.[21]

The rate constant determined here for hydration of dihydro-1,4-dioxin, $k_{H^+} = 1{\cdot}8 \times 10^{-5}$ M^{-1} s^{-1}, makes this substance 31,000 times less reactive than its mono-oxo analog, 2,3-dihydropyran, **5**, for which $k_{H^+} = 0{\cdot}28$ M^{-1} s^{-1}.[22] (This comparison includes a statistical factor of two to allow for the fact that there are two reactive sites in dihydro-1,4-dioxin but only one in 2,3-dihydropyran.) Alkoxy substituents are known to stabilize carbon—carbon



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*Extrapolation of a relationship between α and log k_{H^+} for a series of vinyl ethers[19] leads to the prediction $\alpha = 0{\cdot}90 \pm 0{\cdot}06$ for the hydrolysis of dihydro-1,4-dioxin.

double bonds,[23] and such stabilization would lower the free energy of the hydration reaction's initial state, raising its free energy of activation and slowing the reaction rate. It is significant, however, that the present rate retardation corresponds to a difference in free energy of activation, $\delta\Delta G^{\ddagger} = 6{\cdot}1$ kcal mol^{-1}, which is significantly greater than the double bond stabilization parameter of an alkoxy group, $D = 5{\cdot}2$ kcal mol^{-1}.[23] The difference could be caused by an additional transition-state destabilizating effect of the second oxygen atom, whose electron-withdrawing inductive effect would oppose the positive charge being generated on the substrate as a proton is being transferred from the catalyst. The magnitude of this additional effect may be estimated at about one order of magnitude on the assumption that the Brønsted exponent for this reaction is $\alpha \cong 0{\cdot}9$ (see earlier footnote) and $(1\text{-}\alpha)$ $(5{\cdot}2) = 0{\cdot}5$ kcal mol^{-1} of the alkoxy group double bond stabilization will consequently still be expressed in the reaction's transition state. This leaves $6{\cdot}1 - (5{\cdot}2 - 0{\cdot}5) = 1{\cdot}4$ kcal mol^{-1} for the additional transition state destabilizing effect, which corresponds to an 11-fold rate reduction.

ACKNOWLEDGMENT

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REFERENCES

1. M. Feitizen and I. Hanna, *Synthesis*, 806–807 (1985).
2. V. S. Tsivunin, V. G. Zaripova, I. N. Zapirov, and Sh. A. Nasybullin, *Zh. Obshch. Khim.*, **51**, 318–324 (1980).
3. R. K. Summerbell and L. K. Rochen, *J. Am. Chem. Soc.*, **63**, 3241–3244 (1941).
4. For a recent review, see A. J. Kresge, *Accts. Chem. Res.*, **20**, 364–370 (1987).
5. C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324–5329 (1952); J. E. Whiting and J. E. Edward, *Can. J. Chem.*, **49**, 3799–3806 (1971).
6. R. D. Moss and J. Paige, *J. Chem. Eng. Data*, **12**, 452–454 (1967); *C.A.* **67**, 64325a (1967).
7. J. Gierer and I. Pettersson, *Acta Chem. Scand.*, **22**, 3183–3190 (1988).
8. R. A. Cox and K. Yates, *Can. J. Chem.* **59**, 2116–2124 (1981).
9. A. J. Kresge, H. J. Chen, G. L. Capen, and M. F. Powell, *Can. J. Chem.*, **61**, 249–256 (1983).
10. P. Bonvicini *et al.*, *J. Am. Chem. Soc.*, **95**, 5960–5964 (1973); A. Bagno, G. Scorrano, and R. A. More O'Ferrall, *Rev. Chem. Intermediates*, **7**, 313–352 (1987).
11. A. J. Kresge, R. A. More O'Ferrall, and M. F. Powell, *Isotopes in Organic Chemistry*, Vol. 7, E. Buncel and C. C. Lee, Eds, Elsevier, New York (1987), Chapter 4.
12. M. Kilpatrick, *J. Am. Chem. Soc.*, **85**, 1036–1038 (1963).
13. Y. Chiang *et al.*, *J. Am. Chem. Soc.*, **109**, 4000–4009 (1987).
14. A. J. Kresge and Y. Chiang, *J. Chem. Soc.*, 58–61 (1967).
15. A. J. Kresge and T. S. Straub, *J. Am. Chem. Soc.*, **105**, 3957–3961 (1983).
16. S. I. Miller and P. Yonan, *J. Am. Chem. Soc.*, **79**, 5931–5936 (1957); D. R. Kelsey and R. G. Bergman, *J. Am. Chem. Soc.*, **93**, 1953–1961 (1971).
17. A. Skrabal and A. Zahorka, *Monatsh. Chem.*, **63**, 1–22 (1933).
18. R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615–685 (1954).
19. A. J. Kresge *et al.*, *J. Am. Chem. Soc.*, **93**, 413–423 (1971).
20. J. R. Keeffe and A. J. Kresge, *Techniques of Chemistry*, Vol. 6, Part 1; *Investigations of Rates and Mechanisms of Reactions*, C. F. Bernasconi, Ed., Wiley, New York (1986), Chapter XI.
21. W. P. Jencks and J. Regenstein, *Handbook of Biochemistry*, Chemical Rubber Co., Cleveland, Ohio (1970), p. J-190.
22. A. Kankaanpera, *Acta Chem. Scand.*, **23**, 1465–1470 (1969).
23. J. Hine, *Structural Effects on Equilibria in Organic Chemistry*, Wiley, New York (1975), pp. 270–276.