Secondary Deuterium Isotope Effects for Hydrolysis of Acetals and Orthoformates

By H. Bull, T. C. Pletcher, and E. H. Cordes*

(*Department of Chemistry, Indiana University, Bloomington, Indiana* 47401)

Summary Kinetic secondary deuterium isotope effects for the hydrolysis of ethyl orthoformate and propionaldehyde diethylacetal reveal that the transition state resembles the substrate in the former case and the carbonium-ion intermediate in the latter; for substituted benzaldehyde diethylacetal hydrolysis, the transition states increasingly resemble the carbonium-ion intermediates as the electron withdrawing power of the polar substituent increases.

Isotope effects on reaction rates have proved useful in a number of instances as indicators of changes in mechanism or transition-state geometry as a function of substrate structure, solvent, and the like. For example, α-deuterium isotope effects, which depend principally on changes in force constants between the ground and transition states at the point of isotopic substitution, have provided a powerful tool for distinguishing between nucleophilic (S_N2) and limiting (S_N1) mechanisms in several solvolytic reactions.[1-6] We report similar isotope-effect studies for several reactions of well established pathway: the hydrolysis of acetals derived from aliphatic and aromatic aldehydes and of ethyl orthoformate. The observed isotope effects reveal a striking change in transition-state structure as a function of the stability of the carbonium ions.

A number of independent lines of evidence establish that the acid-catalysed hydrolysis of acetals, ketals, and ortho-esters occurs with rate-determining formation of carbonium-ion intermediates.[7] For hydrolysis of acetals and ketals, carbonium-ion formation is probably preceded by substrate protonation while, in contrast, substrate protonation and carbonium-ion formation appear to be concerted processes for hydrolysis of ortho-esters. The extent of carbonium-ion formation in the transition state for hydrolysis of these species is not clear, although several indications suggest that it may change with changes in substrate structure.

Secondary deuterium isotope effects for the compounds studied are collected in the Table. The ratios of rate constants are considered to be accurate to within ±0·01.

Two important conclusions may be drawn from the data. First, the variation in isotope effect for hydrolysis of the substituted benzaldehyde diethylacetals very strongly suggests that the extent of C–O bond cleavage in the transition state increases markedly as the stability of the derived carbonium ion diminishes. A transition state with little or no C–O bond stretching should yield an isotope effect near unity, while one in which this bond is fully cleaved should yield an isotope effect near 1·23.[2,4] The observed changes cannot be accounted for in terms of increasing nucleophilic participation by solvent since just such a case has been previously identified and the changes, as expected, are in the opposite direction.[3] The change in transition-state structure as a function of substrate reactivity for hydrolysis of the benzaldehyde acetals is perhaps the largest yet observed among carbonium-ion processes; the tendency of the transition state increasingly to resemble the product carbonium ion as substrate reactivity decreases (corresponding to a decrease in carbonium-ion stability) is in qualitative agreement with the predictions of Leffler,[8] Hammond,[9] and Thornton.[10]

Secondary deuterium isotope effects on the rates of hydrolysis of benzaldehyde diethylacetals, propionaldehyde diethylacetal, and ethyl orthoformate

p-Nitrobenzaldehyde diethylacetal[a] ..	1·15
Benzaldehyde diethylacetal[a]	1·09
p-Methoxybenzaldehyde diethylacetal[a] ..	1·04
Propionaldehyde diethylacetal[b]	1·17
Ethyl orthoformate[a]	1·05

[a] Reaction conducted in aqueous solution at 25°. Values of pH maintained constant by use of dilute acetate or phosphate buffers.

[b] Reaction conducted in 50% aqueous dioxan containing dilute hydrochloric acid at 25°.

The α-deuterium isotope effects for the hydrolysis of α-phenethyl chlorides are, in contrast to the results reported here, independent of the nature of the polar substituent.[1] This is consistent with, and evidence for, distinct rate-determining steps in the two sets of reactions: ion-pair dissociation for the phenethyl chlorides and carbonium-ion formation for the acetals.[1,7]

Second, comparison of the isotope effect for the hydrolysis of ethyl orthoformate and propionaldehyde diethylacetal with those for hydrolysis of the benzaldehyde acetals reveals, in light of the above discussion, that the transition state for the former substrate has little, and that for the latter substrate has much, carbonium ion character. These conclusions accord with our expectations in light of the transition-state structure–carbonium-ion stability correlation developed above.

Generalizing, it seems fair to conclude that hydrolysis of orthocarbonates and ortho-esters is characterized by reactant-like transition states, while hydrolysis of acetals and ketals derived from aliphatic substrates is characterized by carbonium-ion-like transition states. Acetals and ketals derived from aromatic substrates may be expected, as is the case directly studied here, to occupy either of the above categories, or an intermediate one, depending on the nature of polar substituents (*e.g. p*-methoxybenzaldehyde diethylacetal is a "phenyligous" orthoformate). These generalizations account for several experimental observations including (i) the fact that rate constants for hydrolysis of substituted benzaldehyde diethylacetals and substituted methyl orthobenzoates are correlated by σ, and not σ^+, substituent constants[11–13] and that values of ρ are $-3{\cdot}35$ [11,12] and $-1{\cdot}1$,[13] respectively; and (ii) that ketals are generally more reactive than the ortho-esters derived from them by the replacement of an alkyl group by an alkoxy-group even though the carbonium ion derived from the ketal is less stable than that derived from the ortho-ester. This follows since the reactant-like transition state for ortho-ester hydrolysis may be destabilized more by inductive electron-withdrawal of the alkoxy relative to the alkyl group than stabilized by electron donation through resonance from the alkoxy-group as originally suggested by DeWolfe and Jensen.[14,15] Thus, the relative energy of the transition states for ketal and ortho-ester hydrolysis cannot be rationalized on the basis of comparative ground-state and intermediate-state energies. This is a particularly complicated example in which rate constants and equilibrium constants exhibit divergent behaviour with a simple structural change in the substrate.

The extent of proton transfer from the hydrated proton or other acid to the substrate in the transition state (nearly complete) as judged from Brønsted α values for ortho-ester hydrolysis,[16,17] does not reflect the extent of C–O bond cleavage in the transition state as judged from the α-deuterium isotope effects. This finding emphasizes the dangers in drawing detailed inferences concerning transition state structures from values of Brønsted exponents.

We acknowledge a most helpful discussion with Professor V. J. Shiner, jun. This research was supported by the National Institutes of Health and the National Science Foundation.

(*Received, March 2nd*, 1970; *Com.* 299.)

---

[1] V. J. Shiner, jun., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, 1968, **90**, 418.
[2] V. J. Shiner, jun., M. W. Rapp, M. Wolfsberg, and E. A. Halevi, *J. Amer. Chem. Soc.*, 1968, **90**, 7171.
[3] V. J. Shiner, jun., M. W. Rapp, and H. R. Pinnick, jun., *J. Amer. Chem. Soc.*, 1970, **92**, 232.
[4] A. Streitwieser, jun., and G. A. Dafforn, *Tetrahedron Letters*, 1969, 1263.
[5] J. A. Llewellyn, R. E. Robertson, and J. M. W. Scott, *Canad. J. Chem.*, 1960, **38**, 222.
[6] K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *Canad. J. Chem.*, 1960, **38**, 1505.
[7] For review, see: E. H. Cordes, *Progr. Phys. Org. Chem.*, 1967, **4**, 1.
[8] J. E. Leffler, *Science*, 1953, **117**, 340.
[9] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[10] E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 2915.
[11] T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, 1968, **90**, 4081.
[12] R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *J. Phys. Chem.*, 1969, **73**, 1898.
[13] K. Koehler and E. H. Cordes, unpublished observations.
[14] R. H. DeWolfe and J. L. Jensen, *J. Amer. Chem. Soc.*, 1963, **85**, 3264.
[15] For several points of view concerning this matter, see ref. 14 and: (i) R. H. DeWolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, 1969, **34**, 848; (ii) C. A. Bunton and R. H. DeWolfe, *ibid.*, 1965, **30**, 1371; (iii) R. K. Chaturvedi, J. Adams, and E. H. Cordes, *ibid.*, 1968, **33**, 1652.
[16] H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, 1960, **82**, 5123.
[17] A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, 1965, **87**, 4593.