Chart I

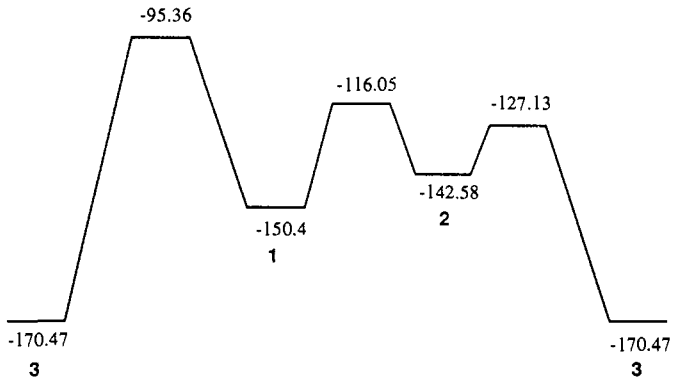
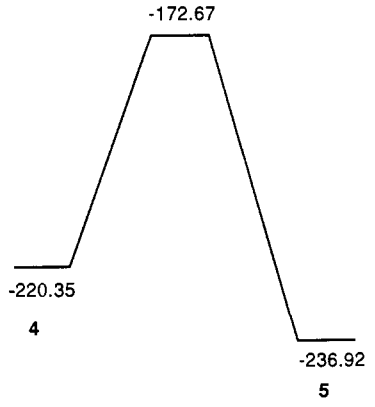


Chart II



can proceed by a pericyclic mechanism, without, however, identifying it as a [3,3]-sigmatropic process. It should be noted here that TSs of this type have been invoked in the case of the aldol reaction.[12] The TS for the metalloclaisen reaction adopts a chair conformation as one would expect by analogy with the Cope or Claisen rearrangements.[13]

The minimum energy reaction path for the formation of product in the case of the monomeric species is (see Chart I) first the conversion of **1** to **2** which then in the next step gives **3**. The rate-determining step for this reaction is predicted to be not the formation of the final product **3** but the formation of **2**. Therefore, the E_a, which for the moment neglects the involvement of dimer, is predicted to be 26.5 kcal/mol.

We next carried out calculations for the dimeric form of the RR. Our calculations predict dimerization to be exothermic by about 5 kcal/mol; implying that the RR should exist as a dimer in solution or in the crystal. This agrees with the experimental evidence that the RR is indeed a dimer in the solid state.[4] The authors responsible for the crystal structure of the RR pointed out that there are two possible pathways by which the RR can react to form product.[4] The first is a 1,3-sigmatropic shift of methylene carbon to carbonyl carbon while the second involves attachment of the carbonyl carbon to the transannular methylene (six-centered TS). These authors favored the latter reaction path. We have studied both pathways. While we found a TS for the 1,3-sigmatropic reaction, no TS could be located for the alternative reaction path. We found that this latter pathway broke apart the dimer at a great energetic cost, while the former led smoothly to product **5**. The reaction profile for the dimer is given in Chart II.

The E_a for product formation in the case of the dimer is 47.7 kcal/mol, and in order for us to compare this figure with that of the monomer reaction we have to include the heat of dimerization (ΔH_{dim}) of the monomer. For the ΔH_{dim} of **1** we arrive at a value of 5.3 kcal/mol, hence the E_a for the conversion of **4** into **3** is 31.8 kcal/mol. However, since we underestimate the stability of four-coordinate zinc we feel that this E_a probably represents a lower limit to the actual E_a. Regardless, we feel that the Reformatsky reaction occurs via the monomeric form of the RR, because unless our ΔH_{dim} is underestimated by over 15.8 kcal/mol the dimeric form of the RR cannot be competitive with the monomeric form.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research (Contract no. AFOSR 86-0022), the Robert A. Welch Foundation (Grant no. F-126), and the National Science Foundation (Contract CHE 87-12022). Part of it was conducted by using the supercomputing resources of the Center of Theory and Simulation in Science and Engineering at Cornell University, which receives funding in part from the NSF, New York, and IBM corporation. K.M.M. thanks Professor Roald Hoffmann for his support and guidance during his stay at Cornell.

(12) See, for example: Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078 and references cited therein.
(13) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

Direct Experimental Evidence for Cleavage of Both Exo- and Endocyclic C–O Bonds in the Acid-Catalyzed Reaction of Alkyl β-Tetrahydropyranyl Acetals

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The mechanistic and stereoelectronic aspects of acetal hydrolysis have attracted a great deal of attention from both organic chemists and biochemists in recent years.[1-3] The continuing interest is due largely to the biological importance of the reaction. A significant objective has been to understand the mode of action of lysozyme.[4,5] Model studies related to the lysozyme problem

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(2) For annual reviews, see: Chapters on "Reactions of Aldehydes and Ketones and Their Derivatives" In *Organic Reaction Mechanisms* John Wiley and Sons: New York, annual volumes, 1965 to the present.

(3) For recent articles, see: (a) Fife, T. H.; Przystas, T. J. *J. Chem. Soc., Perkin Trans. 2* **1987**, 143. (b) Fife, T. H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, *108*, 2425, 8050. (c) Bennet, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287. (d) Gandour, R. D.; Rives, J. T.; Fronczek, F. R. *J. Org. Chem.* **1986**, *51*, 1987. (e) Ueno, S.; Oshima, T.; Nagai, T. *J. Org. Chem.* **1986**, *51*, 2131. (f) Jones, P. G.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1986**, 444. (g) Bennet, A. J.; Sinnott, M. L.; Wijesundera, W. S. S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1233. (h) Hosie, L.; Sinnott, M. L. *Biochem. J.* **1985**, *226*, 437. (i) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.* **1984**, *106*, 6197. (j) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200. (k) Jones, P. G.; Kirby, A. J. *J. Am. Chem. Soc.* **1984**, *106*, 6207. (l) Sinnott, M. L. *Biochem. J.* **1984**, *224*, 817. (m) Hosie, L.; Marshall, P. J.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1121. (n) Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 4884. (o) Przystas, T. J.; Fife, T. H. *Ibid.* **1980**, *102*, 4391. (p) Young, P. R.; Bogseth, R. C.; Rietz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268. (q) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1979**, *101*, 1202. (r) Eliason, R.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 7037. (s) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238. (t) Gorenstein, D. G.; Findlay, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3473. (u) Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113.

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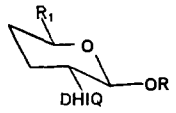
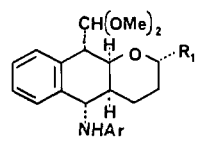
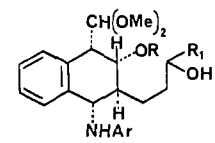
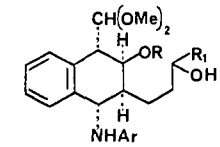
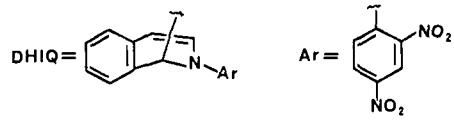
Table I. Trapping Products of the Acid-Catalyzed Cleavage of THP Acetals

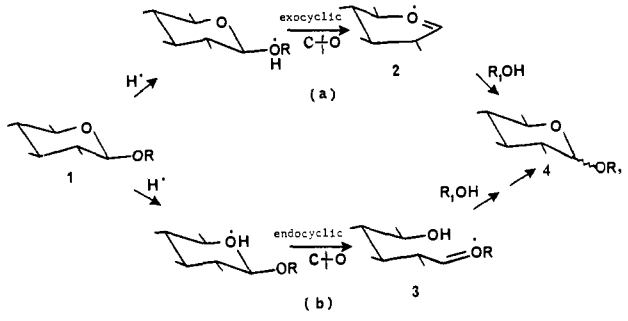
entry	THP acetal[a,b]	products[a,b] and their relative ratios[c,d]		
				
1	**5** (R = Me; R_1 = H)	**6** (R_1 = H) (45.5%)	**7** (R = Me; R_1 = H) (45.5%)	**8** (R = Me; R_1 = H) (9%)
2	**14** (R = Et; R_1 = H)	**6** (R_1 = H) (38%)	**7** (R = Me; R_1 = H) (4%) **15** (R = Et; R_1 = H) (54%)	**8** (R = Me; R_1 = H) (4%) **16** (R = Et; R_1 = H) (0%)
3	**18** (R = Me; R_1 = CH_2OH)	**20** (R_1 = CH_2OH) (45%)	**21** (R = Me; R_1 = CH_2OH) (51%)	**22** (R = Me; R_1 = CH_2OH) (4%)
4	**19** (R = Me; R_1 = CH_2OMe)	**23** (R_1 = CH_2OMe) (45%)	**24** (R = Me; R_1 = CH_2OMe) (51%)	**25** (R = Me; R_1 = CH_2OMe) (4%)

[a] DHIQ and Ar are defined as follows



[b] The structure and stereochemical assignments of the compounds described in this paper are based on high field (400 MHz and 300 MHz) ^{1}H NMR and decoupling experiments studies, high resolution mass spectra, and comparisons of the data with analogous compounds described in our synthetic paper.[11] All THP acetals were single diastereomers. [c] The conversions of THP acetals to tetralins were almost quantitative. The ratios of the products were determined by ^{1}H NMR of crude reaction mixtures. [d] Products and their relative ratios are obtained from the treatment of THP acetals with Dowex-H^+ and methanol.

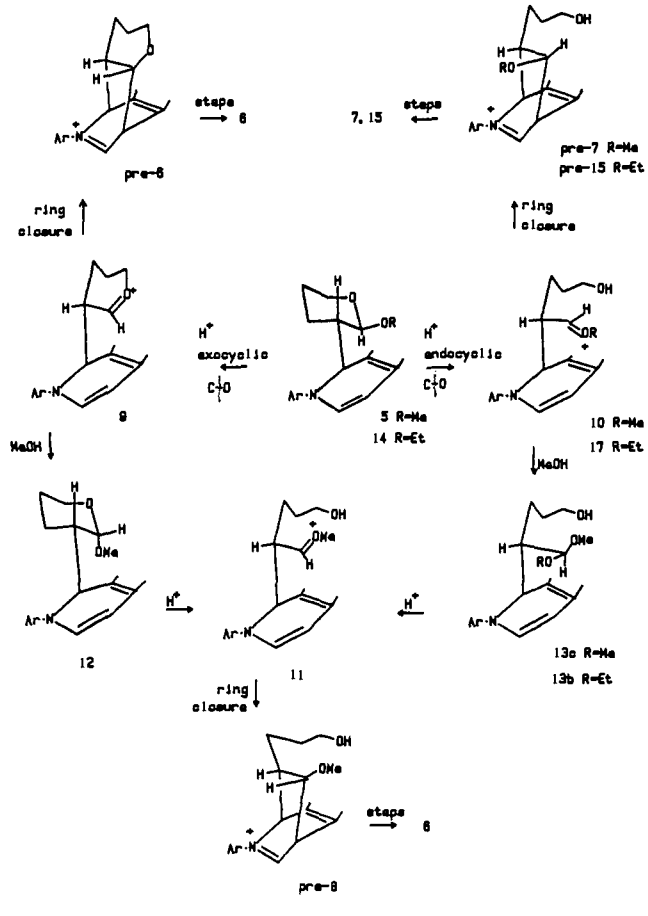
Scheme I



include the acid-catalyzed hydrolysis of glycopyranosides[3c,m,6] and the analogous tetrahydropyranyl (THP) acetals.[7]

Since glycopyranosides (and THP acetals) **1** are unsymmetrical acetals, a major problem in understanding the mechanism of their hydrolysis concerns the identification of the position of C–O bond cleavage. Two pathways are possible: (a) protonation of **1** followed by exocyclic C–O bond cleavage leads to cyclic oxocarbonium ion intermediate **2** and (b) protonation of **1** followed by endocyclic C–O bond cleavage forms a ring-opened oxocarbonium ion intermediate **3** (Scheme I). A large body of evidence, based principally on kinetic studies of glycopyranosides and THP acetals in protic media, overwhelmingly favors mechanism (a).[1,8,9] However, mechanism (b) in protic media has never

Scheme II



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been absolutely ruled out. In fact, on the basis of molecular dynamic simulations, plus structural and stereoelectronic considerations, Karplus has recently suggested mechanism (b) to be a more favorable pathway for lysozyme action.[5]

Since either path (a) or (b) eventually yields the same solvolysis product **4** when alcohol or water is the trapping nucleophile, product studies have not been useful in distinguishing between (a) and (b).[10] An unambiguous way to differentiate between routes (a) and (b) would be to trap the intermediate oxocarbonium ion(s) so as to obtain distinguishable product(s). We report herein the results of trapping experiments which clearly demonstrate that both pathways (a) and (b) are operative in the proton-catalyzed cleavage of alkyl β-THP acetals.

Our trapping method is a C–C bond-forming reaction via intramolecular attack of an enamine on an oxocarbonium ion generated in situ from acid-catalyzed cleavage of an acetal.[11] When our starting acetal **5**, which has two trans diequatorial groups on the THP ring, was stirred with Dowex-50 X 8-H^+ and anhydrous methanol for about 3 days at room temperature, a mixture of three compounds **6**, **7**, and **8** was obtained (Table I; entry 1).

The formation of major products **6** and **7** is easily rationalized by assuming the intermediacy of oxocarbonium ions **9** and **10** formed as a result of exocyclic C–O bond and endocyclic C–O bond cleavages, respectively (Scheme II). Transformations[11] subsequent to the ring closure step in each case then lead to structures **6** and **7**. The formation of minor product **8**, however, cannot be straightforward. The precursor to **8** must be the oxocarbonium ion **11** which could result either from the rotation of oxocarbonium ion **10** around the C–C bond or, alternatively, from the cleavage of acetals **12** and **13a** formed as a result of competitive solvent (methanol) trapping of the oxocarbonium ions **9** and **10**, respectively.[12,13] To test these possibilities compound **14**, the ethyl acetal analogue of **5**, was stirred with Dowex-H^+ and methanol, and four products **6**, **7**, **8**, and **15** were isolated (Table I; entry 2).[14] The absence of product **16** (which could only arise via rotation of the initially formed intermediate oxocarbonium ion **17** followed by ring closure) and the presence of **7** and **8** provide support for the solvent attack mechanism for formation of the minor products.

We also treated THP acetals **18** and **19**, which have all equatorial substituents, with Dowex-H^+ and methanol. The results are summarized in Table I (entries 3 and 4) and are consistent with those obtained in the cases of **5** and **14**.

In summary, we have provided concrete experimental evidence which demonstrates that in proton-catalyzed solvolysis there is the possibility for both exo- and endocyclic C–O bond cleavages of THP acetals.[15] We believe that our findings require a fresh look at the early conclusions favoring exclusive exocyclic C–O bond cleavage of THP acetals[8c,d,h] and at subsequent interpretations based on the early precedent.[7a,f,16] In addition, our method will be important for the examination of the role of stereoelectronic effects in acetal hydrolysis.[1b-d,3c,h,l,m]

Acknowledgment. We are indebted to the National Cancer Institute for Grant CA-39351, to the American Cancer Society for grant CH-272, and to CUNY for PSC research awards which supported this work. The NMR spectrometers used in the research were purchased with funds awarded by NSF-PCM-111745 and NIH-RR-03214.

(9) While our manuscript was in the review process, Guindon reported that dimethylboron bromide in CH_2Cl_2 served to cleave the endocyclic C–O bond in THP acetals and glycosides. (a) Guindon, Y.; Bernstein, M. A.; Anderson, P. C. *Tetrahedron Lett.* **1987**, *28*, 2225. (b) Guindon, Y.; Anderson, P. C. *Ibid.* **1987**, *28*, 2485.

(10) A similar question regarding exo- versus endocyclic carbon–heteroatom bond cleavage arises in the hydrolysis of cyclic ortho esters and related systems. However, due to the formation of different products, the identification of the position of bond cleavage is not ambiguous. (a) For a review see: ref 1d, Chapter 3. (b) For a recent article, see: Khouri, F. F.; Kaloustian, M. K. *J. Am. Chem. Soc.* **1986**, *108*, 6683 and references therein.

(11) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393.

(12) Intramolecular trapping of the oxocarbonium ion **10** by the hydroxyl group may also generate **12**.

(13) We have already observed that the rotation of oxocarbonium ions around the C–C bond in these systems is slow compared to solvent trapping and is almost nonexistent.[11] Also, the formation of acetals **12** and **13** as a result of competing solvent trapping of the oxocarbonium ions is reminescent of the initial formation of **5**.

(14) The increase in the formation of products resulting from the ring-opening mechanism of acetal in the case of **14** as compared to **5** (Table I; entries 1 and 2) is consistent with our earlier observation in these systems that ethanol is a poorer leaving group than methanol.[11]

(15) As a referee states, the observed percentage of endocyclic cleavage is only the minimum since there is no measure for the fraction of reclosure of intermediate, e.g., **10** to starting THP acetal **5**.

(16) Beaulieu, N.; Dickinson, R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531.

1,3-Asymmetric Induction in Intramolecular Reformatsky-Type Reactions Promoted by Samarium Diiodide†[1]

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Received May 20, 1987

Extraordinary strides have been made in recent years in development of synthetic methods which permit stereochemical control in construction of acyclic organic molecules.[3] Perhaps most dramatic have been those conceptual advances which permit 1,3-relative asymmetric induction by carbon–carbon bond-forming reactions utilizing β-heterosubstituted carbonyl substrates.[4] Still, truly general methods for such processes have yet to emerge. For example, few reported methods of 1,3-asymmetric induction provide more than 10:1 diastereoselectivity for representative substrates.[4d-f,j] Many such processes appear to be useful for β-alkoxy aldehydes but not corresponding ketones or vice versa.[4] Finally, no studies of which we are aware have addressed the important problem of 1,3-asymmetric induction in substrates where substituents α to the carbonyl may affect the stereochemical outcome in reactions of interest.

Inherent geometrical constraints imposed by intramolecular carbonyl addition reactions provide an attractive means by which to achieve 1,3-relative asymmetric induction, and this approach has been effectively employed by several research groups.[4d,g-j] Intramolecular Reformatsky reactions of bromoacetates derived from β-hydroxy carbonyl substrates provide a very promising variant of the intramolecular carbonyl addition approach to 1,3-asymmetric induction. However, only limited success has been realized along thse lines with zinc-promoted reactions, as low yields and/or poor diastereoselectivities have been observed in studies reported to date.[5] Our success in utilizing samarium diiodide

† Dedicated to Professor Herbert C. Brown on the occasion of his 75th birthday.

(1) Lanthanides in Organic Synthesis. 8.

(2) Alfred P. Sloan Research Fellow, 1987–1989.

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