J|A|C|S COMMUNICATIONS

On the Synergism Between H_2O and a Tetrahydropyran Template in the Regioselective Cyclization of an Epoxy Alcohol

Jeffery A. Byers and Timothy F. Jamison*

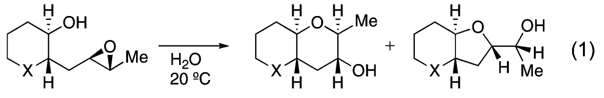
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received January 21, 2009; E-mail: tfj@mit.edu

We previously reported[1] that the combination of a *template*[2] and *water* provided a means to conduct highly regioselective epoxide-opening cascades reminiscent of Nakanishi's proposed biogenesis of the ladder polyether natural products.[3] With the aid of mechanistic studies carried out on the original template (tetrahydropyran **1a**) and its carbocyclic analogue **1b**, we now provide a molecular explanation for these phenomena. In short, the data support two competing pathways for **1a**: one that is unselective and first order in water and another that is highly selective with a second-order water dependence. Moreover, the differences observed between **1a** and **1b** demonstrate unequivocally the essential role of the tetrahydropyran ring oxygen in **1a** in regioselective epoxy alcohol cyclizations.

Consistent with our earlier findings, cyclizations of **1a** in water (eq 1) proceeded selectively to form the six-membered ring product, **2a** (Table 1).[4] The reaction operates under kinetic control, as accumulation of the five-membered ring product (**3a**) was not observed *in situ* and purified **3a** did not isomerize to **2a** when resubjected to the original (20 °C, pH 7, 3 d) or more vigorous reaction conditions (60 °C, pH 7, 7 d).

Table 1. Epoxy Alcohol Cyclizations with Various Additives



1a (X = O)
1b (X = CH_2)

2a (X = O)
2b (X = CH_2)

3a (X = O)
3b (X = CH_2)

entry	X	time (h)	additive	% conversion[a]	2:3[a]
1	O (**1a**)	33	none	58 (4)	11:1 (1)
2	O (**1a**)	33	CTABr[b]	67 (1)	12:1 (2)
3	O (**1a**)	33	LiCl (4 M)	88 (2)	15:1 (1)
4	O (**1a**)	33	$LiClO_4$ (4 M)	73 (3)	12:1 (1)
5	O (**1a**)	33	pH 7 (1 M)[c]	81 (2)	10:1 (1)
6	CH_2 (**1b**)	2	none	80 (12)	1:1.3 (0.1)
7	CH_2 (**1b**)	2	CTABr[b]	71 (7)	1:1 (0.2)
8	CH_2 (**1b**)	2	LiCl (4 M)	93 (4)	1:1.3 (0.1)
9	CH_2 (**1b**)	2	$LiClO_4$ (4 M)	81 (2)	1:1.3 (0.1)
10	CH_2 (**1b**)	2	pH 7 (1 M)[c]	82 (6)	1:1.2 (0.3)

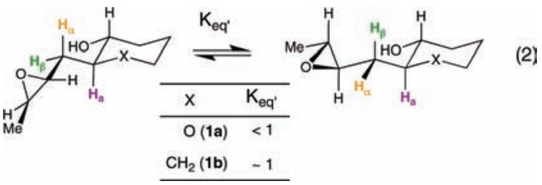
[a] Average of three measurements; average error in parentheses. [b] Cetyl trimethyl ammonium bromide, 2 equiv. [c] K_2HPO_4/KH_2PO_4 buffer.

Several experiments also suggest that the reaction occurs in solution rather than on the surface of water[5] or in micelles (Table 1).[6] Reaction mixtures appeared homogeneous, and more importantly, qualitative reaction rate and selectivity were only minimally affected by surfactants (entry 2). Hydrophobic effects[7] also do not seem important as similar behavior was observed in the presence of salting-out (LiCl) or salting-in ($LiClO_4$) additives (entries 3−4). Ionic strength effects may account for the small rate and selectivity increases in these cases and in those carried out in phosphate buffer (entry 5).

To gain further insight into the role of the tetrahydropyran template, we next conducted a similar set of experiments with a closely related cyclohexyl cognate (**1b**). To our surprise, this seemingly minor structural change (O to CH_2) had profound effects on rate *and* selectivity (Table 1). Cyclization of **1b** was significantly faster and occurred to give a nearly equimolar mixture of **2b** and **3b**. Once again, the reaction was shown to operate under kinetic control (i.e., no isomerization of pure **3b** to **2b**) in solution with little evidence for contributions from hydrophobic effects (Table 1, entries 6−10).

Solution ^{1}H NMR analysis of **1a** and **1b** in D_2O indicated chair conformations for the six-membered rings in both cases (Scheme 1). The epoxide moiety, however, appears to be situated differently for the two compounds. Coupling constants (${}^3J$) between methine H_a and the exocyclic methylene protons (H_α and H_β) of **1a** suggest a strong preference for an unproductive conformation that situates the epoxide away from the hydroxyl nucleophile (eq 2).[8] Analogous resonances for **1b** display no discernible coupling constants, suggesting a more flexible alkyl chain.

Scheme 1. Selected Low Energy Conformations of **1a** and **1b** (^{1}H NMR, D_2O)



The conformational differences between **1a** and **1b** may contribute to the observed rate differences, but it is less obvious how such preferences would bias selectivity. Kinetic experiments (^{1}H NMR) have aided in addressing this issue. Reactions of **1a** and **1b** display pseudo-first-order kinetics (pD 7, KP_i buffer), and consistent with the batch reactions, observed rates for the cyclization of **1a** were more than an order of magnitude slower than for those for **1b** ($k_{obs} = 4.69 \times 10^{-5}\ s^{-1}$ and $7.16 \times 10^{-4}\ s^{-1}$ at 45 °C, respectively). Both reactions also display small normal solvent isotope effects ($k_{H_2O}/k_{D_2O} = 1.33$ and 1.47, respectively), consistent with a proton-transfer event that occurs in or preceding the rate-determining step.

Critical differences between the two substrates were observed for kinetic measurements made in DMSO-d_6/D_2O mixtures. Binary solvent mixtures have previously been used to determine the kinetic order of water in many reactions[9] including epoxide hydrolysis reactions.[9b,c] While this practice has become less common because solvent properties such as polarity and hydrogen-bond donor/accepting ability often complicate analysis,[10] in water-rich DMSO mixtures these properties vary little thereby minimizing their effect.[11]

10.1021/ja9004909 CCC: $40.75

In the event, both substrates displayed pseudo-first-order kinetics with rates that decreased with [D_2O] (55−35 M). The effect of decreasing [D_2O] upon *selectivity*, however, was different for the two substrates with selectivity decreasing slightly for **1a** (**2a/3a** = 11−8), while remaining nearly constant for **1b** (**2b/3b** = 0.7). Using these selectivities, apparent rate constants for the formation of **2** (k_2) and **3** (k_3) could be extracted from the observed rate constants. Linear plots of k_2 and k_3 vs [D_2O] were obtained for **1b** (Figure 1).

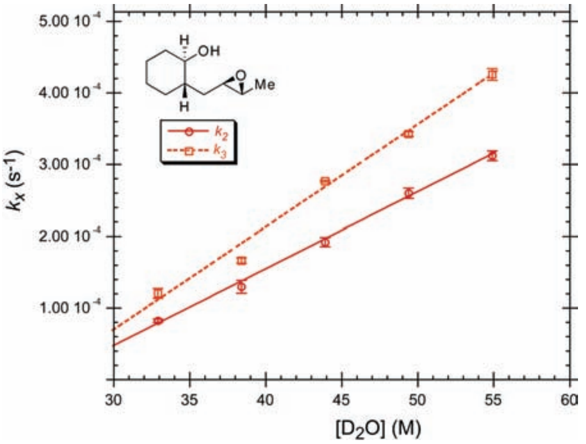


Figure 1. k_2 and k_3 vs [D_2O] (pD 7) for **1b** at 45 °C.

For **1a**, however, only k_3 displayed a linear water dependence. Most striking of all was that the plot of k_2 vs [D_2O] for **1a** contained significant polynomial character (Figure 2).

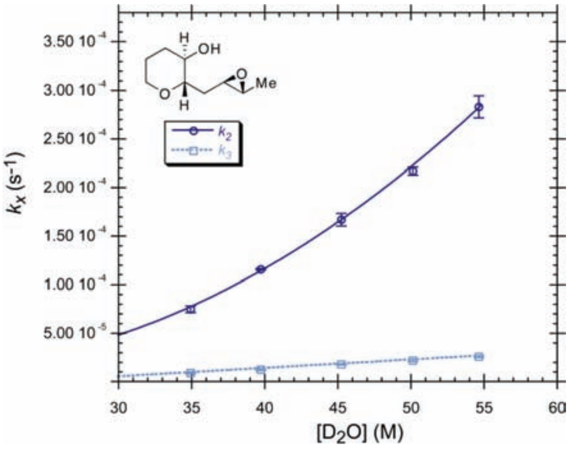


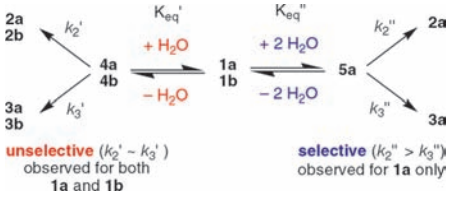
Figure 2. k_2 and k_3 vs [D_2O] (pD 7) for **1a** at 70 °C.

We hypothesize that the epoxy alcohols **1a** and **1b** exist as a rapidly equilibrating mixture of solvated conformers.[9b,12] Cyclization occurs when intermediates situate the epoxy alcohol appropriately for proton transfer and subsequent nucleophilic attack. The number of water molecules that organize the substrate appropriately and that serve to stabilize intermediates or transition states in excess of those required to solvate the epoxy alcohol then become kinetically relevant.

For the cyclohexane template (**1b**), it is apparent that there is at least one intermediate that requires only one additional water molecule for productive reaction (by virtue of the linear k_2 and k_3 vs [D_2O] plots). Moreover, it is likely, but not necessary, that both products are formed from a common intermediate in an unselective reaction (Scheme 2).

The situation is more complicated for the tetrahydropyran template (**1a**). Similar to **1b**, a linear plot of k_3 vs [D_2O] suggests that formation of **3a** is first order in water (Figure 2). Considering the structural similarities between **1a** and **1b**, it is likely that this process resembles the pathway observed in **1b**. The polynomial character observed in the k_2 vs [D_2O] plot, on the other hand, suggests that **2a** is formed at least in part by a second reaction mechanism with a higher order water dependence. Plots of k_2/[D_2O] vs [D_2O] are linear with a nonzero slope, suggesting that the competing pathway is second order in water (Figure 3). A similar plot for k_3 is also linear but displays a slope that is comparatively small, indicating that **3a** is formed with minimal contributions from a pathway that is second-order in water (Scheme 2).[13]

Scheme 2. Proposed Mechanisms for Epoxy Alcohol Cyclizations in Water (Proton Transfer Steps Omitted for Clarity)



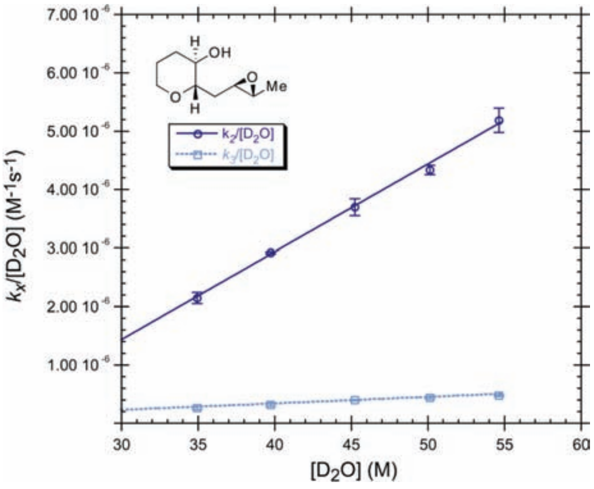
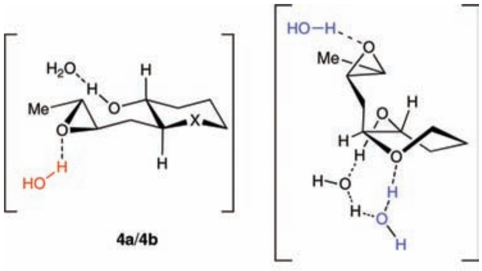


Figure 3. k_2/[D_2O] and k_3/[D_2O] vs [D_2O] (pD 7) for **1a** at 70 °C.

These observations are consistent with two different but not mutually exclusive interpretations. In addition to affecting the ground-state conformation (*vide supra*), the electron-withdrawing oxygen atom in the template likely decreases the nucleophilicity of **1a** relative to **1b**. The more nucleophilic **1b** may be sufficiently reactive such that only one water molecule is required to activate the epoxide for productive cyclization. Slower reaction rates for **1a** result in a competition between pathways requiring one and two water molecules. Formation of the larger ring is preferred for **1a** because the electronegative oxygen in the template discourages buildup of charge on the epoxide carbon proximal to the template. The availability of a pathway that is second order in water for **1a** further stabilizes the charge in the transition state, thus enhancing the effect of the tetrahydropyran oxygen and encouraging a later transition state, both of which increase selectivity for **2a**.

An alternative interpretation of these data relies on a conformational difference between the intermediates that lead to unselective and selective reactions (i.e., **4a/4b** and **5a**). The most likely intermediate common to **1a** and **1b** (i.e., the pathway that is first order in water) is a chairlike intermediate such as **4a/4b** (Figure 4). On the other hand, a reactive intermediate with the tetrahydropyran ring in a twist conformation, such as **5a**, satisfies all of the requirements for a proposed intermediate for the selective pathway (Figure 4).



4a/4b

5a

Figure 4. Possible intermediates for epoxy alcohol cyclizations. The red and blue water molecules indicate the number and not necessarily the identity of water molecules that are kinetically relevant. The black water molecules generically represent the waters of solvation.

The second-order water dependence is explained because **5a** is ideally situated for hydrogen bonding from exogenous water molecules.[14] Although three explicit water molecules are depicted for **5a** in Figure 4, we propose that one of these molecules originates from the solvated ground state. It is also possible that there is a more extensive hydrogen-bonding network involving additional waters of solvation. The kinetic accessibility of **5a** is also feasible as the formation of twist conformers are estimated to require ca. 10 kcal/mol,[15] while $\Delta G^{\ddagger}$ determined for the cyclization of **1a** is greater than 20 kcal/mol. Third, a pathway involving a twist conformation may favor **2a** because the nucleophile trajectory in **5a** differs significantly from that in **4a**. Computations suggest that this factor is most important in determining the regioselectivity for epoxy alcohol cyclizations.[16] Finally, selectivity differences between **1a** and **1b** can be explained by **5a** because the carbocyclic **1b** does not have a H-bond acceptor to accommodate the additional water molecules required for the selective pathway via an analogous twist conformation.

It is important to note that the two competing pathways proposed for **1a** are of different kinetic order. This point is particularly relevant for explaining why a selective pathway is not observed for **1b**. A twist-boat intermediate analogous to **5a** but without involvement of an additional water molecule is indeed kinetically accessible for **1b**,[15] but the absence of the extra [water] factor in the rate law for such a pathway apparently provides for cyclization rates that do not compete with the pathway proceeding through **4b**.

Further experimentation is needed to delineate how the factors outlined above contribute to selectivity in epoxy alcohol cyclizations in water, but in all likelihood product distribution is dictated by both electronic and conformational considerations.

In summary, analysis of the cyclization of **1a** and its carbocyclic analogue **1b** in neutral water suggests that both reactions occur in solution but through mechanistically distinct pathways. This study illustrates the intimate connection between the template structure and the special properties of water; variation of either leads to an unselective reaction. We are currently elucidating the details of this interplay further and hope that the lessons learned from these studies will not only provide clues for the development of new templates and catalysts for regioselective cyclizations of epoxy alcohols but also augment our understanding of related, consecutive epoxide openings ("cascade" reactions).[1]

Acknowledgment. We thank the Petroleum Research Fund of the ACS (47212-AC1) for support of this work; Dr. Jeff Simpson (MIT) for assistance with and analysis of NMR experiments; Chris Morten, Ivan Vilotijevic, and Aaron Van Dyke (all MIT) for insightful discussions; and Li Li (MIT) for obtaining mass spectrometric data.

Supporting Information Available: Experimental procedures, kinetic models, and data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.
(2) In this context, a template is defined as a functional group or collection of functional groups that favors otherwise atypical reactivity and/or selectivity.
(3) Nakanishi, K. *Toxicon* **1985**, *23*, 473.
(4) Alternative methods for regioselective epoxy alcohol cyclizations: (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490. (c) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063. (d) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158. (e) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012. (f) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (g) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. (h) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056.
(5) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, B. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.
(6) (a) Tascioglu, S. *Tetrahedron* **1996**, *52*, 11113. (b) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174.
(7) (a) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (b) Grieco, P. A.; Garner, P.; He, Z.-M. *Tetrahedron Lett.* **1983**, *24*, 1897. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (d) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471.
(8) Spectra were assigned in analogy to C-glycosides, which show similar conformational preferences: (a) Babirad, S. A.; Wang, Y.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4825. (b) Houk, K. N.; Eksterowicz, J. E.; Wu, Y. D.; Fuglesang, C. D.; Mitchell, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 4170.
(9) Leading and most relevant examples: (a) Hammond, G. S.; Reeder, C. E.; Fang, F. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1958**, *80*, 568. (b) Olavi, P.; Virtanen, I. *Suom. Chem. B* **1965**, *B38*, 135. (c) Olavi, P.; Virtanen, I. *Suom. Chem. B* **1966**, *B39*, 115. (d) Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 6221. (e) Henderson, J. W.; Haake, P. *J. Org. Chem.* **1977**, *42*, 3989. (f) Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1984**, *49*, 3161.
(10) For example: (a) El Seoud, O. A.; El Seoud, M. I.; Farah, J. P. S. *J. Org. Chem.* **1997**, *62*, 5928. (b) Humeres, E.; Nunes, R. J.; Machado, V. G.; Gasques, M. D. G.; Machado, C. *J. Org. Chem.* **2001**, *66*, 1163.
(11) Relative permittivity varies slightly in this concentration range: (a) Kaatze, U.; Pottel, R.; Schafer, M. *J. Phys. Chem.* **1989**, *93*, 5623. (b) Puranik, S. M.; Kumbharkhane, A. C.; Mehrotra, S. C. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 433. See Supporting Information for other linear free energy relationships.
(12) Pocker, Y.; Ronald, B. P.; Anderson, K. W. *J. Am. Chem. Soc.* **1988**, *110*, 6492.
(13) Preliminary NMR and kinetic experiments indicate that an internal H-bond impedes cyclization at low [water]. We therefore avoided using log(k_x) vs log[water] for determining the kinetic order in water because a misleading order would be obtained.
(14) Hydrogen bond stabilization of twist conformations: (a) Booth, H.; Gidley, G. C. *Tetrahedron Lett.* **1964**, *23*, 1449. (b) Stolow, R. D.; McDonagh, P. M.; Bonaventura, M. M. *J. Am. Chem. Soc.* **1964**, *86*, 2165.
(15) Lambert, J. B.; Featherman, S. I. *Chem. Rev.* **1975**, *75*, 611.
(16) (a) Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. (b) Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530.

JA9004909