bromo tetrahydrofurans, and the major isomer **14** was reduced with tri-*n*-butylstannane[15] to **15**. Saponification of **15**, followed by exhaustive silylation, furnished **16** which, upon brief exposure to tetra-*n*-butylammonium fluoride, was selectively deblocked at the C(13) silyl ether to yield **17**. Activation of **17** in a form (**19**) suitable for coupling with the lower half of **1** was accomplished by reaction with 2-(trimethylsilyl)ethyl α-bromoacetate,[16] which afforded **18**, and then with α-bromoacetyl bromide. The potassium carboxylate **20** from saponification of **12** condensed smoothly with **19** to produce **21**. Treatment of the latter with fluoride furnished a monohydroxy acid which underwent lactonization[17] to yield the macrocycle **22**.

Contraction of **22** was effected with 2 equiv of base, and entrapment of the intermediate ene diolates with trimethylsilyl triflate afforded in good yield the unstable dilactone **23** (mixture of *E* and *Z* isomers) as a material exhibiting conspicuous fluorescence on TLC. Exhaustive desilylation of **23** with tetra-*n*-butylammonium fluoride, followed by brief exposure to mineral acid, furnished a highly nonpolar heptaol **24** that was found to be identical in spectroscopic properties and chromatographic behavior with material previously obtained by degradation of boromycin.[2c,18] Finally, **24**, upon treatment with anhydrous trimethyl borate in methanol at reflux, afforded **25** ($[\alpha]^{20}_D$ + 88.8°), identical by comparison of ^{1}H and ^{13}C NMR spectra, IR spectra, and optical rotation with a sample of desvalinylboromycin ($[\alpha]^{20}_D$ + 93.9°) obtained (sodium-free) from natural **1**. Since **25** has already been converted to **1** by esterification with BOC-D-val, followed by treatment with trifluoroacetic acid,[4] this sequence constitutes a synthesis of boromycin.

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Supplementary Material Available: $[\alpha]_D$, IR, ^{1}H NMR, ^{13}C NMR, and analytical data for compounds **6**, **8**, **10**, **12**, **13**, **15**, **16**, **18**, **19**, **21**, **22**, **24**, and **25** (4 pages). Ordering information is given on any current masthead page.

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Does the Mechanism of Symmetric Methyl Transfer to Water from Water Differ from That for Transfer to Water from Other Leaving Groups?

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We have measured the rates of acid-catalyzed ^{18}O exchange between L_2O and CH_3OL in H_2O and D_2O (eq 1, L = H or D).

$$L_2O + CH_3{}^{18}OL \xrightarrow[L^+]{k_{ex}{}^L} L_2{}^{18}O + CH_3OL \qquad (1)$$

The value of $k_{ex}{}^H/k_{ex}{}^D$ (1.63 at 140 °C when $[H^+] = [D^+] = 1$ M) is larger than the values of k^H/k^D observed for other S_N2 reactions of L_2O (≲1.3 at much lower temperatures)[1] and could result either from a dynamic solvent effect or from acid/base catalysis.

Table I. Observed Rate Constants and Isotope Effects of 140 °C[a]

$[H^+]^b$	$[MeOH]^b$	$10^5 k_{ex}{}^{H\,c}$	$[D^+]^b$	$[MeOD]^b$	$(k^H/k^D)/(K_a{}^H/K_a{}^D)$
1.024	1.01	6.19	1.021	1.01	1.64
1.050	0.50	6.25	1.013	0.50	1.62
0.503[d]	0.50	3.01	0.499[d]	0.50	1.63

[a] All values in each line are for one pair of reactions (H and D) that were run concurrently. [b] M at ca. 20 °C. At 140 °C, thermal expansion and solvent vaporization combine to reduce these values by ca. 7%. [c] From eq 2; units are s^{-1}. Standard deviations of all $k_{ex}{}^H$ and $k_{ex}{}^D$ values, as estimated from the scatter of observed δ values, were ≤1%. [d] $LiClO_4$ added to maintain ionic strength = 1.0 M.

Reactions were run in concurrent pairs (one in H_2O, one in D_2O) in sealed ampoules immersed in an oil bath at 140.0 ± 0.3 °C. The ampoules contained aliquots of solutions of $CH_3{}^{18}OL$ (0.67 atom % ^{18}O)[2] in $H_2O/HClO_4$ and in $D_2O/DClO_4$. Six H_2O and six D_2O ampoules were withdrawn from each pair of reactions during the course of 3 half-times. The CH_3OL in each ampoule was isolated by distillation followed by GC and pyrolyzed to CO,[3,4] and the δ value[5] was measured with a Micromass 602E isotope ratio mass spectrometer. Each k_{ex} was evaluated by least-squares fit of those δs to eq 2, where δ_∞, $(\delta_0 - \delta_\infty)$ and k_{ex} are the fitted parameters.

$$\delta_t - \delta_\infty = (\delta_0 - \delta_\infty)e^{-k_{ex}t} \qquad (2)$$

If the mechanism of this exchange is as usually assumed,[6] prior equilibrium hydron transfer to CH_3OL followed by bimolecular attack by L_2O (eq 3 and 4),

$$L_3O^+ + CH_3OL \underset{}{\overset{(K_a{}^L)^{-1}}{\rightleftharpoons}} L_2O + CH_3OL_2{}^+ \qquad (3)$$

$$L_2O + CH_3OL_2{}^+ \xrightarrow{k^L} L_2OCH_3{}^+ + OL_2 \qquad (4)$$

application of the McKay derivation[7] shows that $k_{ex}{}^L$ is related to the rate and equilibrium constants in that mechanism by eq 5. The parenthetical sum in eq 5 cancels when the H/D isotope

$$k^L/K_a{}^L = k_{ex}{}^L/\{[L^+]([L_2O] + [CH_3OL])\} \qquad (5)$$

effect (IE) on $k^L/K_a{}^L$ is evaluated from a pair of runs in which $[CH_3OD] = [CH_3OH]$ and $[DClO_4] \approx [HClO_4]$, since the molar volumes of H_2O and D_2O differ by less than 0.1% at 140 °C[8] (eq 6). Observed values of $k_{ex}{}^H$ and $(k^H/k^D)/(K_a{}^H/K_a{}^D)$ are given in Table I.

$$\frac{k^H/k^D}{K_a{}^H/K_a{}^D} = \frac{k_{ex}{}^H[D^+]}{k_{ex}{}^D[H^+]} \qquad (6)$$

The value of $K_a{}^H/K_a{}^D$ is known[9] to be 0.95 ± 0.02 at 25 °C. Assuming its temperature dependence to be purely exponential ($K_a{}^H/K_a{}^D = e^{-\delta\Delta H^\circ/RT}$) predicts a value of 0.96$_4$ at 140 °C. Thus the mean of the $(k^H/k^D)/(K_a{}^H/K_a{}^D)$ values in Table I (1.63 ± 0.01) corresponds to $k^H/k^D \approx 1.57$ at 140 °C for the rate-determining displacement step (eq 4).

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0002-7863/89/1511-0792$01.50/0

This value of k^H/k^D is much larger than is expected for the secondary deuterium IE of the four exchangeable Ls. If the transition state (TS) has the positive charge equally divided between the two oxygens, $L_2O^{+1/2}\cdots CH_3\cdots OL_2^{+1/2}$, then that secondary IE is given by eq 7, where the ϕs are deuterium fractionation factors[10] relative to L_2O for $CH_3OL_2^+$ and the TS. For this symmetric TS, $(k^H/k^D)_{sec}$ thus should be near 1.00.[11] If some positive charge resided on CH_3, then the lower charge on oxygen would increase ϕ_{TS}, causing $(k^H/k^D)_{sec} < 1.00$. Assuming the TS to be unsymmetric does not change these conclusions.[12]

$$(k^H/k^D)_{sec} = (\phi_{MeOL_2^+})^2/(\phi_{TS})^4 \quad (7)$$

Therefore a factor near 1.57 must be contributed to k^H/k^D by sources other than the substitution of D for H in the internal structures of reactants and TS. Possible other sources are solvent effects, either static or dynamic,[15] and acid/base catalysis.[16] If the standard partial molal free energies for transferring reactants and TS from H_2O into D_2O (without exchange) are not equal, then a *static* solvent effect, $e^{\Delta\Delta\bar{G}^\circ_{Tr}/RT}$, will be present.[15] If charge transfer is strongly coupled to changes in solvent polarization, then a *dynamic* solvent effect will be present.[17-20] If the mechanism involves acid/base catalysis, then coupling of hydron motion into the reaction coordinate and/or strong hydrogen bonding in the TS can increase k^H/k^D.

It is very unlikely that the static solvent effect could be as large as 1.57 at 140 °C. If this value resulted from a static effect with a purely exponential temperature dependence, $k^H/k^D = (1)e^{\Delta\Delta\bar{H}^\circ_{Tr}/RT}$, then $\Delta\Delta\bar{H}^\circ_{Tr} = 0.37$ kcal mol^{-1} and $k^H/k^D = 1.87$ at 25 °C. However, it almost always is true that $|\Delta\bar{H}^\circ_{Tr}| > |\Delta\bar{G}^\circ_{Tr}|$,[21] suggesting that the preexponential factor in k^H/k^D is < 1, so that at 25 °C, a static solvent effect would lead to $k^H/k^D > 1.87$ and $\Delta\Delta\bar{G}^\circ_{Tr} > 0.37$ kcal mol^{-1}. Since $|\Delta\bar{G}^\circ_{Tr}| < \Delta\bar{H}^\circ_{Tr} < 0.03$ kcal mol^{-1} for transfer of H_2O without exchange,[21] the difference between the $\Delta\bar{G}^\circ_{Tr}$ values for TS and $CH_3OH_2^+$ would need to be >0.34 kcal mol^{-1} in order for the static solvent effect to be this large; tabulated values[21] of $\Delta\bar{G}^\circ_{Tr}$ for univalent cations suggest that this difference should not be nearly so large. Thus it is likely that k^H/k^D contains a significant contribution from a dynamic solvent effect or from acid/base catalysis.

Both a large dynamic solvent effect and acid/base catalysis could result from the mechanism predicted for this methyl transfer to L_2O from L_2O. We have proposed[15,22] that methyl transfers to L_2O from other leaving groups (e.g., halide$^-$, RSO_3^-, thiophene) occur via a "partly coupled" mechanism in which the rate-determining step is a solvation change. Our analysis of why those transfers follow that unusual mechanism requires that the symmetric transfer to L_2O from L_2O must follow a different mechanism with a symmetric TS that is tightly coupled to its solvation. In such a "coupled"[19] or "polarization caging"[17] mechanism, the transferring methyl is carried across from leaving group to nucleophile in a potential well created by the solvent polarization, and a dynamic solvent effect results from the polarization change being slower in D_2O than in H_2O. The strong hydrogen bonding expected to be part of that tight coupling could set the stage for coupling hydron motion into the reaction coordinate and shifting the mechanism to simultaneous acid and base catalysis by L_3O^+ and L_2O.

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(12) The Principle of Detailed Balance[13] allows an unsymmetric TS, $L_2O^{\delta+}\cdot\cdot CH_3\cdots{}^{18}OL_2^{(1-\delta)+}$, for this symmetric reaction if half of the TSs have this structure and half have its complement, $L_2O^{(1-\delta)+}\cdots CH_3\cdot\cdot{}^{18}OL_2^{\delta+}$,[14] so that $\phi_{TS}^4 = [(\phi_{L_2O})^{\delta}(\phi_{MeOL_2^+})^{1-\delta}]^2[(\phi_{L_2O})^{1-\delta}(\phi_{MeOL_2^+})^{\delta}]^2 = (\phi_{MeOL_2^+})^2$.
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Stereochemistry of the Visual Cycle

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The stereochemical changes which accompany the processing of vitamin A in the eye as part of the visual cycle are unusual and interesting. The enzymatic isomerization of free *all-trans*-retinol (*1*) (vitamin A), probably via an activated intermediate, to 11-*cis*-retinol (*2*) occurs with inversion of stereochemistry at C-15 (Scheme I)[1] and C-O bond cleavage.[2] The retinol dehydrogenases that oxidize *all-trans*-retinol and 11-*cis*-retinol do so with opposite stereochemistries with respect to the methylene hydroxyl group (Scheme I).[1] In both the bovine (pigment epithelium derived) and amphibian visual systems, the *all-trans*-retinol dehydrogenases are *pro*-R specific, and the 11-*cis*-retinol dehydrogenases are *pro*-S specific.[1] This is also true for the cone only visual system of the lizard Anoleis carolensis.[3] This consistently opposite stereochemistry of the dehydrogenases is intriguing and suggests that the isomerase and dehydrogenases operate from the same face of the vitamin A molecule. Note that although a formal inversion of stereochemistry occurs during the isomerization reaction, this result can easily be accounted for by a mechanism in which C-O bond cleavage and reformation occurs from the same face of the enzyme with retention (Scheme II). In this communication the stereospecificities of the dehydrogenases were examined with respect to the nicotinamide cofactors in order to further explore the stereochemistry of these enzymes.

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