Quantitative Assessment by 1D-EXSY NMR of Stereoelectronic Control in Acid-Catalyzed Exchange between Stereoisomeric 2-Methoxy-1,3-dioxanes and Methanol

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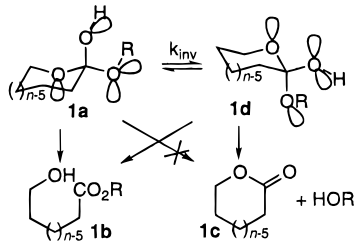
Abstract: Rates of acid-catalyzed methoxy exchange between methanol and the three diastereomers of 2-methoxy-4,6-dimethyl-1,3-dioxane (**6**) were measured in benzene, and the rates for the two cis diastereomers were measured in methanol/chloroform. Rate constants were evaluated using a 1D-EXSY NMR pulse sequence and a weighted linear least squares analysis. Rates of methanol attack on the cationic intermediate (**8**) show 24-fold axial selectivity in benzene and 9-fold selectivity in methanol/chloroform. A ring-opening mechanism for equatorial exchange can be rejected, since rate constants k_{ea} and k_{ae} for direct axial/equatorial epimerization are zero. These results demonstrate that antiperiplanar lone pairs are more effective in this system than syn, although the effect is worth no more than 2 kcal/mol.

Introduction

Stereoelectronic control,[1] also known as the kinetic anomeric effect or as the antiperiplanar lone pair hypothesis (ALPH),[2] is a topic of current interest[3] and wide acceptance.[4] According to this hypothesis,[5] cleavage of a tetrahedral intermediate is facilitated by one or two lone pairs antiperiplanar to the leaving group.[1] The antiperiplanar conformation is preferred because the overlap between a lone pair and the σ^* orbital of the bond being cleaved is maximized at a dihedral angle of 180°. This preference is similar to the well-established stereochemistry in β-eliminations,[6] and it is supported by MO calculations.[7] If it holds, then by the principle of microscopic reversibility, attack antiperiplanar to a developing lone pair is also preferred.

There is no doubt that an orthogonal lone pair is much less effective than one that is periplanar. An estimate of the energy benefit is 21 kcal/mol, based on the calculated barrier to rotation in $CH_3O\text{-}CH_2^+$.[8] An experimental comparison is the 19-kcal/mol greater activation energy for hydrolysis of a bridgehead 9-oxabicyclo[3.3.1]nonyl acetal.[9] A qualitative example is the stability to acid hydrolysis of 2,2,4,4-tetramethylcyclobutane-1,3-dione monodimethylketal, which can be explained by the orthogonality of the lone pair on oxygen and the p-orbital on the ketal carbon, owing to conformational restraints imposed by the C-methyls.[10]

Scheme 1. Hydrolysis of a Hemiorthoester[a]



[a] Only the two lone pairs antiperiplanar to a preferred leaving group are shown.

The area of current doubt regarding ALPH is whether an antiperiplanar lone pair provides any advantage over a syn one, and this proposal has elicited some strong opposition.[11] One of the first reactions claimed to show this sort of stereoelectronic control was the hydrolysis of a cyclic hemiorthoester (**1a**, n = 6), which (at pH > 3) cleaves to give only the hydroxy ester (**1b**, n = 6),[5] as shown in Scheme 1. In **1a** the exocyclic C−O bond lacks two antiperiplanar lone pairs, so the absence of lactone (**1c**, n = 6) plus alcohol was taken as evidence for the hypothesis. (Although the lone pairs are often considered to be in sp^3-hybridized orbitals, as drawn, it is more proper[2,12] to focus on the pure-p lone pair of the ring oxygen, which is orthogonal to the exocyclic C−O bond.)

However, the corresponding five-membered hemiorthoester (**1a**, n = 5) also gives only the hydroxy ester (**1b**, n = 5).[5] Since ring inversion in five-membered rings is a very rapid pseudorotation, conformer **1d** (n = 5), with two lone pairs antiperiplanar to exocyclic C−O, is kinetically accessible. Therefore, lactone (**1c**) should be produced, and its absence casts doubt on this purported evidence for stereoelectronic control. A likely explanation[13] is that product-development control favors the more stable hydroxy ester over the lactone.

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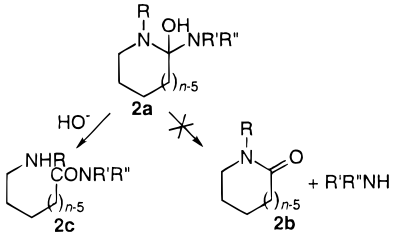
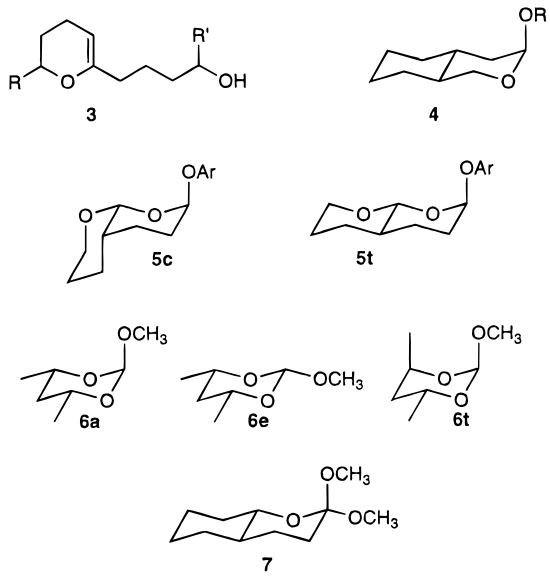
To avoid bias due to product stabilities and provide an unambiguous test of stereoelectronic control, hydrolysis of cyclic amidines, via the hemiorthoamide (**2a** in Scheme 2), was studied. Initially the absence of lactam product (**2b**, R = R′ = R" = H, *n* = 5, 6, 7) was taken as evidence of stereoelectronic control.[13] However, this was found to be due to a difference in leaving abilities.[14] When the leaving abilities are balanced (**2a**, R′ = CH_3, R = R″= H), the selectivity for amino amide (**2c**, *n* = 6) is ≤93% and vanishes in five- and seven-membered rings.[14] Similar behavior was seen with four-membered ring amidines and with fully *N*-methylated analogs (**2a**, R = R′ = R″ = CH_3, *n* = 5, 6, 7).[15] Therefore it was concluded that stereoelectronic control is weak even in the best case, namely six-membered rings, and absent in five- and seven-membered ones, just as with β-eliminations.

Scheme 2. Hydrolysis of a Hemiorthoamide



One explanation for the absence of stereoelectronic control is the proposal that a synperiplanar lone pair can be equally effective.[14] Computations suggest that acid-catalyzed cleavage of $CH_2(OCH_3)_2$ proceeds through the synperiplanar conformation.[16] Likewise, in the hydrolysis and ozonolysis of an oxabicyclo[2.2.2]octyl acetal a synperiplanar lone pair can provide assistance similar to that of an antiperiplanar one.[17] Despite these and other[18] counterexamples to ALPH, proponents continue to reject assistance by syn lone pairs.[19] The low stereoselectivity (only 50−60% axial) in acid-catalyzed cyclization of **3** was instead attributed to competitive reaction via a twist-boat conformation.

There do exist examples of stereoelectronic control. A weak one is that **4** undergoes acid-catalyzed hydrolysis only 1.5 (R = CH_3) or 7 (R = *p*-nitrophenyl) times as fast as its equatorial epimer.[20] A stronger example is the hydrolysis of **5c** (Ar = *p*-nitrophenyl), which is 200 times as fast as that of **5t**.[21] The classic case of high stereoselectivity is Eliel's 2-methoxy-*cis*-4,6-dimethyl-1,3-dioxane, where the axial stereoisomer (**6a**) reacts smoothly with Grignard reagents and hydride-donor reagents, whereas the equatorial (**6e**) either reacts very slowly or is epimerized before it reacts.[22] Some other orthoesters also show a preference for cleavage or attack of axial alkoxy.[5] One quantitative measure of this preference is from the acid-catalyzed exchange between CD_3OD and **7**, whose axial methoxy exchanges 1.9−12.1 times as fast as equatorial, depending on solvent.[23]



In contrast, it is perplexing that in the gas phase neither **6** nor the analogous 1,3-dithiane shows any stereoselectivity, and even in solution there is only a 4:3 preference for axial attack of methanethiolate on the 1,3-dithian-2-yl cation.[24] These examples suggest that the influence of stereoelectronic control may depend on the contribution required from the lone pair. It has been suggested that in the base-catalyzed hydrolysis of amidines[14] and amides[25] the oxyanion of the tetrahedral intermediate is such a strong internal nucleophile that the orientation of the nitrogen lone pairs becomes less important.

The question of stereoelectronic control is a fundamental one about how reactivity depends on the relative orientation of lone pairs and bonds. It is still an area of considerable uncertainty and controversy.[26] Some researchers invoke stereoelectronic control[27] when the observed stereoselectivity could be due to other effects, such as product stabilities, ring strain, or steric effects. Still others have proposed causes for stereoselectivity besides stereoelectronic control, such as electrostatics, leaving-group ability, or conformational necessity.[28] Stereoelectronic

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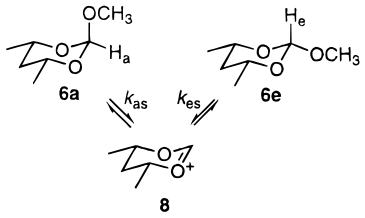
control has been proposed to promote cleavage of the desired bond by enzymes and enzyme models.[29] Much of the interest is for purposes of synthesis, where it offers a novel method for control of stereochemistry. Usually steric effects are used to direct an incoming nucleophile along the least hindered path. If preferential addition occurs antiperiplanar to a lone pair, this becomes an alternative for selective creation of a chiral center.[30] To what extent can this be effective?

Proposal

We seek a quantitative measure of stereoelectronic control in a favorable case, namely a six-membered ring without any internal nucleophile that would moderate the benefit of two antiperiplanar lone pairs. Such a case, albeit qualitative, is 2-methoxy-*cis*-4,6-dimethyl-1,3-dioxane, where only the stereoisomer **6a** with methoxy axial is reactive.[22] For a quantitative measure of relative reactivities, under conditions where both stereoisomers react, we have measured the rates of acid-catalyzed methoxy exchange of **6a** and **6e** with methanol, along with the trans isomer (**6t**) for comparison. A preliminary report has been published.[31]

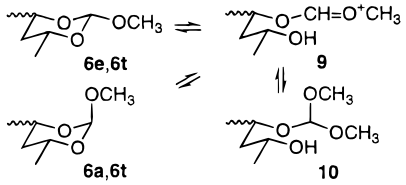
This is a favorable system. The two ring oxygens provide a double stereoelectronic effect. The cis methyls hold the conformation fixed against ring inversion, which would permit a syn lone pair to become anti. Scheme 3 shows the mechanism for methoxy exchange, adapted from the well-established mechanism for orthoester hydrolysis.[32] The reaction proceeds through a common cationic intermediate **8** from either **6a** or **6e**, and the rate-limiting step is the cleavage of the axial or equatorial C−O bond. The leaving-group abilities are balanced since they are both methanols.

Scheme 3. Mechanism of Acid-Catalyzed Methoxy Exchange of 2-Methoxy-*cis*-4,6-dimethyl-1,3-dioxanes (**6**) with Methanol



To the extent that stereoelectronic control is operative, the axial methoxy should exchange measurably faster than the equatorial. However, rapid equatorial exchange would not necessarily refute the hypothesis. There is an additional, ring-opening mechanism for exchange, via intermediate **9**, as shown in Scheme 4. A ring-opening mechanism has been invoked to account for a related counterstereoelectronic orthoester hydrolysis.[33] The transition state for formation of **9** from any of the stereoisomers of **6** is stabilized by two antiperiplanar lone pairs. Methanol can then combine with **9** to form acyclic orthoester **10**, which upon recyclization allows methoxy exchange. Since this mechanism avoids a stereoelectronically unassisted pathway, even for **6e**, it is necessary to detect its contribution.

Scheme 4. Ring-Opening Mechanism for Acid-Catalyzed Exchange Among Stereoisomeric Orthoesters and Methanol



The macroscopic rate constants necessary to characterize stereoelectronic control are the forward and reverse rate constants k_{ij} for exchange from site i to site j, where i and j are axial, solvent, and equatorial methoxy groups. NMR methods can measure all of these at equilibrium in a single sample. Measurements at equilibrium avoid systematic error due to consumption of catalyst during the course of a chemical reaction.[23,34] This method also eliminates the need to separate the stereoisomers and permits inclusion of **6t**. Chemical exchange is manifested in both the C_2-methine (O_3CH) and the C_2-methoxy (OCH_3) signals. The methoxy signals respond to exchange with solvent as well as any direct epimerization via the ring-opening mechanism. The methine signals afford complementary information. They undergo exchange only when there is epimerization, and not if the configuration at C_2 is retained even when the methoxy signals do exchange. To distinguish these processes, the macroscopic rate constants for methine exchange are designated as k'_{ae} and k'_{ea}, where the designations a and e refer to the configuration of the stereoisomer, so that the equatorial methine proton of **6a** is labeled CH_a.

Measuring all the site-to-site rate constants is possible by 2D-EXSY,[35] although this is exceedingly time-consuming. More practical are various magnetization-transfer methods that require selective excitations (saturation or inversion).[36] However, the signals of **6** and methanol are so closely spaced (although benzene as solvent provides a greater dispersion) that excitation of nearby signals interferes with the selectivity.

A variant called 1D-EXSY utilizes a series of experiments, each with a 90°-t_1-90°-t_m-90°-t_2(obs) pulse sequence,[37] and with a judicious choice of t_1's.[38] After the second 90° pulse the deviations from equilibrium of the observed magnetizations or intensities are given by eq 1, where ω_j is the chemical-shift

$$(m_0)_{ji} = 1 + \cos[(\omega_j - \omega_i^{o})t_{1i}] \qquad (1)$$

frequency of the jth site and ω_i^{o} is the carrier frequency in the ith experiment. The kinetic information is derived from the response to these initial perturbations. The time dependence of the magnetizations can be expressed[39] as eq 2, where t_m is

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the mixing time during which they relax to their equilibrium

$$\mathbf{m} = e^{-\mathbf{R}t_m}\mathbf{m}_o = [\sum_{r=0}^{\infty}(-1)^r t_m{}^r \mathbf{R}^r]\mathbf{m}_o \qquad (2)$$

values, $\mathbf{m}$ is a $1 \times N$ column matrix of the deviations of magnetizations or observed intensities from their equilibrium values, and $\mathbf{m}_o$ is the $1 \times N$ column matrix of those deviations (eq 1) at $t_m = 0$. The rate information is expressed by the $N \times N$ matrix $-\mathbf{R}$, whose off-diagonal elements $-\mathbf{R}_{ij}$ are the rate constants k_{ji} and whose diagonal element $\mathbf{R}_{ii}$ is the sum of all rate constants for exchange from site i plus the reciprocal of the longitudinal relaxation time T_{1i}.

The column matrices $\mathbf{m}$ and $\mathbf{m}_o$ can be placed beside each other to form square matrices, $\mathbf{M}$ or $\mathbf{M}_o$, whose jth row corresponds to the jth site and whose ith column corresponds to the ith initial set of perturbations. Then eq 2 becomes eq 3, where $\mathbf{M}_o{}^{-1}$ is the matrix inverse of $\mathbf{M}_o$. This equation has the

$$\mathbf{M}\mathbf{M}_o{}^{-1} = e^{-\mathbf{R}t_m} \qquad (3)$$

same form as in 2D-EXSY,[35] for which it was shown[40] that linearization leads to eq 4, where $\mathbf{X}$ is the matrix that diagonalizes $\mathbf{A}$ to Λ. Thus each element of $\mathbf{R}$, and all site-to-site rate constants, can be evaluated.

$$\ln(\mathbf{M}\mathbf{M}_o{}^{-1}) = \mathbf{X}(\ln \Lambda)\mathbf{X}^{-1} = -t_m\mathbf{R} \qquad (4)$$

A further requirement is that these exchange rates must be within the NMR time scale. The rate is easy to regulate by adjusting the concentration of catalytic acid. Another problem is that two different rates must be measured. In contrast to the usual 2D-EXSY methods, which evaluate rates at only one optimum[41] t_m, 1D-EXSY can use a list of mixing times. However, as with the logarithm of any decreasing quantity, errors in $\ln(\mathbf{M}\mathbf{M}_o{}^{-1})$ increase with t_m.

A weighted linear least-squares fit to eq 4 was therefore devised to provide the rate constants with good precision.[38] The slope and intercept for the fit of data at n mixing times to $y = ax + b$ are given by eqs 5 and 6, where $y = -t_m\mathbf{R}_{ij} = (\ln \mathbf{M}\mathbf{M}_o{}^{-1})_{ij} = [\mathbf{X}(\ln \Lambda)\mathbf{X}^{-1}]_{ij}$ and $x = -t_m$. The proper weighting

$$\hat{a} = \frac{(\sum w)(\sum wxy) - (\sum wx)(\sum wy)}{(\sum w)(\sum wx^2) - (\sum wx)^2} \qquad (5)$$

$$\hat{b} = \frac{(\sum wx^2)(\sum wy) - (\sum wx)(\sum wxy)}{(\sum w)(\sum wx^2) - (\sum wx)^2} \qquad (6)$$

factors are given by eq 7, where the various derivatives can be expressed in terms of quantities obtained in solving eq 4. These

$$w = 1/\sum_{m,n}\left[\sum_k\left(\frac{\partial \mathbf{X}_{ik}}{\partial \mathbf{M}_{mn}}\ln \lambda_k(\mathbf{X}^{-1})_{kj} + \mathbf{X}_{ik}\frac{1}{\lambda_k}\frac{\partial \lambda_k}{\partial \mathbf{M}_{mn}}\mathbf{X}^{-1}{}_{kj} + \mathbf{X}_{ik}\ln\lambda_k\frac{\partial \mathbf{X}^{-1}{}_{kj}}{\partial \mathbf{M}_{mn}}\right)\right]^2 \qquad (7)$$

expressions look formidable, but they are easy to evaluate on a computer. Thus it is possible to calculate each rate constant $k_{ji} = -\mathbf{R}_{ij}$ and an estimate of the error in that rate constant.

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Experimental Section

Materials. 2,4-Pentanediol, (2*R*,4*R*)-pentanediol, *p*-toluenesulfonic acid (TsOH) monohydrate, trimethyl orthoformate, methyl formate, gadolinium nitrate pentahydrate, benzene-d_6 (Aldrich), methanol (Fisher), and chloroform-*d* (Cambridge Isotope Labs) were purchased and used without further purification.

Synthesis. The three diastereomers of 4,6-dimethyl-2-methoxy-1,3-dioxane (**6**) were synthesized from trimethyl orthoformate and the mixed 2,4-pentanediol stereoisomers according to the method of Eliel and Nader.[22] The mixture of three diastereomers was obtained in high purity following distillation through a short Vigreux column: bp 59−63 °C (10 mmHg) (lit.[1] bp axial: 57−58 °C (18 mmHg), equatorial: 72−73 °C (18 mmHg)), ^{1}H NMR (benzene-d_6): δ 5.49 (s, 1H, **6t**: C*H*(OR)$_3$), 5.47 (s, 1H, **6a**: C*H*(OR)$_3$), 5.14 (s, 1H, **6e**: C*H*(OR)$_3$), 4.18 (m, 1H, **6t**: C*H*CH$_3$), 4.09 (m, 2H **6a**: C*H*CH$_3$), 3.78 (m, 1H, **6t**: C*H*CH$_3$), 3.46 (s, 3H, **6e**: OC*H*$_3$), 3.33 (m, 2H, **6e**: C*H*CH$_3$), 3.25 (s, 3H, **6t**: OC*H*$_3$), 3.05 (s, 3H, **6a**: OC*H*$_3$), 1.4−1.2 (m, 6H, **6**: C*H*$_2$), 1.2−1.0 (d, 18H, **6**: CHC*H*$_3$).

The trans diastereomer (**6t**) was synthesized from (2*R*,4*R*)-pentanediol by the same method: bp 68 °C (30 mmHg), ^{1}H NMR (benzene-d_6): δ 5.49 (s, 1H, C*H*(OR)$_3$), 4.18 (m, 1H, C*H*CH$_3$), 3.78 (m, 1H C*H*CH$_3$), 3.25 (s, 3H, OC*H*$_3$), 1.34 (m, 2H, C*H*$_2$), 1.14 (d, 3H, CHC*H*$_3$), 1.00 (d, 3H, CHC*H*$_3$).

Sample Preparation. An acid stock solution of 0.13 M *p*-toluenesulfonic acid in methanol was prepared. To shorten spin−lattice relaxation times to 3−4 s, 4.2 mM Gd(NO$_3$)$_3$ was included. A 25-μL sample of the mixture of orthoester isomers was dissolved in 1.0 mL of benzene-d_6 with 5 μL of the stock solution. This concentration of acid gave rapid enough methoxy exchange without causing significant coalescence of the axial and methanol signals.

An acid stock solution of 0.048 M *p*-toluenesulfonic acid and 4.2 mM Gd(NO$_3$)$_3$ in methanol was also prepared. A sample containing 0.50 mL of the mixture of orthoester isomers, 0.20 mL of acid stock solution, and 0.20 mL of CDCl$_3$ (for lock) was prepared.

Samples were kept as dry as possible to prevent hydrolysis. The amounts of water from Gd(NO$_3$)$_3$·(H$_2$O)$_5$ and TsOH·H$_2$O are insignificant. Fortunately, some hydrolysis does occur, primarily of the more reactive trans orthoester (**6t**), whose proportion is lower in the kinetic sample than in the original distillate. The presence of water may also have been responsible for a decrease in rate that becomes marked within 2 days. Fresh samples were therefore prepared before each kinetic experiment. Signals of methyl formate (δ 8.04, 3.74 in CDCl$_3$) and trimethyl orthoformate (δ 4.94 in CDCl$_3$), or of derivatives with these chemical shifts, were present in nearly all samples.

Other Solvents and Catalysts. Following the reaction in more polar solvents was not possible. Solutions in CD$_3$CN or CD$_3$NO$_2$ lost catalytic activity within a few hours owing to an unknown process. DMSO is unsuitable because it levels the acidity of TsOH and eliminates the catalysis. A mixture of 0.50 mL of orthoester, 0.20 mL methanol/acid stock solution, and 0.20 mL of CDCl$_3$ was the most polar medium usable. It is unfortunate that such a high concentration of less polar orthoester was necessary, but reducing its proportion would result in dynamic range problems or coalescence of the HOCH$_3$ and OCH$_{3a}$ signals. The minimum CDCl$_3$ to maintain a stable lock signal was 0.20 mL.

Lewis acid catalysis was investigated by substituting BF$_3$·methanol for TsOH. The rate constants were unchanged within experimental error. Thus BF$_3$ is not serving directly as a catalyst, but instead the Brønsted acidity of the BF$_3$·methanol is responsible for the catalysis.

^{1}H NMR Spectroscopy. All NMR spectra were acquired on a Varian Unity 500 spectrometer at 500 MHz. Probe temperature was 24 ± 0.2 °C. Before each set of experiments the probe was tuned, and 90° pulse widths were optimized. Chemical shifts are reported relative to residual CHCl$_3$ (δ 7.26) or residual benzene-d_5 (δ 7.15).

Signal Assignments. Table 1 lists chemical shifts of the stereoisomers of **6** in both solvent mixtures. The assignments of CH$_t$ and OCH$_{3t}$ of the trans diastereomer (**6t**) were made using the genuine compound synthesized from (2*R*,4*R*)-pentanediol. The assignments of

Table 1. Chemical Shifts of Methine and Methoxy Signals of **6** in Methanol/$CDCl_3$ and Benzene-d_6.

signal	δ ($CDCl_3$)	δ (C_6D_6)
CH_t	5.36	5.49
CH_a	5.26	5.47
CH_e	5.12	5.14
OCH_{3e}	3.38	3.46
OCH_{3t}	3.29[a]	3.25
$HOCH_3$	3.30	3.08
OCH_{3a}	3.24	3.05

[a] Observed only when methanol was absent.

CH_a, OCH_{3a}, CH_e, and OCH_{3e} of the two cis diastereomers (**6a**, **6e**) had been made on the basis of the dipole moments of the separated stereoisomers, and they agree with an anomeric stabilization of **6a**.[22] The OCH_{3t} signal is resolved in benzene. In $CDCl_3$ it could be resolved only in the absence of methanol or by adding $EuCl_3$, which shifts the methanol signal upfield and exposes the OCH_{3t} signal at its original chemical shift. The assignments in $CDCl_3$ were made by comparing the integrations, and Table 1 shows that the signals appear in the same sequence.

A fourth signal in the methine region, at δ4.94, was present in all samples after the addition of acid. Addition of trimethyl orthoformate to a sample in $CDCl_3$ without catalytic acid gave a signal at nearly the same chemical shift (δ4.90, methoxy signal at δ3.24). Addition of trimethyl orthoformate to a solution with catalytic acid and methanol increased the intensities of the signals at δ4.94 and δ3.30, without producing a signal at δ3.24. We therefore assign the δ4.94 signal to an acyclic orthoformate (**10**) whose methoxys exchange rapidly with methanol.

The equilibrium constants [**6a**]/[**6e**] were calculated from the integrated OCH_{3a} and OCH_{3e} signals and were 2 and 3 in benzene-d_6 and methanol/$CDCl_3$, respectively. These are close to the previously observed value of 2 in ether.[22]

2D-EXSY. A standard 2D-NOESY pulse sequence (Varian's *noesy*) was employed with hypercomplex phase cycling.[42] A mixing time of 0.25 s and a relaxation delay of 12 s were used. The sweep width in both dimensions was 2905 Hz, with 4096 points along ω_2 and 220 0.1-ms increments along ω_1. The total time required was 12 h.

1D-EXSY. Parameters were a sweep width of 3200 Hz, 30 272 data points, eight scans per spectrum, and a relaxation delay of 30 or 18 s. The carrier frequencies were set successively to the frequencies of increasingly upfield methoxy signals, and t_1 was set to $\pi/(\Delta\omega)$, where $\Delta\omega$ is the frequency difference between the carrier and one of the other signals. This inverts the site at the carrier, restores the magnetization at that other site, and perturbs the magnetization(s) at the other site(s). For the three-site kinetics in $CH_3OH/CDCl_3$ the t_1's were 13.3, 13.3, and 7.4 ms, corresponding to successive inversions of H_e, H_s, and H_a magnetizations and restorations of H_s, H_e, and H_e. Mixing times were 0.0001, 0.02, 0.04, 0.08, 0.11, 0.15, 0.2, 0.32, and 30 s, applied in randomized sequence. Acquiring the full data set requires 2−3 h. For the four-site kinetics in benzene the (randomized) t_m's were 0.018, 0.2, 0.4, 0.6, 0.8, 1.2, 1.6, 2, and 25 s and the t_1's were 2.7, 6.2, 2.7, and 28.1 ms, corresponding to successive inversions of H_e, H_t, H_s, and H_a and restorations of H_s, H_s, H_e, and H_s. Line broadening of 0.5 Hz was applied. Peak intensities were obtained by measuring peak heights and normalizing according to integrated intensities so as to correct for different line widths. Equilibrium intensities were averaged over the three or four experiments in the data set and subtracted from the intensities at $t_m = 0$ and each successive t_m to construct the matrices $\mathbf{M}_0$ and $\mathbf{M}$.

Site to site rate constants were measured from both the methoxy and methine regions of the spectrum in the same sample on the same day and with the same mixing-time list. The methine region was treated as two independent two-site systems, axial/equatorial and trans/orthoformate. Only one viable data set was acquired.

Calculations. Rate constants were calculated according to eqs 6−9. Data sets that gave negative values of k_{as}, k_{sa}, k_{es}, or k_{se} were excluded from the analysis. Data points that gave negative values in one element of the $\mathbf{MM}_0^{-1}$ matrix, negative eigenvalues, or complex eigenvector matrices were excluded from the least squares analysis for that data set. If more than two data points in any given data set could not be used, the entire data set was excluded, but data sets whose rate constants did not satisfy microscopic reversibility were not excluded.

Eleven viable data sets were obtained for the methanol/chloroform solvent, and five sets were obtained for benzene. The ratio k_{sa}/k_{se} was calculated for each of the N data sets, and the best estimate of the ratio for each solvent system was evaluated as the geometric mean. The percent error in the estimated ratio is calculated as $100[\exp(s/N^{1/2})-1]$, where s is the sample standard deviation of the ratios.

Rate constants were calculated from the 2D-EXSY intensities by dividing by the relative populations and taking the logarithm of the resulting matrix by the matrix diagonalization method.[40]

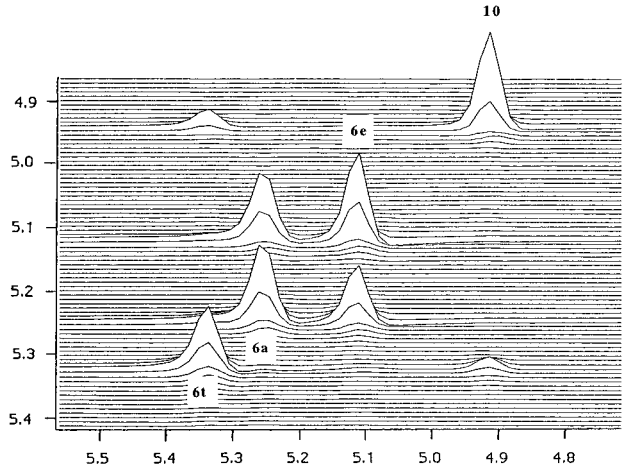

Figure 1. 500-MHz 2D-EXSY spectrum of orthoesters **6** in methanol/$CDCl_3$ showing, from left (rear) to right (front), trans (**6t**), axial (**6a**), equatorial (**6e**), and orthoformate (**10**) methine peaks and cross-peaks.

Results

2D-EXSY Kinetics. The diagonal and off-diagonal methoxy signals overlap in the methanol/$CDCl_3$ mixture. There appear to be cross peaks between all pairs of signals, but they are not well enough resolved to permit quantitative measurements. Figure 1 shows the well resolved methine region. A large cross peak is present between the axial (**6a**) and equatorial (**6e**) signals. A smaller cross peak is present between the trans signal (**6t**) and the orthoformate signal (**10**). The absence of other cross peaks justifies the treatment of the methine exchange as two independent two-site systems. Rate constants k' for the methine exchange are shown in Table 2.

Table 2. Site-to-Site Rate Constants from Methine Region of **6** in Methanol/$CDCl_3$

i	j	k'_{ij}, s^{-1} [a]	k'_{ij}, s^{-1} [b]
a	e	4	3.9 ± 0.2
e	a	4	4.6 ± 0.1
o	t	1	1.6 ± 0.3
t	o	0.6	0.6 ± 0.2

[a] From 2D-EXSY. [b] From 1D-EXSY.

Rate Constants from 1D-EXSY Experiments. Figure 2 shows a plot of the methoxy region from a representative series of EXSY experiments in methanol/$CDCl_3$. Table 3 shows the site-to-site rate constants from this set of experiments as well as the geometric means of the eleven data sets. The error estimated from the least squares fits is overoptimistic, as is also clear from the failure of forward and reverse rate constants to satisfy microscopic reversibility. The geometric means of the rate constants for the methoxy exchange in benzene are shown

(42) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48,* 286.

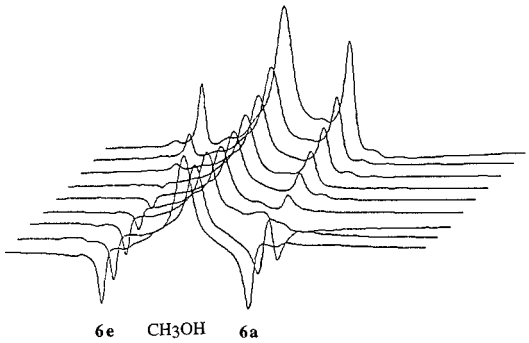

Figure 2. Methoxy region from a representative series of EXSY experiments in methanol/$CDCl_3$. The peaks correspond to equatorial (**6e**), solvent methanol, and axial (**6a**), respectively. Spectra from front (left) to back (right) correspond to mixing times 0.0001, 0.02, 0.04, 0.08, 0.11, 0.15, 0.2, 0.32, and 30 s.

Table 3. Site-to-Site Rate Constants for Methoxy Exchange of Orthoesters **6** in Methanol/$CDCl_3$ Calculated from One Set of Data and the Geometric Means and Errors as Calculated from All 11 Data Sets

i	*j*	k_{ij}, s^{-1}	$\langle k_{ij} \rangle$, s^{-1}	% error
s	e	0.6 ± 0.1	0.5	10
s	a	4.4 ± 0.2	4.8	7
e	s	6.7 ± 0.8	6.7	13
a	s	10.2 ± 0.5	7.3	7

Table 4. Geometric Means of Five Measurements of the Site-to-Site Rate Constants for Methoxy Exchange of Orthoesters **6** in Benzene-d_6

i	*j*	$\langle k_{ij} \rangle$, s^{-1}	% error
s	e	0.04	67
s	t	2	21
s	a	1	16
e	s	0.1	25
t	s	5	17
a	s	2	34

in Table 4. In all cases k_{ea} and k_{ae} were zero within experimental error, so there is no direct exchange between axial and equatorial methoxys.

Although Tables 2−4 list absolute rate constants, these are of no intrinsic significance because they would vary with the amount of acid catalyst. What we want are rate ratios, which represent relative reactivities. The best estimates of the ratios of k_{sa} to k_{se} in both solvent systems are presented in Table 5.

Discussion

Relative Reactivities. Figure 2 demonstrates that both the axial (upfield) methoxy of **6a** and the equatorial (downfield) methoxy of **6e** are exchanging with methanol. It can also be seen that the axial is exchanging more quickly than the equatorial. The quantitative data in Tables 3 and 4 show that the axial methoxy does undergo faster exchange than does the equatorial methoxy, but the trans isomer **6t**, which is resolvable in benzene, shows the fastest exchange of all.

In order to use these relative reactivities to derive a quantitative assessment of stereoelectronic control, it is necessary to decide whether forward or reverse rates should be compared. To do so it is necessary to take account of the relative stabilities of the isomers and the position of the transition state along the reaction coordinate. It is also necessary to consider the contribution of the ring-opening pathway.

Thermodynamic Stabilities. Of the three diastereomers of 2-methoxy-4,6-dimethyl-1,3-dioxane the axial form (**6a**) is the most stable, owing to the anomeric effect.[2] This difference in stability between axial and equatorial may affect their relative reactivities to methoxy exchange.

Table 5. Average Relative Reactivities of **6a** and **6e**

solvent	$\langle k_{sa}/k_{se} \rangle$	% error
benzene	24	52
methanol/$CDCl_3$	9	12

The trans isomer (**6t**) should be the least stable of the three diastereomers, owing to the axial methyl group. This destabilization makes the ring-opening reaction (Scheme 4) more favorable, and this can lead to the rapid methoxy exchange that is seen. Indeed, this isomer is also most sensitive to hydrolysis during the preparation of the samples, and it is the one that is in equilibrium with an acyclic form (**10**). The absence of other methine cross peaks in the 2D-EXSY spectrum shows that there is no appreciable acyclic orthoformate in equilibrium with **6a** or **6e**.

Lateness of Transition State. The ability of antiperiplanar lone pairs to influence the stereochemical preference can depend upon the position of the transition state along the reaction coordinate. If the transition state for C−O cleavage is very late, without any interaction remaining between the leaving group and the carbocation center, it will resemble the intermediate oxacarbenium ion, **8**. Since this is the same ion regardless of reactant, the two transition states would be of equal energy and selectivity would be lost. This loss is seen in crystals, where there is no preference for antiperiplanar approach of an anion to 6-ethoxytetrahydropyrylium ion.[43]

If the transition state is early, it resembles the reactant, protonated on its methoxy group, which is either axial or equatorial. According to the reverse anomeric effect, whereby a cationic group prefers to be equatorial, **6e**·H^+ might be more stable than **6a**·H^+, but this has been refuted.[44] Instead, according to ab initio MO calculations on trihydroxymethane,[45] protonation of **6a** is favored by >5 kcal/mol, and the stabilities are consistent with other calculations showing that an oxygen whose lone pair is anti to a C−O bond is less basic.[46] (This differs from chelation to $MgBr_2$, which is much more favorable for the equatorial isomer.[47]) Then, if the transition state resembles **6**·H^+, **6a** will be more reactive, by an amount that may be considerable.

Even if the transition state is at neither of these extremes, but rather with the C−O bond partly broken, there will be a substantial energy difference due to the relationship to the adjacent lone pairs. Such a "late" transition state is predicted by the Hammond postulate and is generally assumed by proponents of ALPH.[19] The C−O bond is elongated, and the steric interactions of the methanol group with the axial hydrogens are weak. However, there is still sufficient C−O bonding that the σ^* orbital can interact with the lone pairs on the oxygens, especially if they are antiperiplanar.

Quantitative Measure of Stereoelectronic Control. Since the stereoisomeric orthoesters themselves have different stabilities, it is necessary to eliminate this reactant-energy contribution to the relative reactivities and focus only on the stereoelectronic control. The 1D-EXSY method provides all rate constants, not

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only forward (methoxy to methanol) but also reverse (methanol to methoxy). To the extent that the transition states are late, they lack the anomeric and steric interactions that make **6e** slightly less stable than **6a**. Therefore the forward rate constant for **6e** is increased by the relief of that instability. In the reverse direction, intermediate **8** is attacked by a methanol molecule from either an axial or an equatorial approach. The energy difference between the two transition states is due only to the stereoelectronic effect. Therefore the ratio k_{sa}/k_{se} for the reverse reactions is the better measure of the benefit of antiperiplanar lone pairs.

The data in Table 5 show that there is a preference for attack of methanol antiperiplanar to two lone pairs, relative to attack syn to those lone pairs. In benzene the rate acceleration is 24-fold. In methanol−$CDCl_3$ with a high concentration of orthoester the acceleration is a more modest 9-fold. Therefore the stereoelectronic benefit of two antiperiplanar lone pairs is worth no more than 1 or 2 kcal/mol.

Furthermore, the reaction of **6e** cannot be occurring through a boat or twist-boat conformation or through a ring-inverted conformation. Such conformations have been invoked when reactions seem to utilize a syn lone pair, in order to sustain ALPH.[19,33] However, here the stereoelectronic $\Delta\Delta G^{\ddagger}$ is so small, whereas those other conformations are at least 5 kcal/mol higher in energy. Therefore we can conclude that antiperiplanar lone pairs are favored, but syn lone pairs are nearly as effective. If the latter are disfavored by only 2 kcal/mol, then there is no need to proceed via high-energy conformations that permit anti lone pairs.

Although this conclusion is based on rate constants k_{sa} and k_{se} for the reverse reactions, it is not dependent on that choice. Were the comparison based on the forward rate constants for cleavage, the benefit ascribed to antiperiplanar lone pairs would be even lower, since the (less accurate) rate ratios k_{as}/k_{es} are then only 1.1 and 20 in the two solvents.

Selectivity is slightly higher in benzene, although the error in k_{se} is large, since this rate is near the lower limit of the NMR time scale. In the more polar environment solvation stabilizes the intermediate cation, so that less stabilization is needed from the adjacent lone pairs, whose orientation becomes less critical. This is a general phenomenon. Selectivity decreases as the transition states become more stable, whether by solvation, by increased leaving-group ability, or by an internal nucleophile that expels the leaving group.

Little can be concluded from the rate constant k_{st} of **6t**, since it is not comparable to k_{se} and k_{sa}. According to the data in Table 4, the trans form undergoes the fastest exchange. It is likely that this exchange proceeds in part through the ring-opening mechanism.

Methine Exchange and Ring-Opening Processes. It is necessary to verify that the rapidity of equatorial exchange is not due to the ring-opening mechanism of Scheme 4, which would permit methoxy exchange through a stereoelectronically assisted pathway. It would also permit the epimerization of **6a** and **6e**, and the nonzero k'_{ea} and k'_{ae} in Table 2 would seem to be evidence for the incursion of this mechanism. However, there is no direct axial/equatorial epimerization, since 1D-EXSY rate constants k_{ea} and k_{ae}, for methoxy exchange, are definitely zero. This means that epimerization is occurring through capture of methanol by the intermediate (**8**), but with inversion of the original configuration.

A comparison of the rate constants for methine and methoxy exchanges confirms this pathway. If k_{ea} and k_{ae} are zero, then the rate constants for epimerization are given by the rate constants for methoxy exchange, multiplied by the probability of inversion of configuration, as in eqs 8 and 9. From the rate constants in Table 3, the values of k'_{ea} and k'_{ae} are calculated to be 5.9 and 1.2 s^{-1}, respectively. The average of these is in

$$k'_{ea} = k_{es}\frac{k_{sa}}{k_{se} + k_{sa}} \tag{8}$$

$$k'_{ae} = k_{as}\frac{k_{se}}{k_{se} + k_{sa}} \tag{9}$$

adequate agreement with the average from Table 2, considering the departures of forward and reverse rate constants from microscopic reversibility.

The trans stereoisomer (**6t**) also undergoes methine exchange but with the acyclic orthoformate (**10**). This is the evidence for exchange by ring-opening. According to the rate constants in Table 2, this exchange is slower than that of the cis diastereomers (**6a** or **6e**), but according to the methoxy rate constants in Table 4 (in a different solvent) it is faster. This suggests that there is a direct pathway for methoxy exchange, in addition to the ring-opening.

Conclusions

In the acid-catalyzed methanolysis of the epimers of *cis*-4,6-dimethyl-2-methoxy-1,3-dioxane the rates of exchange for both the stereoelectronically assisted and unassisted reactions can be measured. Depending on solvent, the axial epimer (**6a**) undergoes exchange 9 to 24 times as fast as the equatorial (**6e**). Even in this most favorable case for stereoelectronic control the two antiperiplanar lone pairs are worth only 1−2 kcal/mol, which is not exceptionally large. The weakness of the effect could be rationalized by assuming[19] that the transition state resembles the oxacarbenium ion, but the need for such an *ad hoc* assumption risks rendering ALPH an empty hypothesis.

Though small, the stereoelectronic control in reaction of these orthoesters is larger than seen in amidines,[14] where small conformational changes can improve overlap between the leaving group and a nitrogen lone pair that is syn, as in E2 eliminations. This is more difficult for the pure-p lone pair of an oxygen, which is orthogonal to the leaving group. Moreover, in amidine hydrolyses the oxyanion is so strong an internal nucleophile that the orientation of the nitrogen lone pairs is less important. As the electronic demands on the lone pairs increase, as in orthoesters, their orientation becomes more critical. These results are also consistent with the observations that alane reagents in ether react only with **6a**, that the hydride is delivered predominantly axially, and that the selectivity is even higher in the reaction with Grignard reagents.[22] Consequently, the stereoselectivity becomes sufficient for synthetic purposes, and synthetic strategies may be designed to take advantage of stereoelectronic control.

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