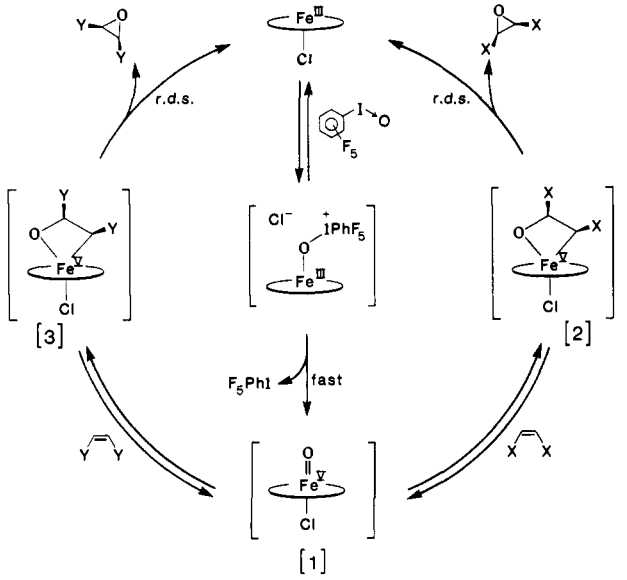

Figure 1. Proposed catalytic cycle for the competitive epoxidation between two different olefins.

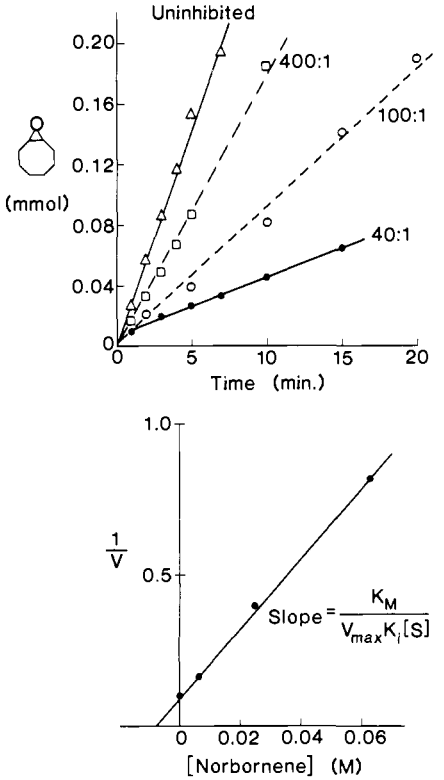

Figure 2. (Upper Graph) Cyclooctene oxide production vs. time for several cyclooctene/norbornene competitive epoxidation runs. The ratios shown are the initial cyclooctene:norbornene ratios. The concentration of cyclooctene was held constant while the amount of norbornene was varied. The total reaction volume was held constant (0.6 mL). (Lower Graph) Dixon plot of the results shown above. V = velocity; K_M = Michaelis constant; K_i = inhibition constant; [S] = cyclooctene concentration.

Attempts to characterize rigorously these intriguing species are ongoing.

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Solvent Water and the Biological Group-Transfer Potential of Phosphoric and Carboxylic Anhydrides

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Phosphoric anhydrides take part in many chemical and physical processes in living systems, and there are indications that carboxylic anhydrides may be formed as reactive intermediates during the action of certain enzymes.[1,2] These compounds have large negative group-transfer potentials in water.[3] Their reactions tend to occur in the active sites of enzymes where water is relatively scarce, and it would be of interest to know the extent to which solvent water affects their equilibria of hydrolysis. Large positive entropy changes that accompany hydrolysis of pyrophosphate derivatives suggest that solvation effects could play a major role in determining positions of equilibria of these reactions,[4] and molecular orbital calculations support this possibility.[5]

Effects of solvent water on these reactions could be evaluated directly if the affinities of anhydrides for water were available for comparison with those of the products of their hydrolysis. Unfortunately phosphoric anhydrides with dissociable protons, such as ATP, are too polar for direct measurement of their equilibria of distribution between water and nonpolar environments. In addition, acid anhydrides tend to be unstable in water. To circumvent these problems, we have measured apparent distributions of acetic anhydride and tetraethyl pyrophosphate at various concentrations between water and chloroform after timed intervals of mixing. Results were extrapolated back to the initial time of mixing, in order to obtain the distribution coefficient of the unhydrolyzed compound at the time of mixing. By comparison of the distribution coefficients of an anhydride and of reactant water with those of the acids produced by its hydrolysis, it should be possible to estimate the equilibrium constant for hydrolysis of the anhydride in wet chloroform (Scheme I).

Solutions of acetic anhydride or tetraethyl pyrophosphate (0.02–1.00 M in D_2O-saturated $CDCl_3$, 5 mL) were introduced into a Mixxor apparatus (Cole-Palmer Co., 10-mL capacity) along with $CDCl_3$-saturated D_2O (5 mL) containing 0.3 M KCl, these components having been previously adjusted to 20 °C in a water bath. Complete mixing was achieved in 15 s (eight strokes of the piston), and the phases were allowed to clear during the following 15 s. The aqueous phase was then removed for analysis. Tetraethyl pyrophosphate was determined in the D_2O phase using a Varian EM-390 NMR spectrometer (δ 1.5 for methyl groups), with pyrazine as an internal integration standard. Acetic anhydride was determined by allowing complete hydrolysis to occur in the aqueous phase over a period of 1 h. Acetic acid was then tritrated potentiometrically with standard KOH. These experiments were repeated after mixing intervals of 2, 5, 10, 15, and 20 min, and the results were extrapolated to obtain a value at zero time. Half-times for hydrolysis in water are approximately 7 h for tetraethyl phosphate[6] and 6 min for acetic anhydride.[7] Anhydrides favor the chloroform phase (see below), so that their effective half-lives were in fact longer under the conditions of the distribution experiments, approximately 2 h for acetic anhydride and 300 h for tetraethyl pyrophosphate.

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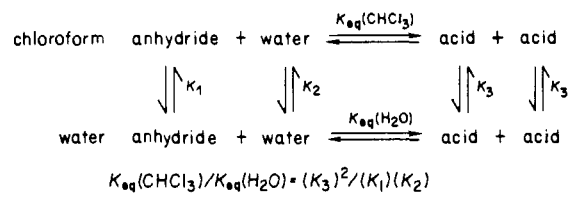
Scheme I



$$K_{eq}(CHCl_3)/K_{eq}(H_2O) = (K_3)^2/(K_1)(K_2)$$

Table I. Estimated Free Energies of Hydrolysis of Acetic Anhydride, Pyrophosphoric Acid, and ATP in Wet Chloroform

	Ac_2O	PP	ATP
ΔG(app) for reaction in dilute aqueous solution at pH 7[a]	−21.8[e]	−8.0[f]	−7.6[g]
ΔG(app) for reaction of nonionized compounds[b]	−15.7	−8.9	−6.6[g]
ΔG(app) incorporating actual concentration of water[c]	−13.3	−6.5	−4.4
ΔG for reaction in wet chloroform at 25 °C[d]	−11.6	−1.8	+0.3

[a] Free energies (in kcal) based on a standard state of 1 M total stoichiometric concentrations of reactants and products (except hydrogen ion) in neutral aqueous solution, with water activity taken as unity (convention III, ref 3). [b] Free energies based on a standard state of 1 M uncharged reactants and products and activity of pure water taken as unity (convention I, ref 3). K_a values of reactants and products were obtained from ref 3 for Ac_2O, from ref 16 for PP, and from ref 17 for ATP. [c] Obtained by dividing apparent equilibria of hydrolysis of nonionized compounds (convention I) by 55.5 M. [d] Obtained by correcting for the difference in distribution coefficients between reactants and products (see text). [e] 25 °C, ref 10. [f] 25 °C, ref 16. [g] 30 °C, ref 17, for cleavage to ADP and inorganic phosphate.

At 20 °C and ionic strength 0.3, distribution coefficients favored the chloroform phase by a factor of 19 for acetic anhydride and 40 for tetraethyl pyrophosphate. Self-association of these anhydrides had not been expected to occur to a significant extent in either chloroform or water.[8] These distribution coefficients showed no systematic or significant variation (less than 20%) as the total amount of anhydride present was caused to vary over a 50-fold range, from 0.02 to 1.00 M introduced into the chloroform phase at the outset. Variation would have been expected if either of these anhydrides tended to self-associate in either of the two phases.

Distribution coefficients between water and wet $CHCl_3$ have been measured previously for water ($K_2 = 5.6 \times 10^{-4}$), acetic acid ($K_3 = 0.025$),[9] and diethyl phosphate ($K_3 = 2.7 \times 10^{-3}$).[8] By comparing distribution coefficients of reactants and products (Scheme I), one is led to infer that the equilibrium constant for hydrolysis of acetic anhydride is less favorable in wet chloroform than in water by a factor of 17, i.e., 3.7×10^8, as compared with a value of 6.3×10^9 measured in water.[10] This effect is more pronounced in the case of tetraethyl pyrophosphate, so that the equilibrium constant for its hydrolysis is 3070-fold less favorable in wet chloroform than in water. If these factors are applied to equilibrium constants that have been determined for aqueous reactions, it becomes evident (Table I) that hydrolysis of acetic anhydride to unionized products remains highly exergonic in wet chloroform, whereas equilibrium constants for hydrolysis of pyrophosphoric acid derivatives approach unity.

Other work indicates that myosin binds ATP in such a way that its free energy of hydrolysis becomes much less negative than it was in free solution.[11] The present results support suggestions by George et al.[5] and by Hayes et al.[4] that this could be achieved by abstracting reacting portions of the substrates from solution into relatively waterless surroundings. The considerable energetic cost of stripping water from ATP could presumably be paid in part by binding of the relatively hydrophobic[12] adenosine moiety, and there is evidence in adenylate kinase for a dominant role of distant binding sites for both the phosphoryl donor and the acceptor in stabilizing intermediates in the transfer of phosphoryl groups.[13] Actin binding appears to promote dissociation of ATP from myosin, perhaps by inducing a conformation change.[11] This effect could presumably arise if the binding sites of ATP were transformed, in the course of actin binding, from a relatively buried to a relatively exposed configuration. The present results are also of interest in relation to the suggestion that evolutionary pressure may have tended to favor enzyme mechanisms in which equilibria between reactants and products approach unity on the catalytic surface more closely than they do in free solution, a tendency that has been observed in numerous kinases.[14] This objective might tend to be accomplished if binding sites for ATP and phosphoryl group acceptors had evolved in such a way as to remove the reacting portions of substrates and products, at least in part, from water.

It seems fair to conclude that the large negative free energies of reactions of phosphoric anhydrides, like those of intermediates in protein biosynthesis,[15] can be understood to a large extent in terms of the differing strengths of solvation of reactants and products, leaving relatively little to be explained in terms of intrinsic chemical properties of reactants and products as they would be observed in the absence of solvent water.

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Asymmetric Oxygenation of Chiral Imide Enolates. A General Approach to the Synthesis of Enantiomerically Pure α-Hydroxy Carboxylic Acid Synthons

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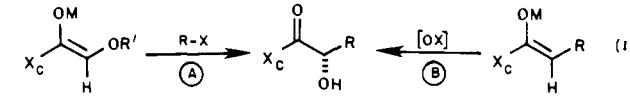
Homochiral α-hydroxy acids, and simple derivatives thereof, have proven to be a versatile class of molecules which have been extensively exploited in asymmetric synthesis.[1] For example, malic, mandelic, and tartaric acids are routinely employed as chiral synthons as well as precursers to both chiral ligands and auxiliaries.[2,3] By inspection it is evident that the generation of these target structures might be accomplished via the application of chiral enolate technology (eq 1). Recently, two independent



(1)

reports have described the development of camphor-based chiral glycolate enolate synthons and their respective diastereoselective alkylation studies (eq 1A).[4,5] In addition, Tamm and co-workers have demonstrated that MoOPH oxygenates camphor-derived ester enolates with moderate levels of diastereoselection (eq 1B).[6]

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