the solvent dependence. However, this is not a complete explanation. Comparisons between X-ray structural data of porphyrins and porphyrin radical cations show that oxidation results in little change in nuclear configuration.[10] Similarly, IR and Raman spectroscopic evidence suggests that reduction of quinones to their radical anions principally results in changes in the C–O distance.[11] These data point back to the solvent as a principal contributor to the reorganization energy. Current work is focusing on these problems.

In conclusion, two principal features of these molecules allow us to clearly observe inverted rate vs. $-\Delta G$ behavior at high exothermicities. First, the donor–acceptor distance is restricted, and, second, the highly exothermic charge recombination reactions do not produce electronically excited states of the donor or acceptor.

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1,8-Biphenylenediol Is a Double-Hydrogen-Bonding Catalyst for Reaction of an Epoxide with a Nucleophile

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The reaction of phenyl glycidyl ether with diethylamine in butanone solution is catalyzed by hydroxyl compounds, with the

$$\mathrm{PhOCH_2\overset{\frown O\frown}{CH}CH_2 + Et_2NH \xrightarrow{ArOH} PhOCH_2CHOHCH_2NEt_2} \quad (1)$$

catalytic activity of meta- and para-substituted phenols increasing with their increasing acidity.[1] We have found that 1,8-biphenylenediol, which is known from X-ray crystal structures of its adducts to be capable of forming two strong hydrogen bonds simultaneously to the same oxygen atom,[2] is a significantly better catalyst for this reaction than would be expected from data on meta- and para-substituted phenols, 1-biphenylenol, and 8-methoxy-1-biphenylenol. As shown by the Brønsted plot of slope 0.18 in Figure 1 (based on data in Table I), 1,8-biphenylenediol is 3 times as good a catalyst, per hydroxyl group, as it would be if its point fell on the Brønsted line; its catalytic activity is that expected for a phenol that is about 600 times as acidic. The other derivatives of 1-biphenylenol are no better catalysts than would be expected from the Brønsted plot. Neither is the diol catechol, whose hydroxy groups are not well placed for simultaneous hydrogen bonding with a common oxygen atom.

The kinetics of reaction 1 at 30 °C were followed by VPC measurements on the concentration of the epoxide relative to that of naphthalene, present as an internal standard (~0.08 M). The rate follows kinetic eq 2, in which E, N, and A are the epoxide,

$$-dE/dt = (k_c[\mathrm{ArOH}] + k_a[A] + k_u)[E][N] \quad (2)$$

amine, and alcohol product. The values of k_a (9.4×10^{-6} M^{-2} s^{-1}) and k_u (3.5×10^{-6} M^{-1} s^{-1}) were obtained from runs in which no catalyst was added.[3] The extent of the background reaction, defined as the value of $(k_a[A] + k_u)/(k_c[\mathrm{ArOH}] + k_a[A] + k_u)$ at half-reaction, ranged from 13% to 40% of the total reaction. Concentrations used were around 0.2 M phenyl glycidyl ether, 0.3 M diethylamine, and 0.03–0.15 M catalyst.

The reaction mechanism presumably involves protonation, by the acid catalyst, of the epoxide oxygen atom as it is displaced from carbon by the attacking amine. The relatively small Brønsted α of 0.18 suggests that the extent of proton transfer in the transition state is not very large. By itself, however, it does not tell whether cleavage of the C–O bond runs ahead of formation of the O–H bond, so that the epoxide oxygen atom has become more negative in the transition state than it was in the reactant or not. The observation of double-hydrogen-bonding catalysts shows the oxygen probably has become more negative and hence

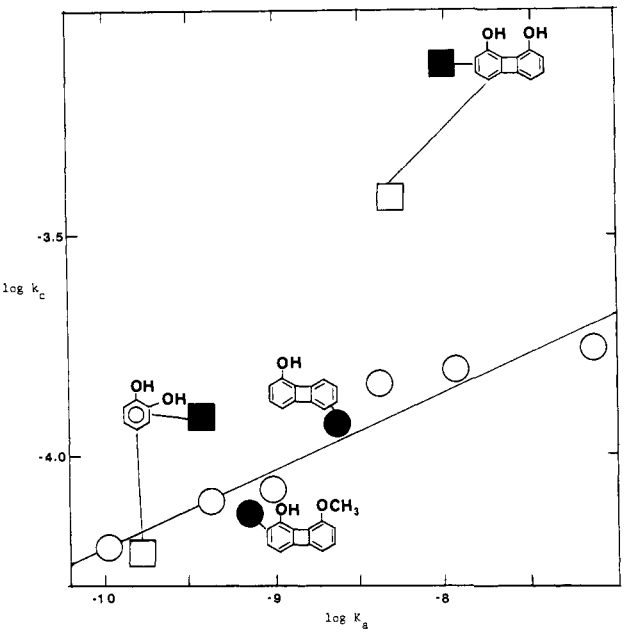

Figure 1. log–log plot of catalysis constants in the reaction of diethylamine with phenyl glycidyl ether vs. ionization constants for the catalyst. (○) meta- and para-substituted phenols, (●) monohydroxy derivative of biphenylene, (■) uncorrected data for a diol, (□) statistically corrected data for a diol.

Table I. Catalysis Constants for Reaction of Diethylamine with Phenyl Glycidyl Ether[a]

catalyst	$10^5 k_c$, M^{-2} s^{-1}	pK_a[b]
phenol	6.0	9.98[c]
p-chlorophenol	7.7	9.38[c]
m-chlorophenol	8.2	9.02[c]
m-nitrophenol	14.3	8.40[c]
p-cyanophenol	15.3	7.95[c]
p-nitrophenol	17.0	7.15[c]
catechol	11.9	9.49[c]
1-biphenylenol	11.5	8.64[d]
8-methoxy-1-biphenylenol	7.3	9.15[d]
1,8-biphenylenediol	75	8.00[e]

[a] In butanone solution at 30 °C. Calculated by using eq 2. [b] In water at 25 °C. Obtained from the source noted. [c] Körtum, G.; Vogel, W.; Andrussow, K. "Dissociation Constants of Organic Acids in Aqueous Solution"; Butterworths: London, 1961. [d] Hahn, S., The Ohio State University, personal communication, 1984. [e] Miles, D. E. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1982.

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(3) The values of k_a and k_u varied by as much as ±44% and ±7%, respectively, in different runs, but high values of k_a were obtained with low values of k_u. Hence the first-order rate constant $(k_a[A] + k_u)$ for that part of the reaction not resulting from catalysis by ArOH is much less uncertain. In a run using 0.0578 M *p*-nitrophenol, where there was a relatively large amount of background reaction (31%), replacement of k_a and k_u by values 44% larger and 7% smaller, respectively, decreased the calculated value of k_c by less than 0.6%.

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more basic in the transition state for the mono-hydrogen-bonding catalyzed reaction. This more basic oxygen atom should be stabilized more by an additional acidic hydrogen bond.

In view of the ubiquity of hydrogen bonds and the commonness of polyfunctional catalysis in nature, it seems likely that there are naturally occurring multiple-hydrogen-bonding species that bind substrates and catalyze reactions. Decomposing the epoxides that are formed from carcinogenic polynuclear aromatic compounds before these epoxides react with nucleic acids[4] would be a plausible purpose for either a natural enzyme or a man-made drug.

Registry No. Phenyl glycidyl ether, 122-60-1; diethylamine, 109-89-7; 1,8-biphenylenediol, 18798-64-6.

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Recognition of NMR Proton Spin Systems of Cyclosporin A via Heteronuclear Proton–Carbon Long-Range Couplings

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Homonuclear proton–proton spin coupling is normally used to identify the pattern of spin systems which yields the connectivity of atoms in a molecule (constitution). Recent developments in two-dimensional (2D) correlated NMR techniques (e.g., phase-sensitive H,H-COSY,[1] relayed H,H-COSY,[2] proton double-quantum spectroscopy[3]) provide powerful tools to handle even complicated and crowded spectra. However, extensive overlap of proton signals still often prevents or complicates the detection of proton connectivities.

We demonstrate here that it is possible to spread out proton spin systems by observing them on the normally much more disperse carbon signals. For this purpose the new pulse sequence for heteronuclear correlation via long-range coupling (H,C-COLOC[4]) has been used for aliphatic carbons.

$$90°(^1H), t_1/2, 180°(^1H, ^{13}C), (\Delta_1 - (t_1/2)), 90°(^1H, ^{13}C), \Delta_2, \mathrm{acq}(^{13}C, \mathrm{BB}^1H)$$

The H,C-COLOC sequence is especially designed to detect heteronuclear coupling through two and three bonds ($^2J_{CH}$ and $^3J_{CH}$). The experimental details of this sequence are described elsewhere.[4,5]

This sequence has been utilized so far only for quaternary carbon atoms. When the sequence is applied to nonquaternary carbons, the $^1J_{CH}$ couplings evolve during the delay Δ_1 in addition to long-range couplings. This leads to the occurrence of "direct" cross peaks. They can be suppressed by a low-pass J filter.[6] During the delay Δ_2 $^1J_{CH}$ couplings evolve and attenuate the amplitude of the signals from remote C,H-connectivities by a factor $\cos^n \pi J\Delta_2$ for a $^{13}CH_n$ fragment. Therefore Δ_2 has to be chosen in a way that $\cos^n \pi J\Delta_2$ is as near to unity as possible. If the range of $^1J_{CH}$ couplings is small (for peptides $^1J_{CH} = 135 \pm 10$ Hz), such delays Δ_2 are easily found. Nevertheless a selective refocusing of the $^1J_{CH}$ coupling can be achieved with a J-selective π-pulse[7] in the middle of Δ_2.

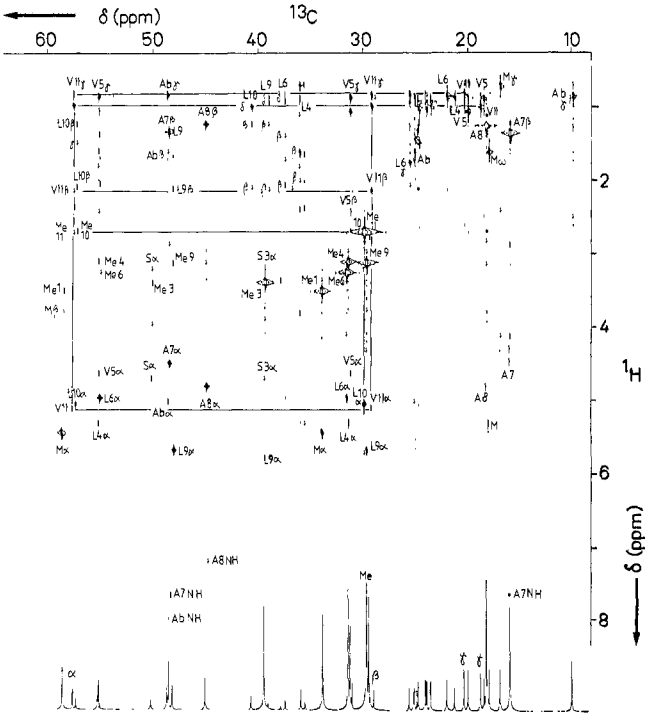

Figure 1. H,C-COLOC spectrum of 500 mg of cyclosporin A in 2.5 mL of $CDCl_3$ and ^{13}C projection of this spectrum (below). 240 increments of 192 scans each, $\Delta_1 = 27$ ms, $\Delta_2 = 37$ ms, duration of one scan 1.25 s, total time 16 h, ^1H frequency 500 MHz. The assignments of most of the cross peaks are given in the contour plot. Cross peaks of MeVal[11] are connected by lines.

However, in our experience the introduction of both spectroscopic tricks did not facilitate the practical evaluation of the spectra.[8] The direct C–H cross peaks provide additional fix-points for the orientation in the spectrum, as they are known from a previously performed H,C-COSY spectrum. The introduction of a J-selective π-pulse yielded additional artifacts due to pulse imperfections.

We demonstrate here the application of the H,C-COLOC experiment to the aliphatic carbon atoms of cyclosporin A (*cyclo*-[-MeBmt[1]-Abu[2]-Sar[3]-MeLeu[4]-Val[5]-MeLeu[6]-Ala[7]-D-Ala[8]-MeLeu[9]-MeLeu[10]-MeVal[11]-])[9] which has a very crowded proton spectrum in the high-field region making the interpretation of the four-Leu systems difficult.[10]

It is possible to solve this problem by the H,C-COLOC experiment which contains carbon *and* proton connectivities of *all* amino acids including their *N*-methyl groups. The contour plot of the H,C-COLOC spectrum of cyclosporin A (Figure 1) exhibits about 120 cross peaks. Carbon signals belonging to the same

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