these authors clearly point out, the proton and metal complex basicities of the wide variety of anions studied are also strongly correlated.[19]

Conclusions. The linear, nonunit slope correlation of methyl and proton acid heats of formation speaks to a fundamental aspect of chemical bonding. A plot with some nonzero intercept and unit slope is consistent with bond additivity. We know that such correlations are often acceptable but can usually be improved by using group additivity.[20] The plot in Figure 2 shows that the group corrections in this case are functionally related. That is, the methyl compounds are intrinsically less sensitive to the nature of A than are the H compounds. Using a simple one-electron picture to describe bonding in simple acids,[21] we can write that the stabilization energy, SE, with respect to the separated orbitals of A and the acid moiety is given by eq 6 where Δ is the difference in orbital energies of A and the corresponding acid moiety (H, CH_3, etc.) and V is the strength of the perturbative interaction. The relative stability of the separated H vs methyl orbitals contributes to the constant (intercept) difference. The methyl compound stabilities are less structure sensitive than are the protonated bases, possibly because methyl can respond better in less favorable overlap situations, owing to its larger number of available orbitals. Generally speaking, the slope of such heat of formation plots will depend on the specific acid moieties involved. The observation of unit slope[16,17] in the metal cation plot suggests, therefore, that the relative perturbative interactions are similar for H and the metal cations. The full implication of these correlations is not yet clear, but the regular behavior observed by us and by Bryndza and Bercaw suggests that it may not be necessary to invoke second-order effects in order to rationalize and understand acid and base behavior for systems with rather wide variation in structure.

$$SE = (\Delta^2 + 4V^2)^{1/2} \quad (6)$$

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Registry No. O_2, 7782-44-7; N_2, 7727-37-9; methyl cation(1+), 14531-53-4.

Diels–Alder Reactions in Nonaqueous Polar Solvents. Kinetic Effects of Chaotropic and Antichaotropic Agents and of β-Cyclodextrin

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Abstract: The Diels–Alder addition reactions of nitrosobenzene with 1,3-cyclohexadiene and of methyl vinyl ketone with 1,3-cyclopentadiene are faster in formamide or in ethylene glycol than in other organic solvents, but not as fast as in water solution. The reactions in these organic solvents are also accelerated by β-cyclodextrin. The kinetic results indicate that there is solvophobic binding of the reactants to each other, or into the cyclodextrin cavity, in these polar solvents. In spite of this, there is no striking increase in endo/exo selectivity, as there is in water. We detect two classes of chaotropic agents. Urea and guanidinium ion, which are normally chaotropic in water and thus decrease the hydrophobic effect and the rate of our Diels–Alder reactions, show no such effect in the organic solvents. These solutes also *decrease* the solubility of benzene in ethylene glycol or in formamide, in contrast to their effects in water. The contrasts indicate that "waterlike" organic solvents still do not share some of the most striking properties of water itself. The results also indicate that the chaotropic effects of urea and of guanidinium ion in water reflect primarily the interaction of the chaotropes with the water, not with the hydrocarbon solutes. By contrast, tetramethylammonium bromide, and even more so tetrabutylammonium bromide, belong to a second class of salting-in agents. They decrease the rate of the Diels–Alder addition of cyclopentadiene to methyl vinyl ketone, and tetramethylammonium bromide increases the solubility of benzene in ethylene glycol and formamide (as it does in water). These tetraalkylammonium cations probably act as pseudodetergents and interact primarily with the solutes, not the solvents.

We have described the remarkable acceleration of Diels–Alder reactions when water is the solvent[1] and the striking increase in stereoselectivity that is seen in some cases.[2,3] The reaction rate of 1,3-cyclopentadiene with methyl vinyl ketone (reaction 1) and with acrylonitrile (reaction 2) was increased by factors of 740 and 30, respectively, when the addition was performed in water rather than in isooctane, and the reaction rate for the addition of *N*-ethylmaleimide to anthracene-9-carbinol (reaction 3) was increased by a factor of 28.

This solvent effect was principally due to the hydrophobic packing of the diene and dienophile, not to a simple polarity effect. As one piece of evidence, the rate of reaction 1 increased by only 12-fold on changing from isooctane to methanol solvent, while that of reaction 2 increased by only 2-fold with the same solvent change.[1] The large discontinuous increase in water is well above any expected polarity effect. Even more striking, in reaction 3 the rate actually *decreases* by a factor of 2.3 when methanol solvent is used instead of isooctane. In reaction 3 the hydrophobic

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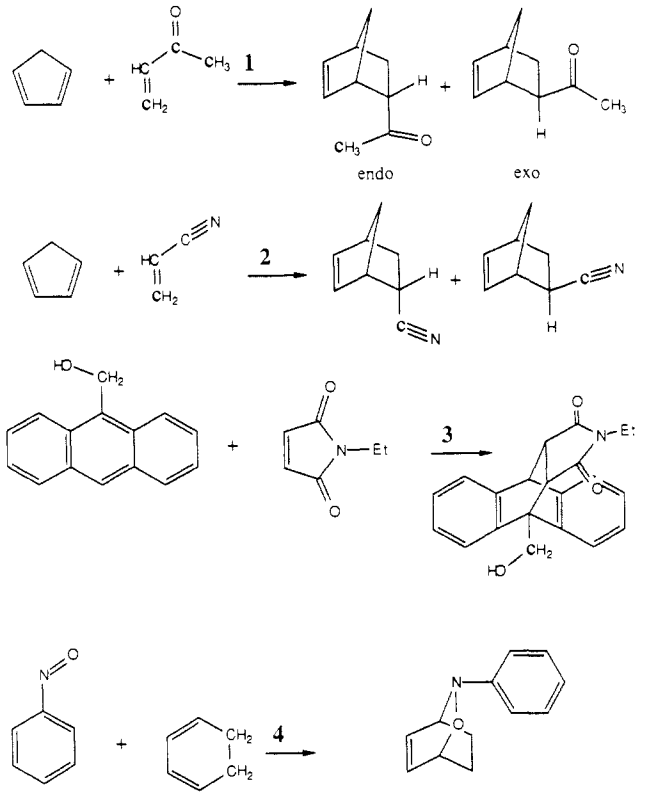

effect increases the rate in water in spite of an expected rate decrease due to polarity alone, as judged by the methanol/isooctane comparison.[1]

Additional evidence was found in the effects of *chaotropic* and *antichaotropic* agents.[4-20] Substances such as urea, which cause the denaturation of proteins or nucleic acids in water solution, are called "chaotropic". On a more fundamental level, urea increases the water solubility of hydrocarbons such as benzene by decreasing the hydrophobic effect. Protein and nucleic acid denaturation in water when urea is added reflects a decreased tendency of hydrocarbon species, such as the hydrocarbon side chains that are normally in the interior of proteins, to stay self-associated and away from the water. Thus chaotropic agents are also frequently referred to as "salting-in" agents if they are ionic. By contrast, most salts decrease the solubility of hydrocarbons in water, leading to the well-known "salting-out" effect.

We found that the chaotropic salt guanidinium chloride (4.86 M) decreased the rate of reaction 3 by a factor of 3.0,[2] although with reaction 1 the decrease in rate was only ca. 2%.[1] However, the antichaotropic salt lithium chloride *increased* the rate of reaction 3 by 2.5-fold,[2] and of reaction 1 by 2.5-fold as well.[1] These hydrophobic effects on reaction rates reflect the tendency of water solvent to promote packing of the reactants so as to minimize the exposed hydrocarbon surface. As might be expected, this also changed the selectivity of the Diels–Alder reactions.

We found that the endo/exo product ratio for reaction 1 was 25.0 ± 0.5 in true water solution, compared with a ratio of 3.85 in neat cyclopentadiene or of 8.5 in ethanol.[2] Thus again water is special. This may in part be because increased solvent polarity favors the endo transition state, with partial charge transfer and secondary orbital interaction between diene and dienophile. However, the endo transition state is also more compact and should be favored by hydrophobic packing effects. In line with this, we found that the endo/exo ratio in true water solution increased to 28.0 ± 0.4 with 4.86 M LiCl but decreased to 22.0 ± 0.8 with 4.86 M chaotropic guanidinium chloride.[3] Related effects were seen with other dienophiles.[2] Remarkably, the catalytic effect of water on the Diels–Alder reaction was such that the large endo/exo ratios persisted to a great extent even with suspensions of cyclopentadiene, in which the bulk of the material was not in solution and the selective reaction occurred by phase transfer.[2]

Grieco has also examined the effect on selectivities of using water in Diels–Alder reactions.[21] He has reported a number of examples of synthetic interest in which the increase in selectivity is useful.[22] Very recently, Schneider has examined the Diels–Alder reaction of cyclopentadiene with diethyl fumarate in various solvents, including water.[23] He reports that the rate correlates well with a solvophobicity parameter described by Abraham[24] that is derived from hydrocarbon solubilities but not with a solvent polarity parameter. Thus, with this system as well the large increase in rate with water as solvent seems clearly related to its hydrophobic effect.

Hydrophobic packing of the diene and dienophile was also involved in our finding that these reactions are catalyzed by appropriate cyclodextrins. We saw that reaction 1 had a 2.5-fold acceleration in the presence of 10 mM β-cyclodextrin, but a 1.7-fold decreased rate in the presence of 10 mM α-cyclodextrin.[1] In reaction 2 the acceleration with 10 mM β-cyclodextrin was 9.0-fold, while 5 mM α-cyclodextrin gave a 23% decrease in rate.[1] Molecular models show that both the diene and the dienophile can fit into a β-cyclodextrin cavity, so the reactions are catalyzed. With the smaller α-cyclodextrin cavity, binding of the diene excludes the dienophile and the reaction is inhibited. With reaction 3 even 10 mM β-cyclodextrin is an inhibitor, the rate decreasing by a factor of 1.6 because the large diene and dienophile cannot both fit into this cavity.[1] Schneider reported that β-cyclodextrin also catalyzes the cyclopentadiene/ethyl fumarate reaction, again by binding both reactants into the cavity.[23] In these cyclodextrin catalyses the comparison is always against reaction in water alone, in which significant hydrophobic packing of the reactants is already present. Thus, the true catalytic effect compared with unassociated reactants is quite a bit larger.

Water is a very special solvent, but some other polar solvents are also strongly self-associated; one might expect to see similar effects in such solvents. Indeed, we reported some time ago that "hydrophobic" binding of hydrocarbon residues into cyclodextrins can become "lyophobic"[25] binding in a polar solvent such as DMSO.[26] Thus, we have now examined rates and endo/exo

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Table I. Second-Order Rate Constants for the Diels–Alder Reaction of 1,3-Cyclopentadiene with Methyl Vinyl Ketone in Various Solvents

solvent	$k_2 \times 10^5$, M^{-1} s^{-1} (20 °C)	ref
isooctane	5.94 ± 0.3	*a*
methanol	75.5	*a*
water	4400 ± 70	*a*
formamide	318 ± 4	*b*
ethylene glycol	480	*b*

[a] Reference 1. [b] This work.

selectivities for two Diels–Alder reactions in the strongly hydrogen-bonded solvents ethylene glycol and formamide. We have also looked at the rate effect of β-cyclodextrin in these media and the effects of agents that in water are either chaotropic or antichaotropic. Further, we have examined the solubility of benzene in these polar solvents in the presence of such agents. These studies give additional insight into the nature of chaotropic effects.

Experimental Procedures

Reagents and Solvents. Nitrosobenzene (Aldrich) was purified by vacuum sublimation, 1,3-cyclohexadiene (Aldrich) and methyl vinyl ketone were distilled under argon immediately before use, and cyclopentadiene was cracked from its dimer immediately before use. β-Cyclodextrin (Amerchol) was recrystallized from water and dried at 80 °C and 0.01 mmHg for 16 h over P_2O_5. Lithium chloride (Fisher certified reagent), lithium perchlorate (Alfa, 99.5% anhydrous), tetramethylammonium bromide (Aldrich, 98%), tetra-*n*-butylammonium bromide (Aldrich, 99%), guanidinium chloride (Mann Research, reagent grade), and urea (Aldrich gold label, 99+%) were used without further purification. Benzene was distilled from CaH_2. Ethylene glycol (Aldrich, 99+% spectrophotometric grade) and DMSO (Aldrich, 99+% spectrophotometric grade) were used without further purification, while formamide (Aldrich, 99+% spectrophotometric grade) was used immediately after filtration through silica.

Kinetic Methods. The reaction of nitrosobenzene (initially 0.23 mM) with 1,3-cyclohexadiene (initially 10.3 mM) was followed by observing the disappearance of the nitrosobenzene band at 309.2 nm in reactions run within a temperature-controlled Beckman DU-8 or DU-8B spectrophotometer. First, 1 mL of cyclohexadiene solution was equilibrated at 20.0 °C for at least 15 min in a cuvette, and then 10 μL of nitrosobenzene solution was added and the cuvette was capped and mixed by repeated inversion. Data were collected for at least 5 half-lives in almost every case, and generally 50 or more data points were used from this range. Pseudo-first-order rate constants were calculated with the KORE program.[27] In all cases good first-order kinetic behavior was observed, with R normally >0.999 99. Three or more runs were performed; the average rate constants and standard deviations are listed in Table III.

In the reaction of methyl vinyl ketone with 1,3-cyclopentadiene, the dienophile was used in excess. The disappearance of cyclopentadiene (initially 1.2 mM in the ethylene glycol runs, initially 2.4 mM in the formamide runs) was followed at 258 nm (in ethylene glycol) or at 265 nm (in formamide) in the presence of methyl vinyl ketone (initially 236 mM). The kinetic procedure was as described above, with the excess reagent being preequilibrated to temperature and then 10 or 20 μL of cyclopentadiene solution being added. With 30 or more data points collected over 5 half-lives, again the correlation coefficient R was >0.999 99. The average rate constants and standard deviations for three or more runs are listed in Table IV.

Salt Effects on the Endo/Exo Product Ratio. Solutions of 150 mM concentration in both cyclopentadiene and methyl vinyl ketone were stirred at room temperature for 30 h. The solutions were then extracted twice with equal volumes of dry diethyl ether, and the extracts were analyzed by gas chromatography on a DB-wax column at 120 °C, on which the endo adduct had a 16.0- and the exo a 12.6-min retention time. The ratios from the average of three injections are listed in Table V.

Salt Effects on the Solubility of Benzene. With formamide solutions, benzene was equilibriated with the solvent for 3 h in a water bath controlled at 20.0 ± 0.5 °C with vigorous shaking for the first few minutes. Then the bottom layer was removed and diluted 21-fold with formamide (adding 50 μL to 1.0 mL), and the concentration of benzene was determined by measurement in 1-cm cuvettes at 265 nm (20.0 °C). The concentrations were determined by calibration with known concentrations of benzene in formamide; the dissolved salts had no appreciable effect on the UV absorbance of benzene and had a negligible UV absorbance themselves, so no corrections had to be applied.

With ethylene glycol solutions, the same procedure was used except that the saturated solution was diluted 101-fold (adding 10 μL to 1.0 mL) before the UV determination (at 261 nm). The results of these solubility determinations are listed in Table VI.

Table II. Endo/Exo Product Ratio in the Diels–Alder Reaction of Cyclopentadiene with Methyl Vinyl Ketone[a]

solvent	endo/exo ratio	solvent	endo/exo ratio
cyclopentadiene[b]	3.85	formamide	8.9
ethanol[b]	8.5	ethylene glycol	10.4
water[b]	25.0		

[a] Reactants at 0.15 M except for the case of neat cyclopentadiene or of water, in which the diene concentration was 7 mM. [b] Data from ref 2.

Table III. Kinetic Data: Nitrosobenzene plus 1,3-Cyclohexadiene

solvent	additive (mM)	$k \times 10^2$,[a] min^{-1}
DMSO	none	1.16 ± 0.02
	β-CD (50)	0.96 ± 0.20
ethylene glycol	none	2.14 ± 0.22
	β-CD (6)	3.96 ± 0.20
	β-CD (10)	5.54 ± 0.14
	β-CD (20)	8.5 ± 0.3
	β-CD (60)	8.54 ± 0.14
	β-CD (80)	8.50 ± 0.57
	LiCl (423)	2.22 ± 0.01
	LiCl (846)	1.75 ± 0.02
	$LiClO_4$ (500)	2.08 ± 0.02
	$LiClO_4$ (1000)	2.10 ± 0.02
formamide	none	2.23 ± 0.07
	β-CD (4)	4.97 ± 0.06
	β-CD (10)	7.97 ± 0.07
	β-CD (20)	10.1 ± 0.05
	β-CD (30)	10.48 ± 0.04
	β-CD (40)	9.8 ± 0.05
	LiCl (1000)	2.19 ± 0.02
	LiCl (2000)	1.92 ± 0.01
	$LiClO_4$ (1000)	2.30 ± 0.02
	$LiClO_4$ (2000)	2.009 ± 0.006

[a] Pseudo-first-order rate constants for the disappearance of nitrosobenzene in the presence of 10.3 mM 1,3-cyclohexadiene. At least three runs were averaged; the errors listed are the standard deviations.

Results and Discussion

Ethylene glycol and formamide are often considered "waterlike",[13-15] but we find clear differences as well as similarities. As Table I shows, the second-order rate constant for the Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone is strongly increased in formamide, and even more in ethylene glycol, relative to such a polar solvent as methanol. However, the rate in water is still 9–14 times faster than in ethylene glycol or formamide. Furthermore, Table II shows that the remarkably high endo/exo ratio seen in water is not seen in formamide or ethylene glycol. In this respect these solvents are similar to ethanol, although they elicit quite a bit more selectivity than does a hydrocarbon solvent.

Darryl Rideout had studied the effect of β-cyclodextrin on the Diels–Alder reaction of nitrosobenzene with 1,3-cyclohexadiene in water (reaction 4).[28] He found that the rate increased by a factor of ~15 when the cyclodextrin concentration was increased to 3.0 mM and then stayed fairly constant up to 10 mM cyclodextrin. This indicates that the reaction is catalyzed by the formation of a ternary complex involving diene, dienophile, and cyclodextrin. Above 3 mM kinetic saturation is seen because the ternary complex is fully formed; the rate would presumably drop at still higher concentrations as the diene and dienophile partition into different cavities.

We have now examined this cyclodextrin effect in three polar nonaqueous solvents. In DMSO we see no rate change up to 50

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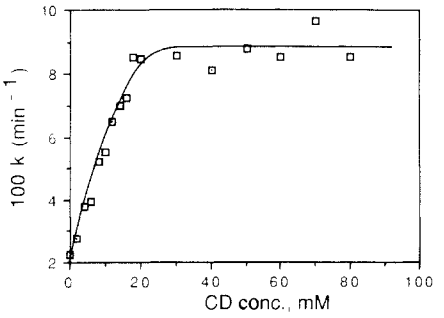

Figure 1. Pseudo-first-order rate constant for the reaction of nitrosobenzene with excess cyclohexadiene as a function of the concentration of added β-cyclodextrin in *ethylene glycol* solvent. The reaction conditions are described under Experimental Procedures.

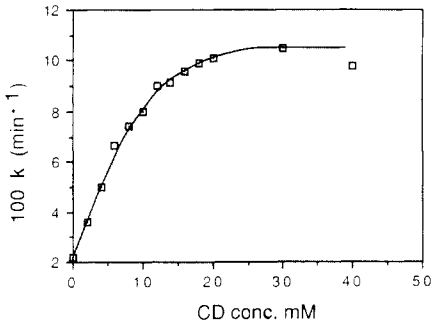

Figure 2. Pseudo-first-order rate constant for the reaction of nitrosobenzene with excess cyclohexadiene as a function of the concentration of added β-cyclodextrin in *formamide* solvent. The reaction conditions are described under Experimental Procedures.

mM β-cyclodextrin; interestingly, the first evidence for cyclodextrin binding in nonaqueous organic solvents was our report[25,26] of lyophobic binding of solutes in DMSO solution. In ethylene glycol, β-cyclodextrin produces acceleration and kinetic saturation. The data of Table III and other data not tabulated are plotted in Figure 1. As can be seen, β-cyclodextrin leads to about a 4-fold increase in the rate at 20 mM cyclodextrin and above. The data of Table III for formamide solution with β-cyclodextrin, and additional unlisted data, are plotted in Figure 2. Here about a 5-fold acceleration occurs, with kinetic saturation at ca. 30 mM. Thus, judged by these results ethylene glycol and formamide do indeed promote binding into cyclodextrin by a solvophobic effect[25] related to the hydrophobic effect seen in water.

In these solvents kinetic saturation requires a ca. 10-fold higher concentration of β-cyclodextrin than is required in water. This supports the conclusion from Table I that formamide and ethylene glycol promote association of cyclopentadiene and methyl vinyl ketone just as water does, but to a lesser extent. The β-cyclodextrin data in Table IV show that cyclodextrin also accelerates the cyclopentadiene/methyl vinyl ketone reaction in both solvents, as expected if the solvophobic effect in these solvents promotes binding into the cyclodextrin cavity. However, Table II shows that these kinetic effects are not reflected in a significant increase in endo/exo selectivity for reaction in the solvents themselves.

Since these data, except for the endo/exo selectivities, indicate that formamide and ethylene glycol are indeed somewhat waterlike, it was of interest to examine the effects of chaotropic and antichaotropic agents. It is fairly well established that in water solution antichaotropic salts are salting-out agents because the solvent is partially tied up by the salts, leading to a volume contraction and less space for the hydrophobic solute.[4-11] By contrast, chaotropic agents such as urea increase the solubilities of hydrocarbons in water. Most workers believe that this is because they break up the water structure,[4-12] but some[16] suggest that the chaotropes interact with the hydrophobic solute instead. We have not located any prior study of the effects of the classic protein-denaturing chaotropic agents urea and guanidinium cation in waterlike pure organic solvents. Some studies have been done

Table IV. Kinetic Data: Cyclopentadiene plus Methyl Vinyl Ketone

solvent	additive (M)	$k \times 10^2$,[a] min^{-1}
ethylene glycol	none	6.76 ± 0.09
	LiCl (0.491)	7.60 ± 0.09
	LiCl (0.982)	8.83 ± 0.35
	$LiClO_4$ (0.965)	12.12 ± 0.05
	GnCl (1.01)[b]	8.90 ± 0.04
	Me_4NBr (0.502)	5.82 ± 0.05
	Bu_4NBr (0.500)	3.66 ± 0.11
	urea (4.02)	9.85 ± 0.18
	β-CD (0.099)	10.67 ± 0.09
formamide	none	4.48 ± 0.32
	LiCl (2.02)	7.57 ± 0.34
	$LiClO_4$ (1.94)	7.77 ± 0.40
	GnCl (2.02)[b]	6.67 ± 0.12
	Me_4NBr (0.485)	3.66 ± 0.16
	Bu_4NBr (0.500)	3.00 ± 0.01
	urea (4.02)	5.81 ± 0.33
	β-CD (0.100)	12.4 ± 0.10

[a] Pseudo-first-order rate constant for the disappearance of 1,3-cyclopentadiene in the presence of 236 mM methyl vinyl ketone. At least three runs were averaged; the errors listed are the standard deviations. [b] GnCl is guanidinium chloride.

Table V. Salt Effects on the Endo/Exo Ratio for the Cyclopentadiene Reaction with Methyl Vinyl Ketone

solvent	additive (M)	endo/exo product ratio
ethylene glycol	none	10.4 ± 1.2
	LiCl (1.02)	10.3 ± 0.7
	$LiClO_4$ (1.00)	10.5 ± 0.6
	GnCl (1.05)[a]	10.0 ± 0.7
	Bu_4NBr (0.50)	11.0 ± 0.1
formamide	none	8.9 ± 0.4
	LiCl (2.09)	10.8 ± 0.4
	$LiClO_4$ (2.00)	10.5 ± 0.3
	GnCl (2.08)[a]	11.0 ± 0.5
	Bu_4NBr (0.50)	10.5 ± 0.2

[a] GnCl is guanidinium chloride.

in aqueous–organic systems, in which the effects seen presumably still involve interaction of the chaotropic agents with water,[9,10] and a few relevant studies are reported in other organic solvents.[18-20]

Our data in Table III on the rate of addition of nitrosobenzene to cyclohexadiene show that the salt effects are very small and not in the expected direction based on their effects in water solution. The perchlorate ion is more chaotropic than is the chloride ion in water, but reactions in both polar solvents were faster in the presence of lithium perchlorate than in the presence of lithium chloride. A chaotropic decrease in solvophobicity should *decrease* the rate.

The data in Table IV are even more striking. All additives except the quaternary ammonium salts increased the rate, even those chaotropic agents that decrease the rate of this Diels–Alder reaction in water solution. Lithium perchlorate is again *more* effective than is lithium chloride, in contrast to the data for water solution. The normally chaotropic guanidinium ion is comparable to the normally antichaotropic lithium ion in ethylene glycol, slightly less rate increasing in formamide. The classic chaotropic agent urea increases the rate in both solvents. As Table V shows, all the added salts had only small effects on the endo/exo product ratio.

We have examined the effects of these additives on the solubility of benzene in formamide and in ethylene glycol, to look for salting-out and salting-in effects. All the additives except tetrabutylammonium bromide (and to a minor extent tetramethylammonium bromide) proved to be salting-out agents, as the data in Table VI indicate. This is consistent with our kinetic findings that all of these additives except the quaternary ammonium salts increase the rates of the reactions.

Clearly we have found no evidence for chaotropic behavior by urea, guanidinium cation, or perchlorate anion in ethylene glycol or in formamide, solvents that in other respects seem to be

Table VI. Solubilities of Benzene (20.0 ± 0.5 °C)

solvent	additive (M)	benzene solubility,[a] M
formamide	none	0.519 ± 0.013
	LiCl (2.32)	0.327 ± 0.011
	$LiClO_4$ (2.00)	0.388 ± 0.014
	GnCl (2.21)	0.399 ± 0.032
	Me_4NBr (0.485)	0.519 ± 0.005
	Bu_4NBr (0.500)	0.717 ± 0.015
	urea (4.16)	0.384 ± 0.006
ethylene glycol	none	0.658 ± 0.052
	LiCl (1.11)	0.464 ± 0.044
	$LiClO_4$ (1.01)	0.486 ± 0.014
	GnCl (1.09)	0.522 ± 0.012
	Me_4NBr (0.500)	0.625 ± 0.007
	Bu_4NBr (0.500)	1.05 ± 0.02
	urea (4.13)	0.373 ± 0.037

[a] Three measurements averaged; the errors are standard deviations.

waterlike. Probably all polar solutes in polar solvents have some antichaotropic effect, tending to decrease the solubility of hydrocarbons by tying up solvent molecules. In water solution with chaotropic materials such as urea or guanidinium ion this effect is overbalanced by the ability of the solute to break up solvent structure, but in formamide and ethylene glycol no such overbalancing is seen. The absence of chaotropic effects and of a greatly increased endo/exo product ratio for ethylene glycol and formamide could simply reflect a weaker waterlike structure. It is more likely that the existence of these phenomena in water solution reflects the detailed three-dimensional icelike cage structure of water,[29] in contrast to the structures of these other hydrogen-bonded solvents.

These results support the idea that the chaotropic effects of urea and similar substances in water reflect their interaction with water, not their interaction with hydrocarbon solutes. In our studies the chaotropic effects that are present in water solution are absent, with the same solutes, in the other hydrogen-bonding solvents.

The decreased rates (Table IV) and increased benzene solubilities (Table VI) with quaternary ammonium bromides in formamide and in ethylene glycol are a different matter. The contrast with the behavior of the other chaotropes suggests that these ammonium salts interact with the *solutes* in all polar solvents, acting as pseudodetergents. Indeed, micellelike structures may be formed.[14,15] As expected from this explanation, the tetrabutyl compound is more effective than is the tetramethyl compound. The contrasting behavior of the two classes of solubilizing agents makes it even clearer that the chaotropes urea and guanidinium cation, and perchlorate anion, are *not* acting as detergents. Instead, they are interacting uniquely with water.

Chaotropic effects are quite useful for confirming the existence of hydrophobic interactions in water solution. We have used them not only to study the Diels-Alder reaction[1-3] but also to detect hydrophobic packing of the transition state in the benzoin condensation.[30] However, there is apparently as yet no substance that produces a solvent-breaking chaotropic effect in solvents such as ethylene glycol or formamide. Thus, in this respect water is still unique.

Conclusions

(1) The Diels-Alder addition reactions of nitrosobenzene with 1,3-cyclohexadiene and of methyl vinyl ketone with 1,3-cyclopentadiene are faster in formamide or in ethylene glycol than in other organic solvents, but not as fast as in water solution.

(2) The reactions in these organic solvents are also accelerated by β-cyclodextrin.

(3) The kinetic results indicate that there is solvophobic binding of the reactants to each other, or into the cyclodextrin cavity, in these polar solvents.

(4) In spite of this, there is no striking increase in endo/exo selectivity, as there is in water. Furthermore, agents such as urea, guanidinium cation, and perchlorate anion that are normally chaotropic in water and thus decrease the hydrophobic effect, and the rate, show no such effect in the organic solvents. These agents also all *decrease* the solubility of benzene in ethylene glycol or in formamide, in contrast to their effects in water.

(5) The contrasts indicate that waterlike organic solvents still do not share some of the most striking properties of water itself.

(6) However, tetraalkylammonium salts do increase benzene solubility, and decrease the rate of the Diels-Alder reaction, in formamide and in ethylene glycol. This indicates that these particular salting-in agents interact with the organic solute, acting as detergents.

(7) The results and contrasts also indicate that chaotropic effects of urea and guanidinium cation in water reflect primarily the interaction of the chaotropes with the water, not with the hydrocarbon solutes.[31]

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Remarkable Effects of a Pentafluorophenyl Group on the Stereoselective Reactions of a Chiral Iron Acyl Complex

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Abstract: A novel chiral iron acyl complex, $[(C_6F_5)Ph_2P](CO)CpFeCOMe$ (PFCHIRAC), is synthesized. The stereoselective aldol and imine condensation reactions with benzaldehyde and benzylideneaniline using the lithium, tin, aluminum, and copper enolates of PFCHIRAC are studied. The reactions give (*R*,S**) products regardless of the metal enolate species with high stereoselectivities (89–99% de). The observed unique stereodifferentiation is rationalized on the basis of an electron donor–acceptor type attractive interaction between the pentafluorophenyl moiety and the enolate oxygen. The variable-temperature NMR (^1H, ^{19}F, ^{31}P) study of the dynamic behavior of PFCHIRAC strongly supports the rationale.

Recently, the usefulness of chiral iron acyls (CHIRACs), $(PPh_3)(CO)CpFeCOR$ (Cp = η^5-cyclopentadienyl), in organic synthesis has been demonstrated by Davies and Liebeskind in their extensive studies on the stereoselective reactions with those com-

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