VOLUME 24 NUMBER 6

ACCOUNTS OF CHEMICAL RESEARCH®

JUNE 1991

Hydrophobic Effects on Simple Organic Reactions in Water

RONALD BRESLOW

Department of Chemistry, Columbia University, New York, New York 10027

Received January 7, 1991 (Revised Manuscript Received March 10, 1991)

The hydrophobic effect[1] is the tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon–water interfacial area. It reflects in part the large cohesive energy of water, whose molecules would better bind to each other than to a hydrocarbon surface. A thermodynamic criterion is sometimes suggested, but hydrophobic aggregation can be driven by either entropy or enthalpy: an improved enthalpy of solvation of a substrate can come at the expense of solvent restriction and entropy loss.

The hydrophobic effect is a principal force determining the structures of proteins and nucleic acids, the binding of substrates to enzymes, and the binding of antigens to antibodies. It causes the formation of micelles and bilayers. In enzyme model systems operating in water, substrate binding into cyclodextrin cavities and into other synthetic cavities is also driven by the hydrophobic effect.

Although we have actively studied such enzyme models for a number of years,[2] we will not discuss them here. Instead, we will describe our evidence that some rather simple organic reactions can show hydrophobic effects when they are carried out in water solution. Striking increases in rates and selectivities have been seen, furnishing evidence on the structures of the reaction transition states. However, simply seeing an increased rate of a reaction in water solution does not establish that a hydrophobic effect is involved. Better evidence for this comes from the use of special *salting-in* and *salting-out* agents.

The Diels–Alder Reaction in Water

Some years ago we set out to determine whether cyclodextrins could catalyze common Diels–Alder reactions in water, by binding both the diene and the dienophile into the cyclodextrin cavity (Figure 1). Indeed we found striking examples of such catalysis.[3] However, control reactions showed that the reactions were also accelerated, if less strongly, by water *itself*.[3] Water is a particularly polar solvent, but it quickly became clear that we were not seeing a simple polarity or hydrogen-bonding effect. For example, in the Diels–Alder reaction of cyclopentadiene with acrylonitrile (Figure 2), a change of solvent from isooctane to methanol accelerates the reaction by a factor of only 2, so the reaction is not very sensitive to solvent polarity or hydrogen-bonding ability, but in water the reaction is an additional 15-fold faster than in methanol. The reaction of cyclopentadiene with butenone (Figure 3) is 12-fold faster in methanol than in isooctane, but in water the rate is 730-fold faster than in isooctane. It seemed unlikely that polarity differences could explain the remarkable rate accelerations in water.

This was certainly clear in the Diels–Alder reaction of anthracene-9-carbinol with *N*-ethylmaleimide (Figure 4). This reaction is actually over 2-fold *slower* in methanol than in isooctane, apparently because in the nonpolar solvent a hydrogen bond helps the dienophile bind to the diene. However, in water the reaction was 65-fold *faster* than in methanol. A special effect was operating in water, and it seemed likely that it was the hydrophobic effect. In the transition state for a Diels–Alder reaction two hydrocarbon surfaces must come together, and this aggregation is favored in water.

Additional evidence was seen from the effect of two special additives. The butenone reaction of Figure 3

Ronald Breslow joined the faculty of Columbia University in 1956 after his Ph.D. work with R. B. Woodward and postdoctoral work with Lord Todd. His work on physical organic chemistry has focused on biomimetic chemistry and on compounds of theoretical interest; it has been recognized by a number of awards.

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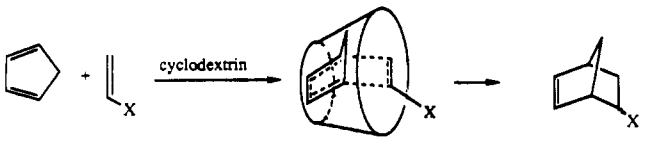
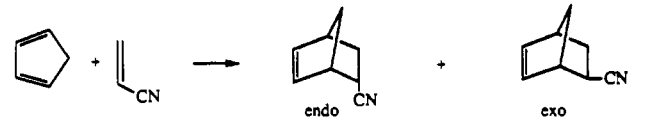


Figure 1.



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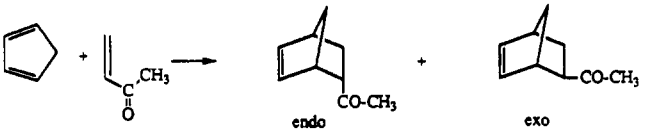


Figure 3.

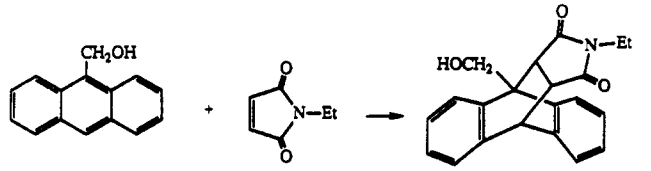
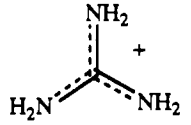


Figure 4.

was faster when lithium chloride was added to the water solvent, but slightly slower when guanidinium chloride was added.[3] As will be discussed later, lithium chloride (LiCl) increases the hydrophobic effect while guanidinium chloride (GnCl) decreases it. We commonly apply this test to help distinguish between hydrophobic effects and simple solvent polarity effects. For instance, the reaction of Figure 4 is 2.5 times faster when 4.86 M LiCl is added, but 3 times *slower* on the addition of 4.86 M GnCl.[4] Such a contrast is expected if a hydrophobic effect is involved. In the last section of this Account we will describe new evidence that a modification of the hydrophobic effect is indeed the cause of these rate changes.



Guanidinium ion

Water as solvent had striking effects on the selectivity of some Diels–Alder reactions, seen both in our work[4,5] and in that of Grieco.[6] At low concentrations where both components are in true solution, the butenone reaction of Figure 3 showed[5] an endo/exo ratio of 25.0 ± 0.5 in water, while in cyclopentadiene the ratio is only 3.85 and in ethanol, 8.5. Polar solvents can favor the endo transition state because secondary orbital interaction in this conformation produces some extra charge separation, but the hydrophobic effect will also favor the more compact endo transition state. Evidence that

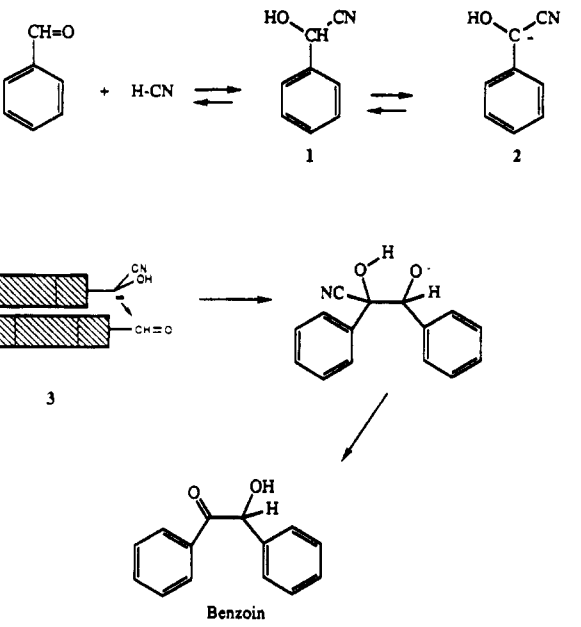


Figure 5.

this makes some contribution is seen from the increase of the ratio to 28.0 when LiCl is added, but a decrease to 22.0 with GnCl.[5] Interestingly, a high preference for endo addition was found even with suspensions in which the cyclopentadiene was over 90% undissolved.[4] Apparently the preferred pathway is for it to enter the water and react with high selectivity, rather than just react less selectively in the neat separate phase.

"Internal Pressure" and the Hydrophobic Effect

Diels–Alder reactions are accelerated by external pressure, which also alters their selectivity.[7] Thus it has been suggested that the effect of water on these reactions can be thought of as reflecting the high "internal pressure" in a water solution because of the high cohesive energy of water. However, in contrast to externally applied pressure there is a limit to the extent of such internal pressure; at a certain point, corresponding to the solubility limit, it will simply squeeze the solute out of solution. In thermodynamic terms, water increases the activity coefficient of the solute but cannot raise its thermodynamic activity above that of the neat solute in a separate phase.

Conversion of the starting materials to the transition-state complex will be favored even if the thermodynamic activity of all components is raised by the hydrophobic effect; the decreased exposure of hydrocarbon surfaces in the transition-state complex means that its activity will not be raised enough to compensate completely for the effects on the starting materials. However, since none of these thermodynamic activities can exceed that of the neat undissolved materials, one might think that the reactions could not be faster in water solution than they are without solvent. This is not the case.

What a water solvent does is furnish the polar and other interactions needed to stabilize the transition state without causing a rate penalty because of dilution by solvent. The large activity coefficient of organic

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species produced by the hydrophobic effect means that even in fairly dilute water solution the reactants have a thermodynamic activity almost as high as that of the undiluted species, and with saturated solutions the thermodynamic activity of the solutes is just as high as for an undiluted reaction mixture. Thus the rate improvement from solvation comes "free" of dilution cost.

The Benzoin Condensation

Reaction of two molecules of benzaldehyde, with catalysis by cyanide ion, affords benzoin (Figure 5). The mechanism under most conditions involves reversible formation of benzaldehyde cyanohydrin (1) and the rate-limiting reaction of its anion 2 with the second benzaldehyde molecule.[8] Loss of cyanide ion then affords benzoin. The expected geometry of this rate-determining addition reaction is shown in 3, in which the planar cyanohydrin anion moves toward tetrahedral as it bonds and the benzaldehyde is attacked along the line[9] of the π^* orbital. This geometry permits the two benzene rings to stack next to each other. If this is indeed the geometry of the transition state, it should be favored by a hydrophobic effect in water solvent. Water has not been the normal solvent for these reactions.

We found[10] that the benzoin condensation of benzaldehyde with CN^- was ca. 200 times faster in water than in ethanol solution, but of course this does not establish that there is a hydrophobic effect. An ionic reaction like this could show large effects from polarity changes alone. Thus we examined the effect of special additives.

As we mentioned earlier, compounds such as LiCl increase the hydrophobic effect, and they therefore decrease the solubility of hydrocarbons in water.[11] Thus LiCl can be called a "salting-out" agent; NaCl is another example. However, some salts *increase* the water solubility of hydrocarbons such as butane or benzene;[11] for instance, guanidinium chloride does so.[12] Studies of these effects show that the cations and anions of such salts should be considered separately. Small ions such as Li^+ and Cl^- decrease hydrocarbon solubility, while large ions such as Gn^+, ClO_4^-, and I^- increase solubility. Thus LiCl has two components that work in the same direction, but with GnCl the increased water solubility of hydrocarbons is seen because the Gn^+ effect dominates the Cl^- effect. Guanidinium salts with large anions are even more effective at solubilizing hydrocarbons.

We examined the use of the LiCl and GnCl contrast with the benzoin condensation, but abandoned it when it became clear that high concentrations of Gn^+ were affecting the pH of the medium.[10] The benzoin condensation requires high pH. Thus we turned[10] to a different contrast: LiCl vs $LiClO_4$. With 5.0 M LiCl the rate of the benzoin condensation in water showed an almost 4-fold increase, while with 5.0 M $LiClO_4$ the rate is almost 4-fold less than without the added salt.

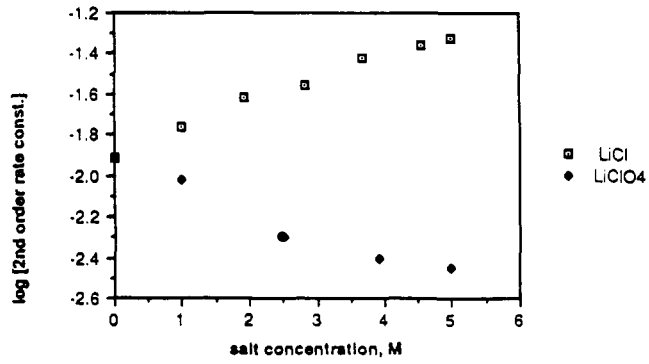

Figure 6. Effects of added LiCl and $LiClO_4$ on the psuedo-second-order (in benzaldehyde) rate constant for the cyanide-catalyzed benzoin condensation with 23 mM KCN at 65 °C in water.

Of course increased ionic strength may affect the rate, but it cannot explain the fact that one rate goes up and the other one down. A plot[10] of the data (Figure 6) showed a smooth increase with LiCl concentration and a smooth decrease with $LiClO_4$.

The conclusion was checked with results from other salts.[10] In contrast to the 400% rate increase with LiCl, LiBr with a larger anion gave only a 35% increase in rate, while LiI *decreased* the rate 5-fold. In the chloride series, KCl gave a 3-fold, not a 4-fold, rate increase while CsCl gave only a 24% increase. Curiously, CsI with two large ions gave a rate increase; the cause of this apparent anomaly is under investigation.

We also looked at the effect of LiCl and of $LiClO_4$ on the water solubility of benzaldehyde.[10] At 20 °C it is soluble to 60 mM in water; with 5 M LiCl this decreases to 27 mM, while with 5 M $LiClO_4$ it increases to 100 mM. Benzaldehyde is of course not a simple hydrocarbon, but the cyanohydrin 1 and the transition state 3 for reaction also combine polar and nonpolar segments. The solubility of benzaldehyde was examined because it is one of the reactants and may mimic the behavior of the others. Again we saw the correlation of solubility effects of the additives with rate effects.

The interpretation of salt effects on reaction rates can be complicated, but the correlation of rate effects with solubility effects suggests that the benzoin condensation indeed shows hydrophobic acceleration in water. The Li^+ probably solvates and solubilizes the polar segments of all these species but the contrasting effects of Cl^- and ClO_4^- are expected if hydrophobicity is involved. The two benzene rings can pack in the transition state, so it has less hydrocarbon surface exposed to solvent than do the two reactants. The evidence supports the idea that the transition state is as shown in 3.

Additional evidence for this comes from studies with cyclodextrins. We find that the benzoin condensation in water is accelerated by γ-cyclodextrin, but slowed by β-cyclodextrin.[10] The two benzene rings of the transition-state structure 3 can both fit into the large cavity of γ-cyclodextrin (eight glucoses in a ring) but not into the smaller cavity of β-cyclodextrin (seven glucoses). Catalysis by γ-cyclodextrin is expected, since binding of the transition state will stabilize it. Inhibition by β-cyclodextrin probably reflects binding of the benzaldehyde cyanohydrin 1 into the cavity, shielding it from further reaction. These findings were used to guide the synthesis of a catalyst for the benzoin condensation that combines the γ-cyclodextrin binding

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with covalent catalysis by an attached thiazolium ring.[13]

Why Do Some Additives Increase the Hydrophobic Effect, While Others Decrease It?

Certain agents that increase hydrocarbon solubility, such as urea or guanidinium chloride, act as denaturants of proteins and nucleic acids. We find that they also decrease the rates of Diels–Alder reactions and benzoin condensations in water, while others that decrease hydrocarbon solubility lead to an increase in those rates. This is consistent with the idea that the rate effects result from hydrophobic interactions. In principle, this correlation is valid whether or not one understands the reasons for the solubility effects. However, we decided to learn more about those reasons.

The salting-out effect of NaCl, LiCl, etc. is quite well understood.[14,15] When such salts dissolve in water there is a volume contraction, electrostriction, as water collapses around the ions to solvate them. Thus there is less empty space for hydrocarbon solutes, and the energy cost to create space for the hydrocarbons is greater. This can be thought of as the energy cost for cavitation, producing a hydrocarbon-sized hole in the solvent. Electrostriction increases the energy cost of cavitation.

The salting-in effect is more controversial. Most people have suggested that large ions (and the non-ionic molecule urea that is also a denaturant) break up the organized structue of water and make cavitation easier.[16] However, the other choice is that salting-in materials improve the solvation of hydrocarbons in some way. The effect of a solubility modifier on the solubility of a hydrocarbon in water can be expressed by eq 1, in which there are terms for its effect on the energy cost of cavitation and on the energy of hydrocarbon solvation.[17] Which of these terms leads to the decrease in hydrophobic effects when salting-in materials are added?

effect of a solubility modifier =
effect on the energy of cavitation +
effect on the energy of solvation

$$\delta(\Delta G^\circ)_{\text{solution}} = \delta(\Delta G^\circ)_{\text{cavitation}} + \delta(\Delta G^\circ)_{\text{solute solvation}} \quad (1)$$

We first looked at a simple question: Is water unique? Ethylene glycol and formamide are often considered "water-like" solvents. Indeed we saw that several Diels–Alder reactions were very fast in these solvents, although not as fast as in water.[18] Schneider has recently shown that a Diels–Alder reaction rate in a variety of solvents correlates with a *solvophobicity* parameter derived from hydrocarbon solubilities, not with the solvent polarity.[19] Solvophobicity, a generalization of hydrophobicity, can also be seen in water-like solvents. We even saw that in such solvents the Diels–Alder reactions are accelerated by β-cyclodextrin just as in water, because of solvophobic packing of the two components into the cyclodextrin cavity (Figure 1).[18]

It was not known whether the contrast between salting-in and salting-out agents extended to these solvents. We examined the solubility of benzene in formamide and in ethylene glycol, with and without additives.[18] LiCl was still a salting-out agent, but now so were $LiClO_4$, GnCl, and even urea! Thus the additives that had decreased the hydrophobic effect in water were now *increasing* the solvophobic effect in these "water-like" solvents. As expected from our correlation, all of these agents now *increased* the rate of the Diels–Alder reaction of cyclopentadiene with butenone (Figure 3) in formamide and in ethylene glycol.[18]

Quaternary ammonium salts did not show this change in behavior. Although tetramethylammonium bromide ($Me_4N^+Br^-$) had almost no effect on the rates or on benzene solubility, tetra-*n*-butylammonium bromide ($Bu_4N^+Br^-$) increased the benzene solubility and decreased the reaction rates both in water *and* in the water-like solvents.[18]

One would expect the Bu_4N^+ to assist the solvation of benzene in a polar solvent. The butyl groups could pack against the benzene ring, driven by solvophobic effects, and the resulting charged complex could then be further stabilized and solubilized by interaction with solvent dipoles. Since the other normally salting in agents (in water) reversed their effect in formamide and ethylene glycol, we thought it likely that they were *not* acting in this way, to solvate the hydrocarbon, but were instead breaking up water structure. If water structure were unique, and it is,[20] we might understand why the effect was not seen in other solvents. However, further work showed that this obvious interpretation was too simple.

We investigated the direct interaction of water with the salting-in and salting-out materials.[17] As eq 1 shows, one possibility is that a salting-in additive makes cavity formation easier; this should show up in the effect of the additive on the surface tension of water. In fact, a common method for measuring surface tension, which is the method we used, involves measuring the pressue required to produce an air bubble at a capillary immersed in the solvent. Such a bubble can be thought of as a large cavity. If salting-in agents make cavity formation easier, by breaking up water structure, one would expect them to lower surface tension.

The effect was the opposite. The salting-in agents GnCl and $LiClO_4$ led to an *increase* in the surface tension of water just as the salting-out agent LiCl did, although the magnitude of the increase was larger with LiCl than with the others (large ions with dispersed charges are less electrostrictive). Similarly, both LiCl and GnCl increased the surface tension of formamide and of ethylene glycol.

This shows that cavitation in water is *not* easier when GnCl or $LiClO_4$ is added; it had been shown earlier[21] that urea also increases the surface tension of water, but the implication for the mechanism of urea denaturation effects was not recognized. If these agents do not make cavitation easier, they must be contributing to the

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solvation term in eq 1. They could act indirectly by somehow making the water a stronger solvater, but we believe that a better picture can be constructed if we assume that they interact directly with the hydrocarbon. Just as with $Bu_4N^+Br^-$, we proposed that they bind to the hydrocarbon solute and bridge between it and the water solvent.[17]

Does the surface tension measurement absolutely rule out the cavitation explanation for hydrocarbon solubilization? Intellectually, cavity formation involves creating a vacuum in the solvent (which is later filled with the hydrocarbon), while the bubbles in the surface tension measurement contain air and are not a vacuum. This would be a problem only in the unlikely possibility that air itself is solvated by water, and that this solvation is somehow decreased by GnCl or $LiClO_4$.

However, the cavities we look at with air bubbles are quite large, not of molecular size. The cavitation explanation of salting-in effects could survive if GnCl or $LiClO_4$ made it harder to produce large cavities, as observed, but somehow easier to produce small ones. It has been pointed out that the difference in curvature could mean that surface tension effects in small cavities and in large cavities can be different in magnitude,[22-25] but there is yet no evidence or argument that the effects will reverse. Unless they do reverse, we have ruled out water structure breaking, and the resulting easier cavitation, as the explanation of salting-in behavior.

Direct solvation interaction by salting-in agents also explains[17] the otherwise curious findings in different solvents. Water has a very high cohesive energy and a very low polarizability, so even ions like Gn^+ or ClO_4^- can solvate hydrocarbons better than the solvent can, and help them dissolve. Since these salts increase surface tension less effectively than does LiCl, for instance, the small cavitation effect in the wrong direction does not overwhelm the solvation effect. However, in more polar organic solvents like formamide and ethylene glycol, the solvent itself interacts better with a hydrocarbon than do these ions; Gn^+ and ClO_4^- now *decrease* hydrocarbon solubility by their normal, if small, electrostrictive effect.

Like common detergents, $Bu_4N^+Br^-$ decreases the surface tension of water. Thus it might be solubilizing hydrocarbons only by its effect on the cavitation term of eq 1. However, if ions like Gn^+ solvate a hydrocarbon, surely Bu_4N^+ does as well. Thus it seems likely that its solubilizing effect on hydrocarbons involves *both* terms of eq 1. It is so nonpolar that it can contribute to hydrocarbon solvation even in the organic solvents formamide and ethylene glycol.

Is There Another Explanation for the Special Salt Effects in the Diels–Alder Reaction?

Water is a hydrogen-bond donor with its two protons, and a hydrogen-bond acceptor with its two unshared electron pairs. Symons has proposed[26] that some salt effects in water solution can be explained by considering the balance between donor and acceptor properties. For example, Li^+ is solvated by the electron pairs, producing an excess of hydrogen-bond-donor sites and thus "acidifying" the water, while Cl^- will solvate by coordinating with the protons of water and thus making the solvent more "basic". Large dispersed ions are more weakly solvated by water, so a salt like Gn^+Cl^- might make water more basic. By this theory, $Li^+ClO_4^-$ would make water more acidic, the small lithium ion not being fully counterbalanced by the weakly solvating larger perchlorate ion. Could some of our salt effects on the Diels–Alder reaction be explained with these ideas?

If the reaction of Figure 4 were accelerated by a hydrogen-bonding effect of water, notwithstanding the methanol results, then Gn^+Cl^- might slow it by binding the Cl^- to some water protons.[27] We instead ascribe the slowing to the salting-in effect of the guanidinium cation. Luckily, it is easy to distinguish between these explanations.

We have examined the effect of $LiClO_4$ and of $GnClO_4$ on the Diels–Alder reaction of Figure 4.[28] As the data in Table I show, $LiClO_4$ *slows* the reaction. This is as expected for the hydrophobic explanation, but the opposite of what would be expected if water acidity and basicity were involved. The large perchlorate ion should slow the reaction by a salting-in effect that decreases hydrophobic packing, but the smaller chloride ion should have slowed the reaction if water basicity were involved. The slower rate with $GnClO_4$ than with GnCl (Table I) also indicates the same thing.

The use of special salting-in agents can be valuable in diagnosing hydrophobic acceleration, but it is probably well to use a variety of such agents, as in this case, to exclude other effects.

Table I.
Second-Order Rate Constants for the Addition of *N*-Ethylmaleimide to Anthracene-9-carbinol (Figure 4) in Various Media at 45 °C

solvent	$k_2 \times 10^3$, M^{-1} s^{-1}	k_{rel}
2,2,4-trimethylpentane[a]	8.0 ± 0.7	0.035
methanol[a]	3.4 ± 0.3	0.015
water[a]	226 ± 7	1.000
water[b]	230 ± 2	1.000
water + LiCl (4.86 M)[c]	560 ± 54	2.5
water + LiCl (4.0 M)[b]	498 ± 28	2.2
water + GnCl (4.86 M)[c]	77 ● 10	0.32
water + GnCl (2.0 M)[b]	129 ± 6	0.56
water + $LiClO_4$ (4.0 M)[b]	157 ± 3	0.68
water + $GnClO_4$ (2.0 M)[b]	86 ± 4	0.37

[a] Reference 3. [b] Reference 28. All data are the average of at least three runs, in most cases of five runs. Reactions were carried to at least 7 half-lives. [c] Reference 4 and Ph.D. Thesis of D. Rideout, Columbia University, 1982.

Conclusions

1. Even simple organic reactions in water solution can show hydrophobic effects on rates and selectivities if nonpolar segments of the reactants are brought together in the transition states.

2. Supporting indications for the operation of such hydrophobic effects comes from the use of salting-in and salting-out agents, that change the magnitude of the hydrophobic effect. By use of a variety of such agents, other explanations can be excluded.

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3. Although salting-in agents, and other denaturants such as urea, are often described as water "structure breakers", our evidence is that they function not by making cavitation in water easier but instead by directly solvating the hydrocarbon species. This overcomes their tendency to make cavitation more difficult, as revealed in surface tension measurements.

4. The special effects seen in water make it an attractive possible solvent for many organic reactions, not just biochemical processes. These effects occur *because* of, not in spite of, the poor solubility of many organic compounds in water.

I thank my co-workers, named in the references, for their experimental and intellectual contributions. This work has been supported over the years by the National Institutes of Health.

Electron Nuclear Double Resonance (ENDOR) of Metalloenzymes

BRIAN M. HOFFMAN

Department of Chemistry, Northwestern University, Evanston, Illinois 60208

Received February 4, 1991 (Revised Manuscript Received May 3, 1991)

Electron paramagnetic resonance (EPR) techniques have long been a major tool in efforts to determine the structure and function of metalloenzyme active sites.[1] Much of the information EPR provides about the composition, structure, and bonding of a paramagnetic metal center is obtained through the analysis of the hyperfine coupling constants that represent interactions between the spin of the unpaired electron(s) and the spins of nuclei associated with the metal center, endogenous ligands, or bound substrate.[2] These coupling constants are calculated from splittings seen in the EPR spectrum, but for most metallobiomolecules, the splittings are not resolvable and the information they carry is lost. Electron nuclear double resonance (ENDOR) spectroscopy recovers this information.[3]

An ENDOR experiment provides an NMR spectrum of those nuclei that interact with the electron spin of the paramagnetic center, and the ENDOR frequencies directly give the electron-nuclear coupling constants. The occurrence of a nuclear resonance transition is not detected directly, but rather as a change in the EPR signal intensity, hence the classifications as a double-resonance technique. As an NMR method the spectral *resolution* of ENDOR can be as much as 3 orders of magnitude better than that of conventional EPR, and this permits the detection and characterization of electron-nuclear hyperfine interactions for systems whose EPR spectra show no hyperfine splittings. Moreover, ENDOR spectroscopy is inherently *broad-banded*: It is comparably easy to detect ENDOR signals from every type of nucleus. In our studies of biomolecules we have examined signals from ^{1}H, ^{2}H, ^{13}C, $^{14,15}N$, ^{17}O*, ^{33}S*, ^{57}Fe, ^{61}Ni*, $^{63,65}Cu$*, and $^{95,97}Mo$* nuclei that are present either as constitutive components of a metalloenzyme active site or as part of a bound ligand or substrate, with (*) indicating the first such investigation. This list shows that with proper isotopic labeling it is possible to characterize *every* type of atomic site associated with a paramagnetic center, as we have done in the study of aconitase.[5] With these benefits goes the additional virtue of *selectivity*. Only nuclei that have a hyperfine interaction with the electron-spin system being observed give an ENDOR signal. For example, unlike the case of Mössbauer spectros-

Table I.
Representative Metalloenzyme Active Sites

well-characterized	"black boxes"
blue copper proteins[10]	nitrogenase[6]
heme proteins[9]	Fe-hydrogenase I, II[14]
resting state	**reaction intermediates**
nitrogenase	horseradish peroxidase, Cpd I[11]
Ni-hydrogenase (Ni A, B)[13]	cytochrome *c* peroxidase, ES[12]
sulfite reductase[15a]	Ni-hydrogenase (Ni C)[13]
cytochrome oxidase, Cu_A[16a]	sulfite reductase, doubly reduced[15b]
	cytochrome oxidase, Cu_B[16b]
active-site structure	**substrate interactions**
nitrogenase[6]	aconitase[5a-c]
Rieske [2Fe-2S] center[8]	Fe-hydrogenase I, II[14]
aconitase[5d]	CO dehydrogenase[17]
	xanthine oxidase[18]

Brian M. Hoffman earned a S.B. degree at The University of Chicago in 1962 and a Ph.D. from Caltech (with Harden McConnell) in 1966. After a postdoctoral year at MIT (with Alex Rich), he joined the faculty at Northwestern University, where he holds a joint appointment in the Department of Chemistry and in the BMBCB Department. In addition to this work in magnetic resonance, members of his group are engaged in studies of long-range electron transfer within protein complexes, as well as in the synthesis and characterization of new molecular metals and magnets. He and his wife boast of four daughters that have a current average age of 11.3 years, with a mean-square deviation of 103 years squared.

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0001-4842/91/0124-0164$02.50/0