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Published on Web 03/13/2002

Antihydrophobic Cosolvent Effects for Alkylation Reactions in Water Solution, Particularly Oxygen versus Carbon Alkylations of Phenoxide Ions†

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Received October 3, 2001

Abstract: Antihydrophobic cosolvents such as ethanol increase the solubility of hydrophobic molecules in water, and they also affect the rates of reactions involving hydrophobic surfaces. In simple reactions of hydrocarbons, such as the Diels−Alder dimerization of 1,3-cyclopentadiene, the rate and solubility data directly reflect the geometry of the transition state, in which some hydrophobic surface becomes hidden. In reactions involving polar groups, such as alkylations of phenoxide ions or S_N1 ionizations of alkyl halides, cosolvents in water can have other effects as well. However, solvation of hydrophobic surfaces is still important. By the use of structure−reactivity relationships, and comparing the effects of ethanol and DMSO as solvents, it has been possible to sort out these effects. The conclusions are reinforced by an ab initio computer model for hydrophobic solvation. The result is a sensible transition state for phenoxide ion as a nucleophile, using its oxygen *n* electrons to avoid loss of conjugation. The geometry of alkylation of aniline is very different, involving packing (stacking) of the aniline ring onto the phenyl ring of a benzyl group in the benzylation reaction. The alkylation of phenoxide ions by benzylic chlorides can occur both at the phenoxide oxygen and on ortho and para positions of the ring. Carbon alkylation occurs in water, but not in nonpolar organic solvents, and it is observed only when the phenoxide has at least one methyl substituent ortho, meta, or para. The effects of phenol substituents and of antihydrophobic cosolvents on the rates of the competing alkylation processes indicate that in water the carbon alkylation involves a transition state with hydrophobic packing of the benzyl group onto the phenol ring. The results also support our conclusion that oxygen alkylation uses the *n* electrons of the phenoxide oxygen as the nucleophile and does not have hydrophobic overlap in the transition state. The mechanisms and explanations for competing oxygen and carbon alkylations differ from previous proposals by others.

Introduction

Hydrophobic Effects on Solubilities and Rates. When organic reactions are performed in water they can be influenced by the hydrophobic effect,[1] which reflects the high energy of a water interface with a nonpolar molecule or region. As we have reported previously, Diels−Alder reactions[2−7] and the benzoin condensation[8−10] show such effects. The hydrophobic effect itself can lead to higher rates for these reactions in water than in other solvents, and higher endo selectivity for Diels−Alder reactions. It can be diagnosed by seeing the effect of added substances that increase or decrease the hydrophobic effect; prohydrophobic additives are generally simple salts such as sodium or lithium chloride, while antihydrophobic additives include salts of large ions such as guanidinium perchlorate.[11] We have shown that such antihydrophobic ions, which are often used as protein denaturants, function by bridging between the nonpolar surface and the water solvent.[6]

Cosolvents such as ethanol also serve as bridging species in water, diminishing the hydrophobic effect. This is most easily diagnosed from the increased solubility of nonpolar substances in such mixed solvents. Because solubility is an equilibrium constant, its log reflects a free energy of solution, and the increased solubility produced from an antihydrophobic additive to water can be described in terms of a change of the free energy of solution. This free energy change is directly proportional to the log of the ratio of the solubilities with and without the cosolvent.

Antihydrophobic agents such as organic cosolvents have been very useful as a method of experimentally measuring the

† Taken in part from the Ph.D. theses of M. Uljana Mayer (1999) and Kevin Groves (2001), Columbia University.

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10.1021/ja012293h CCC: $22.00

solvation properties of transition states for reactions in water, particularly the amount of exposed hydrophobic surface area relative to that of the starting materials.[4,5,7,9,10,12,13] The use of small amounts of cosolvents allows us to observe a change in solvation of hydrophobic surfaces while preserving the essentially aqueous environment. In choosing the concentration of the cosolvent, we want to maximize the magnitude of experimentally measured hydrophobic solubility perturbation without changing the properties of the solution so drastically that the solvent structure is no longer waterlike.

Grunwald has proposed two additive terms to describe the partial molar thermodynamic properties of water-rich aqueous alcohol solutions.[14a] The first term, called the "isodelphic" term, describes effects on a solute where the bulk aqueous solvent network theoretically remains unchanged upon addition of small amounts of an alcohol cosolvent. The second term, called the "lyodelphic" term, describes effects due to changes in the solvent network resulting from the cosolvent. For our studies, we wish to maximize the isodelphic effects, which include the solvation of hydrophobic surfaces, while minimizing the lyodelphic effects, which involve a significant change from pure water structure. We can do this by keeping cosolvent concentrations low enough as to remain under isodelphic conditions with negligible lyodelphic effects.

Haak and Engberts[14b] have described a critical hydrophobic interaction concentration, or "chic", for organic cosolvents in water and related it to Grunwald's isodelphic/lyodelphic analysis. In solutions with alcoholic cosolvent concentrations above the chic, there are not sufficient water molecules for the formation of complete hydration shells of the alcohol, and lyodelphic effects become important. Under these conditions, the alcohol molecules will form clusters, which create microheterogeneity in the solution. Cosolvent effects on solutes will then reflect interactions of the solute with the clusters, often showing very complex solvation effects and large temperature dependencies.[14b] Below the chic, however, lyodelphic effects do not come into play, and the solutions remain isodelphic in nature.

For the experiments in this work we have predominantly used 20% v/v ethanol (which corresponds to 7.2 mol % or 13 water molecules per ethanol molecule) to probe organic displacement reactions for changes in exposed hydrophobic surface area and other effects. We have performed solubility measurements of benzene in pure water and water with 5%, 9%, 13%, and 20% v/v ethanol. The natural log of the ratio of the solubility with cosolvent to that in pure water, which is proportional to the change in free energy of solvation by the cosolvent, was plotted against the ethanol concentration.[15] We saw that the aqueous free energy solubility perturbations of benzene were completely linear with respect to ethanol concentration all the way up to 20% v/v. Thus ethanol−ethanol interactions in solutions at 20% ethanol are minimal, and we have not drastically altered the aqueous structure of the solvent. Because the 70% increase in aqueous solubility of benzene by 20% ethanol is well outside the experimental error for measuring rate constants, which is ±5% or better, we consider 20% ethanol to be sufficient for measuring changes in the amount of hydrophobic surface of a reaction as it reaches its transition state.

Table 1. Solubilities in Water and Cosolvent Solubility Perturbations by 20% Ethanol and 20% DMSO (Error ≤ 5%)[a]

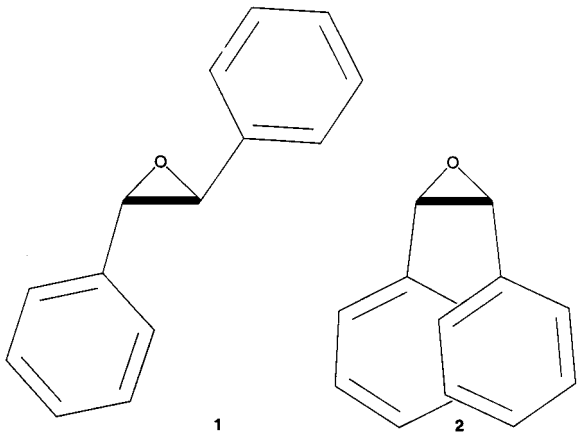
	S_{water} (mM)	$S_{20\%\ EtOH}/S_{water}$	$S_{20\%\ DMSO}/S_{water}$
benzene	21 ± 1	1.7	1.8
N-methylaniline		1.8	
benzaldehyde[b]		1.8	
benzyl phenyl ether	0.080 ± 0.003	3.9	5.3
p-nitrobenzyl chloride	0.7	2.3	3.4
p-nitrobenzyl bromide	0.2	2.2	3.6

[a] The data except for those of footnote b are results from this work. Thus, the table could be in the Results and Discussion section, but is placed here for intellectual reasons. [b] Reference 9.

The aqueous solubility perturbations by 20% v/v ethanol on benzaldehyde and *N*-methylaniline are essentially the same as that of benzene (Table 1), indicating that interactions of the cosolvent with the substituent aldehyde and amino groups are small. We conclude that the dominant effect of 20% ethanol on neutral hydrophobic molecules is to solvate hydrophobic surfaces and that the bulk structure of the solvent network remains similar to that of pure water.

We find that DMSO (dimethyl sulfoxide) is even more effective at solvating the hydrophobic surfaces than is ethanol (Table 1), even though DMSO is a more polar molecule with respect to dielectric constant. The contrast between ethanol and DMSO cosolvents in water has proven to be a valuable tool in exploring mechanisms.

We see that the free energy changes induced by ethanol cosolvent are proportional to the extent of the nonpolar surface in the solute; for a given concentration of ethanol, for instance, compounds with two fully exposed phenyl groups, such as (*E*)-diphenyloxirane **1**, have twice as large a $\delta\Delta G^\circ$ as those with one phenyl group.[10] Compounds with two partially overlapping phenyl groups, such as (*Z*)-diphenyloxirane **2**, have $\delta\Delta G^\circ$s midway between 100% and 200% of those for monophenyl compounds, reflecting the fact that partial packing of the phenyls on each other diminishes the amount of nonpolar surface exposed to the water solvent. Thus, we proposed that antihydrophobic cosolvent effects on reaction rates in water solution could be quantitatively interpreted in terms of the amount of hydrophobic surface that becomes shielded from the solvent in the transition state (TS) for a reaction (Figure 1).



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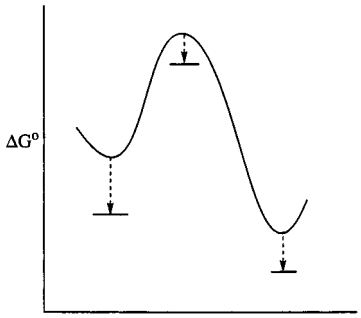

Figure 1. Cosolvents may lower the free energy of the reactants, products, and transition state for a reaction performed in water. The lowering of the free energies of reactants and products can be determined from the effects of the cosolvents on their solubilities, while the lowering of the energy of the transition state can be determined from the change in the reaction rate if the cosolvents have no other effect.

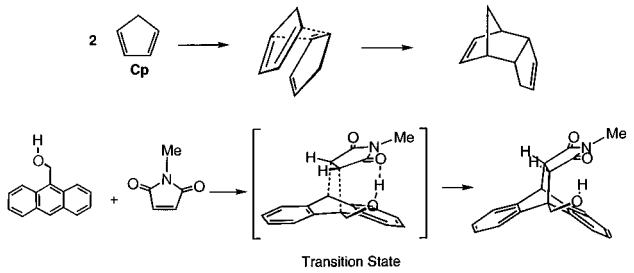

Figure 2. The Diels−Alder dimerization of 1,3-cyclopentadiene in water has a transition state in which one face of each ring is hidden from the solvent. The Diels−Alder addition of *N*-methylmaleimide to anthacene-carbinol has a transition state in which about 50% of an anthracene face is covered, but in the product only 10% is covered. These results from our experimental work are consistent with theoretical models.

As Figure 1 shows, if the transition state (TS) of a reaction has the same amount of similar exposed hydrophobic surface as occurs in the starting materials, and if the cosolvent really has no effect other than to help solvate hydrophobic surfaces, then the rate of the reaction will be unaffected by adding the cosolvent to the water solution. That is, the $\Delta G°$ of the TS will be lowered to the same extent as that of the starting materials, so the activation energy and the rate will be unchanged. If the TS is less hydrophobic than the starting materials − for example, if some hydrophobic surface is hidden from solvent in the TS, or if the hydrophobicity of a solvent-exposed reactant decreases in the TS − the cosolvent should slow the reaction by an amount corresponding to the difference in $\delta\Delta G°$ for starting materials and TS. If the TS is more hydrophobic than the starting materials − as happens when a delocalized phenoxide ion is partially neutralized in the TS (see below) − the reaction will be faster with the added cosolvent. The detailed mathematical treatment of the effects has been published elsewhere.[10,12]

We confirmed this idea in the Diels−Alder dimerization of 1,3-cyclopentadiene.[7] The reaction, forming the endo product, was 20% slower in 15% v/v ethanol than in pure water, and the solubility of cyclopentadiene was 25% greater in that solvent. Translating into free energies, this indicates that 46% of each cyclopentadiene ring is concealed from solvent in the TS, completely reasonable for two rings face-to-face and consistent with our quantum mechanical calculations of the TS (Figure 2). With this technique we also concluded that *N*-methylmaleimide covers about 25% of the total surface of anthracene in the TS of their Diels−Alder reaction, but that in the product only 10% of it is covered, both reasonable results (Figure 2).

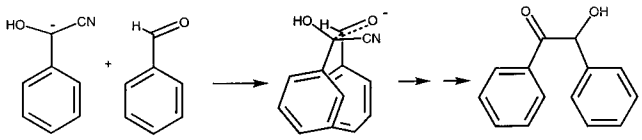

Figure 3. In the benzoin condensation, the rate-determining addition of malononitrile anion to benzaldehyde occurs with packing − but only partial packing − of the phenyl rings in the transition state, because of the stereoelectronic requirements for addition to the carbonyl group.

We also saw that in the cyanide-catalyzed benzoin condensation the phenyl ring of mandelonitrile anion overlaps, but only partially, with the phenyl ring of benzaldehyde at the TS (Figure 3), again consistent with a sensible TS.[9] The nucleophile approaches from the rear of the carbonyl group, leading to about 40% overlap of the two phenyls at the TS.

These conclusions involved the assumption that the only significant rate-modifying effect of the alcohol cosolvents is to solvate the hydrophobic surfaces, and this is probably true for the Diels−Alder reactions. For the benzoin condensation, we are dealing with ions whose solvation might well be affected by nonpolar cosolvents in water. We have also examined the application of our procedure to other reactions such as alkylations, in which solvation of ions is surely important.

Alkylation Reactions. There is much previous work studying solvent polarity effects on reaction rates in alkylation reactions. For example, Grunwald and Winstein[16] studied the solvolysis of *tert*-butyl chloride in various solvents and proposed a linear free energy relationship in which a *Y* value for a given solvent reflected the "ionizing power" of the solvent, its ability to solvate the developing *tert*-butyl cation and chloride ion in the TS. Bentley removed the possibility of nucleophilic participation of solvent at the developing *tert*-butyl cation by examining 1-adamantyl chloride solvolyses,[17] while Kevill and Anderson removed the chloride solvation by examining adamantyl dimethylsulfonium ion solvolysis.[18−20]

For S_N2 displacements, Hughes and Ingold described four charge types, and the dependence of their rates on solvent polarity, depending on the charge on the nucleophile and the electrophile.[21] When a neutral nucleophile and electrophile produce charged products in the TS, polar solvents speed the reaction. When a charged nucleophile and charged electrophile produce neutral products, polar solvents slow the reaction. When there is no net change in charge in the reaction, but one component is charged, there can be some slowing by polar solvents if they solvate the TS less well than they solvate the charged reactant.

Specific solvation of the nucleophile and the leaving group can also have great impact on S_N2 reactions, especially in protic solvents.[22] Hydrogen bonding to the nucleophile and leaving group is particularly important with smaller ions.

These previous studies on solvent effects have focused on the solvation of polar species. There has been little attention paid to the change in solvation of the *nonpolar* species, those that in water exhibit a hydrophobic effect. For example, the

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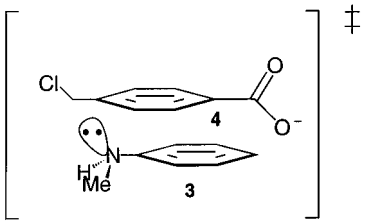
Table 2. Rate Constants in Water and with Added Ethanol and DMSO for the Reactions of 4-Carboxybenzyl Chloride (CBC) and Haloacetamides with Various Nucleophiles under Initial Rate Conditions at 25 °C in M^{-1} min^{-1} (Error ≤ 5%)

nucleophile	electrophile	k_{water}	$k_{20\%\ ethanol}$	$k_{20\%\ DMSO}$	$k_{20\%\ EtOH}/k_{water}$	$k_{20\%\ DMSO}/k_{water}$
N-methylaniline	CBC **4**	0.554	0.418	0.33	0.75	0.60
phenoxide ion	CBC **4**	0.053	0.051	0.053	0.97	1
2,6-dimethylphenoxide ion	CBC **4** (O-alk)	0.018	0.02	0.023	1.06	1.25
2,6-dimethylphenoxide ion	CBC **4** (para-alk)	0.032	0.02	0.018	0.65	0.56
4-nitrophenoxide ion	CBC **4**	0.0082	0.0055	0.0045	0.67	0.55
cyanide	CBC **4**	0.0055	0.0056	0.0066	1.02	1.21
methoxylamine	CBC **4**	0.006	0.0047		0.78	
N-methylaniline	$BrCH_2CONH_2$	0.033	0.021		0.63	
N-methylaniline	ICH_2CONH_2	0.0534	0.037	0.0482	0.7	0.9
phenoxide ion	$BrCH_2CONH_2$	0.022	0.021		0.95	
phenoxide ion	ICH_2CONH_2	0.009	0.009	0.014	1	1.6
2,6-dimethylphenoxide ion	$BrCH_2CONH_2$ (O-alk)	0.013	0.017		1.25	
4-nitrophenoxide ion	$BrCH_2CONH_2$	0.0011	0.0008	0.0011	0.74	1.02
methoxylamine	$BrCH_2CONH_2$				0.79	
hydroquinone dianion	methyl mesylate	0.109	0.164		1.5	
hydroquinone dianion	methyl iodide	0.0149	0.0228		1.7	
phenoxide ion	methyl mesylate	0.022	0.036		1.6	
phenoxide ion	methyl iodide	0.001	0.0021		2.1	

ionization of *tert*-butyl chloride to the *tert*-butyl cation and chloride anion converts a hydrophobic *tert*-butyl group to a hydrophilic one. Thus, part of the decreased rate in water when ethanol is added comes from the better solvation of the *substrate* by ethanol than of the ionic transition state. Our calculation, using the techniques described below for computation of hydrophobic interactions, indicates that this effect on hydrophobic character is significant but cannot account for more than one-half of the entire ethanol rate effect; the various ionic solvation interactions are still important.

We found that the alkylation of *N*-methylaniline (**3**) by *p*-carboxybenzyl chloride (**4**) in water is 25% slowed by 20% v/v added ethanol (Table 2).[23] A sensible TS (**5**) for this process involves overlap of the two phenyl rings of the substrates, as we proposed. The nitrogen electron pair is conjugated with the π system, displacement at the benzylic carbon should come from behind the C−Cl bond, and developing partial cationic character on the benzylic carbon should orient the C−Cl bond perpendicular to the benzene plane. This could lead to the rate decrease with added ethanol. However, two neutral species are forming two ions in this alkylation, and solvent effects on the energy of developing ions in the TS could be important. For example, we see that displacement by methoxylamine on 2-bromoacetamide, for which there is no hydrophobic contribution, is 20% slower in the 20% v/v ethanol/water solvent than that in pure water, reflecting solvation of the polar TS.



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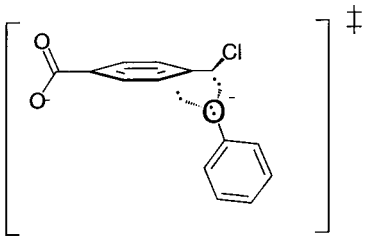
We also examined the alkylation of phenoxide ion by *p*-carboxybenzyl chloride, and saw that in this case there was essentially no rate effect of added ethanol (Table 2).[23] This makes sense for the TS **6** we proposed in which the phenoxide ion attacks with its oxygen *n* electrons, and there is no overlap of the phenyl rings in the TS. Phenoxide has this choice, which aniline does not, and the proposed transition state avoids loss of conjugation of the oxygen electrons with the benzene ring. However, here too it is important to see what other aspects of the TS the cosolvent can affect, besides the energy change that would have resulted if there had been any overlap of the hydrophobic reactants.



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If charge is lost in the TS, as in the alkylation of a phenoxide ion, the less polar mixed solvent can accelerate the reaction, as Hughes and Ingold pointed out.[21] The reactions of methyl mesylate and methyl iodide with phenoxide ion (Table 1) showed large rate increases − 60% and 110%, respectively − upon addition of 20 volume % ethanol.[23] (The difference reflects different solvation demand by the leaving groups, with the larger developing iodide ion requiring less solvent stabilization.)

Cyanide ion, with a basicity similar to that of phenoxide ion, showed rate increases with added ethanol of 20% in the reaction with methyl mesylate, and 70% with methyl iodide.[23] We conclude that a part of the rate increase upon addition of ethanol is caused by decreased hydrogen bonding solvation of the nucleophile lone pairs, but the larger rate effect in the reaction of phenoxide involves an additional factor. In phenoxide ion the negative charge is delocalized into the benzene ring, making the ring less hydrophobic. As the TS is approached the charge is partly lost, the ring becomes more hydrophobic, and this factor should add to the acceleration by ethanol. Our computer modeling, discussed below, supports this interpretation.

O versus C Alkylation of Phenoxide Ions. The alkylation of a phenoxide nucleophile usually results in the exclusive formation of the ether product.[24] However, in certain solvents,

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most notably water, considerable amounts of ortho and para carbon alkylation can occur with some electrophiles.[24−26] A number of possible factors affecting the position of alkylation of phenoxide ions have been discussed in the literature, including the effects of solvent dielectric,[27] reaction heterogeneity,[26,28] S_N1-S_N2 character of the transition state,[29] steric effects,[30] selective solvation,[24] and hydrogen bonding.[25]

Kornblum and Lurie have reported that the alkylation of phenoxide salts that are tightly ion paired in nonpolar solvents often leads to carbon alkylation that is not observed in polar solvents.[28] Curtin et al.[26] also reported that the nature of the cationic counterion influences the amount of carbon alkylation in nonpolar solvents, with smaller cations such as lithium favoring ortho alkylation, while the larger potassium ion favors oxygen alkylation. In nonpolar solvents the cation is very closely associated with the oxygen of the phenoxide anion. In our work in media that are mostly aqueous, no tight ion pairing between a phenoxide anion and a sodium cation is expected.

The S_N1-S_N2 character of a transition state affects the hard−soft character of the electrophile and can influence the course of phenoxide alkylation.[28,31]Steric hindrance can have a powerful effect on the outcome of a phenoxide alkylation. Kornblum has found that 2,6-di-*tert*-butylphenoxide gives mostly oxygen alkylation with methyl iodide, but as the electrophile becomes more bulky, as with ethyl iodide and isopropyl iodide, the reaction is pushed entirely to the less hindered para position.[30]

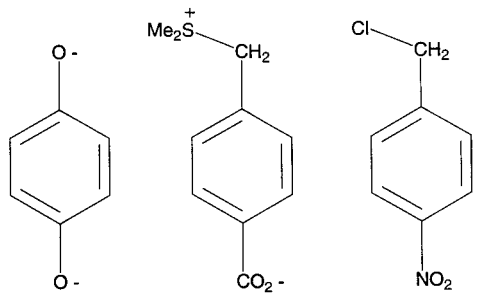
It has been reported that solvents such as water and trifluoroethanol favor carbon alkylation of phenoxides, while only oxygen alkylation is observed in most other polar solvents.[24,25] The data should be taken with some caution, however, as the reactions in water and trifluoroethanol were run as heterogeneous *two-phase* reactions because the allyl halide electrophiles are not soluble in the solvents. To explain these observations, Kornblum[24] states that in these solvents "the oxygen of the phenoxide is so intensely solvated that the availability of the oxygen for nucleophilic displacement is greatly decreased; as a consequence, displacements employing the otherwise unfavored ortho and para carbon atoms compete successfully."

Another factor, not mentioned by previous workers, actually dominates the choice between O and C alkylation of phenoxide ions in water. We have seen that carbon alkylation in water is observed only with certain electrophiles, and we found it to be *accelerated* in water over other solvents.[23] It is not simply seen by default once oxygen alkylation is suppressed by a protic solvent, as others had suggested. In light of our past work demonstrating the powerful role that hydrophobic packing at a transition state can have in influencing the course of Diels−Alder and other reactions, we postulated that hydrophobic effects might also play a role in determining the regiochemistry of phenoxide alkylation.

We have now examined various displacement reactions of phenoxides in aqueous solution, and have found strong evidence that the generally accepted set of factors governing the position of phenoxide alkylation is incomplete. As in our previous work, we have used cosolvents to observe how small changes in the solvent properties affect the rates of reactions and product selectivity. We have combined our interpretations of cosolvent effects with careful control reactions and some computational data to create a revised picture of the alkylation of phenoxides, incorporating effects stemming from both the nucleophile and the electrophile and their mutual interaction in aqueous solution. The result is the discovery that hydrophobic interactions dominate the choice between oxygen and carbon alkylation of phenoxide ions. Another result is to confirm our picture of oxygen alkylation by benzyl chloride involving an *unpacked* geometry, with attack by the *n* electrons of the oxygen.

Results and Discussion

Alkylations. As further evidence for the increased hydrophobicity of a phenyl ring in the TS for phenoxide alkylation, we have examined the reaction of hydroquinone dianion **7** with methyl iodide and methyl mesylate (Table 2). The ethanol cosolvent effects seen were only as large as those for cyanide ion nucleophile, not the larger effects seen with phenoxide ion nucleophile. The hydroquinone dianion never becomes hydrophobic during monoalkylation, since only part of one of the two delocalized charges is neutralized in the TSs.



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Simple phenoxide nucleophile becomes *more* hydrophobic in the TS for reaction with a benzyl chloride as *anionic* delocalized charge is neutralized. At the same time, the benzyl chloride reactant develops some dispersed *positive* charge in the TS, even though the reaction shows strictly second-order kinetics, and this charge will *decrease* its hydrophobicity in the TS. One component becomes more hydrophobic; the other one becomes less hydrophobic. We have performed a number of studies to sort out the various factors involved in such reactions of phenoxide ions.

As one approach, we substituted DMSO for ethanol. As we have described, DMSO at 20% v/v in water is about 50% more effective than is ethanol in lowering the energy of phenyl derivatives by solvation (Table 1), but the aqueous DMSO solution is much more polar than is the ethanol solution.[23] (However, hydrogen-bond donation could be more effective with ethanol than with DMSO.) The dielectric constant of water is 78.5, that of 20% v/v aqueous DMSO is 77.1, while that of 20% v/v ethanol is 72.1.[32,33] If the cosolvent effect is mainly to decrease the dielectric constant of the solvent, and thus its ability

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Table 3. Rate Constants and Cosolvent Effects for the Reactions of *p*-Carboxybenzyl Chloride **4** and *p*-Carboxybenzyl Dimethylsulfonium Chloride **8** with Various Phenoxide Ions in Water[a]

	4			**8**		
	k_{water} (M^{-1} min^{-1})	$k_{20\%\ EtOH}/k_{water}$	$k_{20\%\ DMSO}/k_{water}$	k_{water} (M^{-1} min^{-1})	$k_{20\%\ EtOH}/k_{water}$	$k_{20\%\ DMSO}/k_{water}$
phenoxide	5.3×10^{-2}	0.97	1.00	6.6×10^{-5}	1.50	1.40
2,6-dimethylphenoxide (oxygen)	1.8×10^{-2}	1.06	1.25	3.9×10^{-5}	1.68	1.62
2,6-dimethylphenoxide (*p*-carbon)	3.2×10^{-2}	0.65	0.56	4.4×10^{-5}	0.97	0.72
p-nitrophenoxide	8.2×10^{-3}	0.67	0.55	1.1×10^{-5}	0.84	0.69
N-methylaniline	5.5×10^{-1}	0.75	0.60	2.1×10^{-3}	0.89	0.70

[a] Data are initial rate at 25 °C (error ≤ 5%).

to support charges, ethanol should slow the reactions more than does DMSO. If the cosolvent effect is mainly to solvate nonpolar sections of the reactants and TS − slowing reactions in which either the hydrophobicity or the amount of exposed nonpolar surface decreases in the TS, and speeding others in which they increase − the effect of DMSO should be greater than that of ethanol.

The results are shown in Table 2. The reaction of *N*-methylaniline with 2-iodoacetamide and of *p*-nitrophenoxide ion with 2-bromoacetamide both show rate decreases of about 30% with added 20% v/v ethanol as compared with pure water, but both reactions are almost unaffected by added DMSO. Thus, the cosolvent effects for these reactions reflect the dielectric constant of the medium, not any hydrophobic effects. Both the aniline and the nitrophenoxide put only little negative charge into their phenyl rings. The amino group of aniline is much less basic than is the oxyanion of phenoxide, so there will be much less charge distributed into the aniline ring than for phenoxide ion. In *p*-nitrophenoxide the negative charge is distributed between the oxyanion and the already polar nitro group, with little on the benzene carbons. Thus, in alkylations of aniline and of *p*-nitrophenoxide ion by simple electrophiles there is no large change in the hydrophobic effect, in contrast to the increased hydrophobicity at the TS in such alkylations of unsubstituted phenoxide ion.

However, the reaction rate of *N*-methylaniline with *p*-carboxybenzyl chloride is decreased by 25% with added ethanol, and 40% with added DMSO (Table 2). The reaction of this benzyl chloride with *p*-nitrophenoxide also shows more slowing with DMSO than with ethanol. Thus, in these alkylations there is a decrease in the hydrophobic character of the TS relative to the starting materials. This decrease reflects either (1) some packing of the phenyl rings of electrophile and nucleophile in the TS, or (2) a decrease in the hydrophobicity of the benzyl system as the partial positive benzylic charge in the TS is distributed throughout the phenyl ring. Because the effect is seen with *both* the aniline and the nitrophenoxide ion nucleophiles, the latter of which surely has no packing interaction with the benzyl chloride, partial delocalized cationic charge in the electrophile must be involved. Our computational models described below indicate that a benzyl cation will be much less hydrophobic than a neutral benzene, because of the charge distribution into the phenyl ring. Possible hydrogen bonding to the leaving group could also be altered to a different extent by the two cosolvents.

As another approach to sorting the factors involved, we have replaced the *p*-carboxybenzyl chloride **4** by a *p*-carboxybenzylsulfonium ion **8**, so the leaving group would not develop negative charge. This lets us learn the extent to which altered solvation of a leaving chloride ion plays a role in the cosolvent effects on rates. We prepared compound **8** by reaction of *p*-carboxybenzyl chloride with dimethyl sulfide and examined it in reactions with *N*-methylaniline and with phenoxide and *p*-nitrophenoxide ions. As Table 3 shows, the rate decrease induced by ethanol in reaction of **8** with *N*-methylaniline was significantly less than that for reaction of the benzylic chloride **4**, indicating that some of the chloride rate decrease with added cosolvents results from poorer solvation of the developing chloride ion. Very similar changes were also seen with nucleophilic *p*-nitrophenoxide ion, again indicating the importance of chloride ion solvation.

The data for attack by simple phenoxide ion are most striking (Table 3). While in the benzylic chloride case **4** there was almost no cosolvent effect, with the sulfonium salt **8** there was a 50% rate *increase* with added ethanol, and 40% with added DMSO. Apparently with the benzylic chloride **4** the rate-increasing ethanol cosolvent effect in somewhat desolvating the nucleophilic oxyanion of phenoxide ion − and in solvating the increasingly hydrophobic phenyl ring of the phenoxide − was compensated by the rate-decreasing cosolvent effect on the solvation of the leaving chloride ion, while no such compensation occurred with the sulfonium substrate **8**. Ionic solvation dominates the cosolvent effects, as the greater effectiveness of ethanol than of DMSO indicates. The *net* hydrophobic effects are not large; the increased hydrophobicity of phenoxide ion in the TS is compensated by the decreased hydrophobicity of the partially cationic benzyl group in the TS. There is no reason to invoke hydrophobic packing. Support for the proposal that there is no hydrophobic packing in the TS for phenoxide attack on benzylic chlorides also comes from our studies on cases in which phenoxide ion is alkylated competitively on both oxygen and carbon, as described below.

We have also used *p*-nitrobenzyl chloride (**9**), in which there is surely less delocalized positive charge induced in the TS for substitution than with *p*-carboxybenzyl chloride. In fact, the rate-accelerating effects of a *p*-nitro group in S_N2 reactions of benzyl halides almost certainly reflect some *negative* charge into the benzyl group in the TS, probably by three-center bonding of the nucleophile to both the benzyl and the ipso carbons. However, that charge goes into the nitro group (which even without the charge is polar, not hydrophobic), not onto benzene ring carbons.

We see that 20% v/v ethanol increases the rate of reaction of **9** with phenoxide ion by 20%, while 20% v/v DMSO increases

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Table 4. Minimized Interaction Energies of Ethane with Aromatic Substrates in Water, As Calculated by the ab initio Jaguar Program, and Comparison with Some Experimental Values

	delocalized charge?	calculated ethane interaction energy, kcal/mol	experimental 20% ethanolic solubility perturbation, kcal/mol
benzene	no	−1.40	−0.35
benzaldehyde	no	−1.45	−0.37[a]
N-methylaniline	no	−1.44	−0.35
phenoxide ion	yes	−0.46[b]	
phenoxy radical	no	−1.31[b]	
thiophenoxide ion	yes	−0.16[b]	
thiophenoxy radical	no	−1.21[b]	
anilinium cation	no	−1.19[b]	
N-methylanilinium radical cation	yes	(0)[b,c]	

[a] Reference 9. [b] Average interaction energy with the face of the benzene ring. [c] A slightly positive interaction energy was calculated as a result of forcing the two molecules to occupy the same solvent cavity. We consider this to be zero interaction energy as the real molecules would have the freedom to occupy separate cavities.

the aqueous rate by 30%.[34] Apparently with **9** we are seeing the *increased* hydrophobicity of phenoxide ion as it loses some charge in the TS without seeing the compensating *decrease* in hydrophobicity of a benzyl group as it develops some delocalized charge in the TS.

A Computational Model. To address the contribution of delocalized charge in aromatic rings to hydrophobic effects on reactions, we developed an ab initio computational model using Jaguar 3.0[35] to probe the relative hydrophobicity of aromatic surfaces.[13] In particular, we were interested in modeling how delocalized charge affects the hydrophobicity of a benzene ring in aqueous solution, and how cosolvents might interact with substrates having, or lacking, delocalized charge.

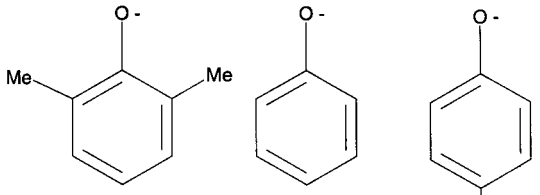
In the model, a hydrophobic probe molecule, ethane, is brought to the surface of various aromatic substrates in simulated water solvent. The position of the ethane is optimized by energy minimization, with the 6-31G** basis set and continuum solvent SCRF, to determine the magnitude of interaction with the surface at several local minima. The ethane molecule and the substrates are first energy minimized individually, and all intramolecular coordinates are constrained during minimization of the intermolecular interactions.

The calculated values are listed in Table 4. The *observed* effects of 20% v/v ethanol in water on the solubility of the compounds, in kcal/mol, are also in that table. These numbers are smaller, since *fully* coordinated ethane in the computer overestimates the effect of only *occasionally* coordinated ethanol in the experiments. However, it is gratifying that the observed solubility $\delta\Delta G°$s for benzene, benzaldehyde, and *N*-methylaniline run parallel to the calculated values for ethane coordination, each observed value being ca. 25% of that calculated for full coordination of an ethane molecule to the substrate in water.

The calculations indicate that a phenoxide ion is only one-third as hydrophobic as is a phenoxy radical (and phenol itself). Because the poorly hydrophobic phenoxide ion will also coordinate ethanol on its phenyl ring to a lesser extent than does neutral phenol, these calculations suggest that almost all of the ethanol stabilization of the hydrophobicity of phenol is likely to be lost when it ionizes to the anion. Conversely, when a phenoxide ion is the nucleophile there will be a significant increase in hydrophobicity, and in its stabilization by ethanol or DMSO, as it loses some of its charge in the TS. Our Brönsted plots of the alkylation of various para substituted phenoxides with *p*-carboxybenzyl chloride **4** indicate that 29% of the charge on the phenoxide ion is neutralized at the TS in water, and 34% in 20% v/v ethanol.[34]

When an aniline is protonated, there is a small decrease in its interaction energy with ethane in water. Thus, in a TS in which the aniline nitrogen is the nucleophile we may see a small decrease in rate caused by nonpolar cosolvents such as ethanol or DMSO, in contrast to the rate increase induced in phenoxide ion as nucleophile. However, when the positive charge is delocalized into the ring, in the cation radical of *N*-methylaniline, all hydrophobicity disappears. This is the result of delocalization of charge, not of the radical, since phenoxy radical is almost as hydrophobic as is benzene. Thus, we conclude that a full benzyl cation would also be minimally hydrophobic and that some hydrophobicity is probably lost in the partially cationic TS for S_N2 displacement on **4** and **8**, but not on **9**.

O versus C Alkylation of Phenoxide Ions. In examining the aqueous alkylation of phenoxides we found that in water 2,6-dimethylphenoxide **10** undergoes 64% para alkylation with *p*-carboxybenzyl chloride **4**, as well as 36% oxygen alkylation (Figure 4). We saw no para alkylation in common organic solvents (ethanol, DMSO, THF). No para alkylation was seen in water (or other solvents) with unmethylated phenoxide **11** as the nucleophile.[23] No para alkylation in water was observed for the reactions of **10** with methyl iodide or 2-bromoacetamide either, clearly demonstrating that the factors that control the position of alkylation are not limited to the nucleophile.



10 **11** **12**

This finding gave us an important way to isolate the factors involved in phenoxide ion benzylations. The starting materials and the leaving groups are the same for oxygen and carbon alkylation, so solvent and cosolvent effects reflect differences in the transition states for the two competing processes.

When we ran the reactions with cosolvents, we observed a difference in the rate perturbation by 20% ethanol and 20% DMSO cosolvents on the para alkylation, which is slowed by both cosolvents, from that of the oxygen alkylation, which is unaffected by 20% ethanol and shows a modest rate *increase* with 20% DMSO (Table 3). Our results in Table 3 suggest that there is a concealed hydrophobic surface area at the TS for the para alkylation reaction of **1** with **2**, but no concealed surface in the TS leading to the oxygen alkylation product. Hydrophobic packing is driving the reaction toward para alkylation in water.

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(35) *Jaguar 3.0*; Schrodinger, Inc.: Portland, Oregon, 1997.

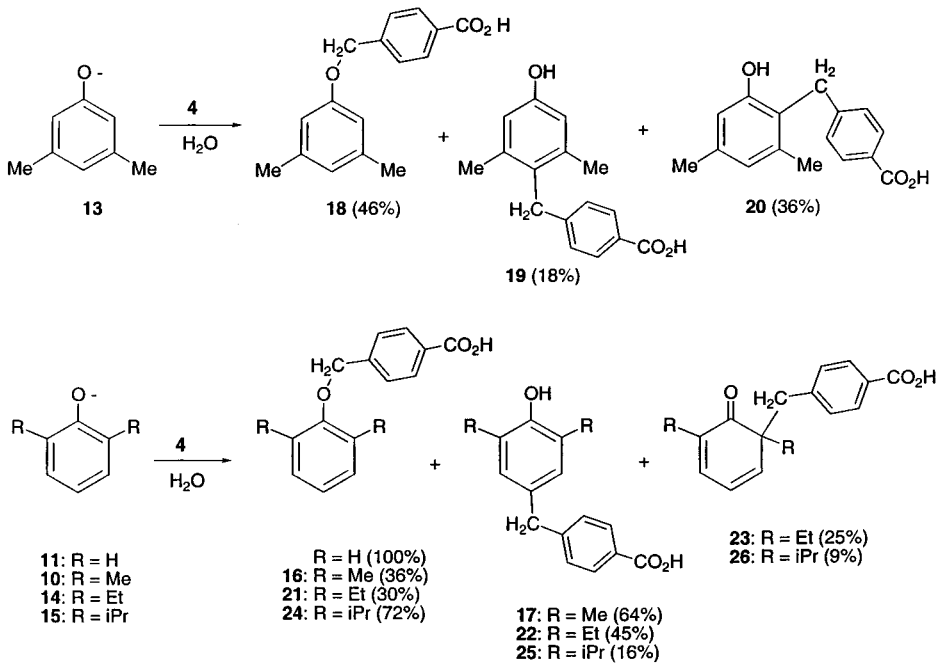

Figure 4. Alkylations of substituted phenoxide ions in water at oxygen, para, and ortho positions.

Our results are contrary to what we would expect only on the basis of selective solvation of the phenoxide oxygen, which was considered to be one of the dominant factors controlling phenoxide alkylation.[24,25,31] If oxygen solvation were the only factor in aqueous solution, we would expect little or no effect of cosolvents on the para alkylation and rate increases for the oxygen alkylation as the cosolvents interfere with water solvation of phenoxide ion. Yet we observe exactly the opposite; the large effect of cosolvents is to *slow* the carbon alkylation, while having a lesser effect on the oxygen alkylation.

Cation association has been implicated in driving phenoxide alkylations toward carbon in nonpolar solvents,[26,28] but considering that the reactions that we have examined were run in at least 80% water and with the reactants completely in solution, the effects of close association of the sodium cation with the phenoxide oxygen do not apply to our results. We would expect greater association of the cation with the oxygen in the solutions with the nonpolar cosolvents, if anything, and hence a greater amount of carbon alkylation with cosolvent; instead, we observe that cosolvents lead to *less* carbon alkylation.

The effect of the S_N1-S_N2 character of our reactions was of some concern, as changes in the mechanism can affect the position of alkylation.[29,31] If the degree of S_N1-S_N2 character were to change in water relative to other solvents, a highly polar solvent such as water would likely favor a more S_N1-like transition state and a subsequent preference to alkylate the harder, more electronegative oxygen of the phenoxide ion. This is the opposite of our observation that **10** prefers to alkylate at the softer para position in water. However, Kornblum and Lurie have reported that highly reactive benzyl cations show a lack of selectivity toward the position of alkylation on phenoxide ions, sometimes resulting in carbon alkylation.[28] Additionally, Sneen et al.[37,38] have reported that the kinetics for some nucleophilic substitutions of benzyl halides in aqueous acetone and benzyl sulfonium ions in water are less than first order in nucleophile, and concluded that a borderline S_N1-S_N2 ion-pair mechanism was operative. Thus, we determined whether we were dealing with a pure S_N2 reaction, an S_N1 reaction, or a borderline ion-pair mechanism.

We performed kinetic order experiments on the aqueous reactions of phenoxide **11**, *p*-nitrophenoxide **12**, and 2,6-dimethylphenoxide **10** (both oxygen and para carbon alkylations) with **4**. For each of the nucleophiles, formation of products and formation of the competing hydrolysis product were monitored over a range of concentrations. In each case, the rate of alkylation of the phenoxides showed a linear relationship with the concentration of phenoxide ion (first order), and, more importantly, the rate of hydrolysis of the benzylic halide was unaffected by the concentration of phenoxide ion.[36] This last result indicates that there is no competition between the nucleophile and the water solvent for a free benzyl cation or a borderline ion-pair reactive intermediate under our conditions, 25 °C in pure water, and that the reaction is truly S_N2.

Steric hindrance was a serious consideration for the interpretation of our initial results. We found that ortho substitution promoted para alkylation of phenoxide with a relatively large electrophile such as **4**, but not with small electrophiles such as methyl iodide, a comparable result to that of Kornblum mentioned previously.[30] However, like selective solvation, steric effects should allow carbon alkylation to compete only by slowing oxygen alkylation, not speeding carbon alkylation. We find that para alkylation is actually accelerated in water; with the two methyl groups in **10**, the overall rate of alkylation by **4** in water decreases by a factor of only 3 as compared with the rate for simple phenoxide **11**, but the proportion of that rate that leads to carbon alkylation increases by at least 30-fold. Thus, we conclude that there must be forces that *activate* para alkylation in aqueous solution, not just suppress oxygen alkylation. The only escape from this conclusion would be a

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(37) Sneen, R. A.; Larsen, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 6031−6035.
(38) Sneen, R. A.; Felt, G. R.; Dickason, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 638−639.

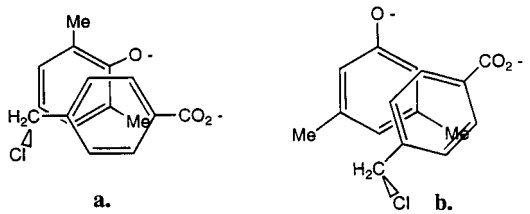

Figure 5. Oblique overlap in the para coupling of (a) **10** with **4** and (b) **13** with **4**.

Table 5. Product Distributions for the Reactions of Alkyl Substituted Phenoxides with **4** in Water at 25 °C

	oxygen %	ortho %	para %
11	100		
10	36		64
13	46	36	18
14	30	25	45
15	75	9	16

mechanism in which the two reactants form a complex in the rate-determining step, and this complex then partitions between oxygen and carbon alkylation subsequently. Our further evidence, described below, shows that this is not the explanation for an increased rate of carbon alkylation in water solution.

The nature of the phenoxide substituents was found to be crucial for determining the amount of carbon alkylated products in water. For instance, of five para monosubstituted phenoxides that we examined, only *p*-cresol, with a methyl substituent, gave any carbon alkylation with **4** in water, in this case 16% ortho alkylation. The other para substituents − methoxyl, chloro, cyano, and nitro − gave exclusively oxygen alkylation of the phenols.

We have also found that hydrophobic methyl groups at any position on the phenoxide ion induced carbon alkylation with **4** in water. We proposed that a stacked transition state leading to carbon alkylation would allow methyl substituents to make contact with the hydrophobic surface of **4**, concealing hydrophobic surface area and resulting in the observed rate decrease by 20% ethanol and a preference for carbon alkylation in water (Figure 5).[23] The oxygen will prefer to attack with its *n* non-π electrons (not conjugated with the benzene ring) such that the two phenyl rings of the reactants are perpendicular to one another, as we have proposed above and previously.[12] For carbon alkylation, however, the two phenyl rings must be parallel, which allows packing to occur. Such a transition state would also explain why only hydrophobic alkyl substituents result in carbon-alkylated products. We propose (Figure 5) that the packing in the para alkylation is oblique, allowing overlap of a methyl group of the phenol while minimizing overlap of the phenoxide oxyanion.

It has long been believed that para alkylation of 2,6-disubstituted phenoxide ions reflected the steric hindrance of the substituents for attack at the oxygen atom and that para alkylation occurred then by default. The clearest rebuttal of this idea − at least for our benzylation reactions in aqueous media − comes from our results with 3,5-dimethylphenoxide ion **13**, as shown in Table 5. In **13** there is no steric hindrance at oxygen; if anything, there is steric hindrance at the ortho and para carbons, and yet benzylation occurs at these carbons, while it does not occur in unsubstituted phenoxide ion. Of course our other findings on substituent effects, and on cosolvent effects, also show that something else is dominating the selectivity in aqueous media.

Table 6. Second-Order Rate Constants (M^{-1} min^{-1} × 10^{-3}) and 20% Ethanolic Rate Perturbations of the Reactions of Various Phenoxides with **4** in Water[a]

	oxygen alkylation		ortho alkylation		para alkylation	
	k_{water} (M^{-1} min^{-1})	$k_{20\%EtOH}$ / k_{water}	k_{water} ($M^{-1}min^{-1}$)	$k_{20\%EtOH}$ / k_{water}	k_{water} (M^{-1} min^{-1})	$k_{20\%EtOH}$ / k_{water}
11	53	0.97				
10	18	1.08			32	0.66
13	70	0.91	55	0.71	28	0.64
14	28	0.99	23	0.78	39	0.61
15	37	0.96	4.3	0.84	10	0.67

[a] Data are initial rate (error ≤ 4%).

We compared the aqueous reaction rates and cosolvent effects of 20% ethanol for the alkylation of a series of alkyl substituted phenoxides by **4**. In addition to simple phenoxide **11** and 2,6-dimethylphenoxide **10**, 3,5-dimethylphenoxide **13** was chosen to control any steric effects the 2,6-disubstitution might have at the oxygen, and 2,6-diethylphenoxide **14** and 2,6-diisopropylphenoxide **15** were chosen to examine the effect of the size of the alkyl substituents on the rates of both carbon and oxygen alkylations. All phenoxides gave some oxygen alkylation, while **10** also gave para alkylation, and **13**, **14**, and **15** also gave both ortho and para alkylation, with the ortho alkylation of the 2,6-disubstituted phenoxides resulting in cyclohexadienone products (Figure 4). Authentic products for the reactions were synthesized in water, as synthesis in any other solvent gave exclusively oxygen alkylation, and characterized by ^{1}H NMR. Table 5 shows product distributions for each of the alkylation reactions in pure water. Aqueous rate data and 20% ethanol rate perturbations for the phenoxide series are shown in Table 6.

The results of the kinetic studies for the alkylation of the phenoxides by **4** revealed, not unexpectedly, that steric effects of 2,6 substitution as well as basicity of the phenoxide affect the rate of the reaction at oxygen. The rate of the oxygen alkylation of 3,5-dimethylphenoxide **13** is about 30% faster than that of simple phenoxide **11**, reflecting an increase in nucleophilicity due to increased basicity (**13** had an identical rate to that of *p*-methoxyphenoxide, which has the same pK_a). The rate of oxygen alkylation of **10** is 66% slower than that of **11**, even though it is more basic, reflecting the steric effects of the ortho methyl substituents. Oxygen alkylation of **14** and **15** was somewhat faster than for **10**, again reflecting increased basicity and possibly decreased oxygen solvation caused by the alkyl substituents, which apparently outweighs any slowing from the increase in steric bulk around the oxygen relative to **10**. All oxygen alkylations showed almost no effect on the rate by 20% v/v ethanol, just as we had seen for a simple phenoxide ion previously.

The rates for alkylation at the para position of phenoxides are more interesting, however. No para alkylation at all was observed with simple phenoxide **11**, but para alkylation was observed for all of the alkyl substituted phenoxides. Figure 6 provides a graphical representation of the second-order rate constants for the oxygen and para alkylations of each of the phenoxides by **4**. The stacked transition state allows for favorable hydrophobic interaction of the benzyl group with the phenoxide phenyl ring and alkyl substituents, accelerating the reaction in water. The position of the alkyl groups does not

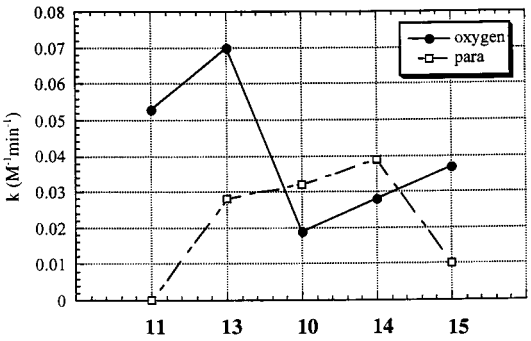

Figure 6. The second-order rate constants of the oxygen and para carbon alkylation reactions of various phenoxide ions with **4** in water.

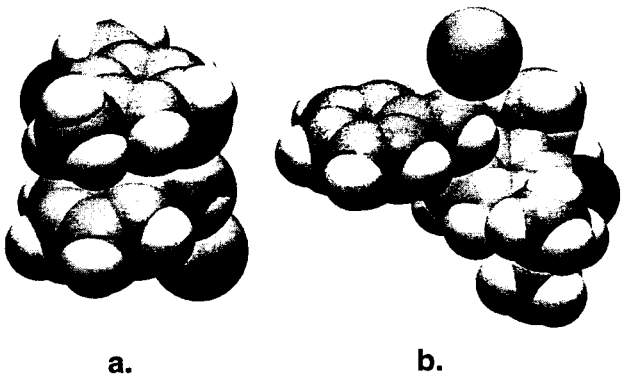

Figure 7. (a) Proposed stacked transition state for the para alkylation of 2,6-dimethylphenoxide **10** with benzyl chloride. (b) Theoretical extended transition state of the reaction of 2,6-diisopropylphenoxide **15** with benzyl chloride, illustrating how isopropyl groups protrude above the face of the phenoxide and interfere with a stacked transition state. The phenoxide ion oxygens are represented by fluorine atoms.

matter since the phenoxide can simply rotate to maximize hydrophobic overlap.

As shown in Figure 6, the rate of para alkylation was relatively unaffected by the position of the alkyl groups, as **10** and **13** showed approximately the same rate of para alkylation. Para alkylation of **14** was just a little faster than that of **10**. Most interestingly, para alkylation of **15** was significantly slower than for **10** or **14**, 4 times slower than 2,6-diethylphenoxide **14**. From this result we conclude that the attack at the para position has a transition state that is *more* sensitive to the steric effects of the ortho isopropyl groups of **15** than is attack at the nearby phenolic oxygen.

The steric hindrance from isopropyl groups for para alkylation of **4** in water indicates that the transition state does indeed involve packing of the aromatic ring of the benzyl group over the ring and alkyl group of the phenoxide, with which the bulky isopropyl groups interfere. The ethyl groups of **14** have the opportunity to turn the outer methyl group away from the face of the phenoxide involved in stacking, providing essentially the same amount of hydrophobic overlap as with **10**. Compound **14** therefore shows no rate disadvantage over **10**. The isopropyl groups of **15**, however, which energetically prefer to remain with their methyl groups almost perpendicular to the aryl ring of the phenoxide, effectively block favorable packing of the benzyl group and slow the para reaction. Figure 7 shows possible transition states of the reactions of benzyl chloride with 2,6-dimethylphenoxide **10** and 2,6-diisopropylphenoxide **15** and illustrates how the isopropyl groups might interfere with the packed transition state proposed for **10**.

The para alkylation of **15** can proceed with hydrophobic packing only if one of the isopropyl groups is rotated into a less favorable orientation such that a methyl group lies more or less in the plane of the aromatic ring (14°−17° out of plane, whereupon it does not interfere with the packing). The energy cost of rotating an isopropyl substituent to thus flatten one surface of **15** was estimated to be about 1.1−1.4 kcal/mol by a gas-phase MM2* calculation on 2,6-diisopropylfluorobenzene using MacroModel.[39] This number is roughly the same amount by which the transition state for the alkylation of 2,6-diisopropylphenoxide **15** is destabilized relative to **10**, **13**, and **14**.

For all para alkylations, 20% ethanolic rate perturbations were the same, resulting in a rate decrease by about one-third (Table 6). Such a rate decrease in 20% ethanol is expected if the transition state involves hydrophobic packing of the starting materials. We judge from these results that the amount of hydrophobic overlap is roughly the same in each case. The data also indicate that hydrophobic packing of the benzyl group against an alkyl substituent (of the right size) on the phenoxide is essential to obtain para alkylation. In the absence of alkyl substituents, or in organic solvents where there is no hydrophobic effect, or with electrophiles with no significant hydrophobic surface, only oxygen alkylation is observed.

The rates of alkylation by **4** at the ortho position of the phenoxides show a less clear trend (Table 6). Alkylation at the ortho position was not observed for **10** or **11**, although the rate of ortho alkylation was almost as fast as oxygen alkylation for **13** and **14**. Relatively slow ortho alkylation was observed in the reaction of **15** with **4**. The observed ortho alkylations showed 20% ethanolic rate decreases ranging between 20% and 30%. The cosolvent rate decreases of the ortho alkylations surely reflect the undoubted hydrophobic packing in the transition states. However, the variability in the rates of ortho alkylation across the series of phenoxides, perhaps as a result of varying steric constraints of the substituents, makes these data more difficult to interpret than those of the para alkylations.

Table 3 shows several contributing factors affecting the overall rates in water and with added cosolvents. (1) Alkylations of phenoxide ions at oxygen lead to an increase in hydrophobicity, and thus a rate increase with cosolvents, which we ascribe to partial neutralization of the delocalized negative charge in the TS. (2) This effect is suppressed with *p*-nitrophenoxide ion. (3) Cosolvents diminish the rate by interfering with solvation of the leaving chloride ion, so this effect is lost with a sulfonium ion leaving group. (4) In water the alkylations of 2,6-dimethylphenoxide ion by *p*-carboxybenzyl chloride or sulfonium ion are somewhat faster at the para position than at the oxygen, but the para alkylation is slowed by added ethanol and even more by added DMSO. The rate of oxygen alkylation is either slightly or significantly increased by the cosolvents. (5) DMSO is more effective than is ethanol at solvating hydrophobic surfaces. Ethanol has a larger effect than does DMSO in decreasing the dielectric constant of the water medium, so the larger cosolvent effects of DMSO in the table indicate that hydrophobic effects are more important than are changes in the dielectric constant of the medium.

For O-alkylation, the hydrophobicity increase for phenoxide ion and the decrease for the benzyl group at the TS apparently roughly cancel each other. These effects should still be present

(39) *Macromodel 7.0*; Schrodinger, Inc.: Portland, Oregon, 2000.

for C-alkylation, but that process has an extra factor − the packing of the benzyl group onto the phenoxide ring with its added methyl groups. This packing is the only sensible interpretation of the various effects of phenyl substituents discussed earlier. Thus, we conclude that the two processes − oxygen and carbon alkylation − do indeed have the transition states shown in Figure 2. This supports our previous conclusion that oxygen alkylation of phenoxides uses their *n* electrons and has no hydrophobic packing in the TS.

Conclusions

The hydrophobic effect can be involved in every reaction in water, or in water with cosolvents. In nonpolar reactions − such as the Diels−Alder dimerization of cyclopentadiene in water − the effect of cosolvents such as ethanol is entirely due to a modification of the hydrophobic effect as the ethanol helps solvate the hydrocarbon substrate. The magnitude of the cosolvent effects, in free energy terms, is completely consistent with the transition state (TS) for the process and the extent to which hydrophobic surfaces become hidden from solvent in the TS.

In reactions with polar reagents and in which there are polarity changes in the TS, cosolvents also modify the ability of the solvent to stabilize polar groups. However, even in such polar reactions as S_N2 displacements on benzylic halides by anilines or phenoxides there are hydrophobic effects on the rates. Some have to do with physically shielding hydrophobic surfaces in the TS, but others have to do with changes in the hydrophobicity of the reactants at the TS. For example, as nucleophilic phenoxide ion attacks an alkylating agent there is less delocalized negative charge into the phenyl ring, and it becomes more hydrophobic. As nucleophilic attack occurs on a benzylic halide there is some positive charge delocalized into the benzene ring, with a decrease in hydrophobicity at the TS.

We have elucidated the factors involved in the rate effects of antihydrophobic cosolvents such as ethanol by the contrasting effects of ethanol and DMSO, by replacing a leaving chloride with a dimethylsulfonium group, by a study with *p*-nitrobenzyl chloride, and by a computer model of the hydrophobic effect. The computer model reveals that charge delocalization is important in hydrophobicity changes for aromatic reactants. From these studies, we have concluded that phenoxide ion as a nucleophile uses its *n* electrons, not π electrons, and that it does not stack on the benzyl electrophile in the TS. This contrasts with aniline nucleophiles, in which a very different geometry of the TS results from the use of π-like electrons. Additional evidence supporting these conclusions comes from the study of competing oxygen and carbon alkylation in phenoxide nucleophiles.

In the case of phenoxide nucleophiles, decreases in solvent-exposed hydrophobic area − resulting from packing of alkyl substituents against the aromatic ring of a benzylic electrophile − influence the regiochemistry of the reaction, selecting for carbon alkylation over oxygen alkylation in water. The use of two cosolvents with different properties, and comparison of various alkylating reagents, have allowed us to distinguish hydrophobic effects from other effects on these reactions, and to confirm our suggested transition states for phenoxide alkylations at oxygen and at carbon.

Experimental Section

Kinetics. *p*-Carboxybenzyl chloride **4** was recrystallized from ethanol/ether. *p*-Carboxybenzyl dimethylsulfonium chloride **8** was recrystallized from acetonitrile/ether. *p*-Nitrophenol was dissolved in methylene chloride (with 5% ethyl acetate to aid solubility), dried over sodium sulfate, filtered, and crystallized by slow addition of hexanes. All of the above reagents were dried under vacuum after purification. All other reagents were purchased with the highest purity possible and used without further purification.

Kinetics studies were performed on an HP1090 Series II liquid chromatograph with a DR5 pumping system and a temperature-controlled autosampler. Rainin Microsorb C-18 reverse phase analytical columns (4.6 mm diameter × 150 mm length) with 5 mm particle size were used with Rainin C-18 guard columns. Analytes were detected with a diode-array UV−vis detector. All HPLC solvents were HPLC grade purchased from Fisher Scientific Co. HPLC water was deionized through a U.S. Filter type I mixed bed deionizer and filtered through Osmonics or Whatman nylon membrane filters with 0.2 mm pore size. Buffers were prepared using an Orion 701 A pH meter with an Orion 8103 Ross combination electrode. The electrode was calibrated against standard buffer solutions (pH 4.0, 7.0, 10.0) obtained from Aldrich Chemical Co.

All second-order kinetics were monitored as initial rates. With the exception of *N*-methylaniline **3**, the nucleophile was used in excess. Stock solutions of the nucleophile and electrophile were prepared fresh with water freshly distilled under argon, and kept in argon-flushed conical flasks with a rubber septum and a needle delivering positive pressure of argon. Necessary base (LiOH) was added to nucleophile solutions. Reagent solutions were sonicated and vortexed to ensure full dissolution of reagents and homogeneity of the solutions. Additionally, stock solutions of pure water, 60% v/v 200 proof ethanol, and 60% v/v DMSO were prepared.

For each reaction, a mixing vial was flushed with argon, and 0.500 mL of each of the two reactants and 0.500 mL of either water, 60% ethanol, or 60% DMSO were added with a pipet. The mixing vial was sealed and vortexed for 45 s during which time an amber HPLC vial was flushed with argon. The reaction solution was transferred to the HPLC vial via syringe and pushed through an Acrodisc 0.2 mm syringe filter. The sample was then thermostated to 25 ± 0.5 °C in the HPLC sample compartment. The HPLC sequence was then started which takes 6−10 injections at fixed intervals. An appropriate method (solvent system/gradient) was devised with mixtures of the reactants and authentic reaction products.

Peaks were detected by UV−vis at wavelengths appropriate to the reactants and products. Reactant and product HPLC peak areas were integrated automatically or manually, as appropriate. Rate of formation of product was used for computation of all rate constants. Starting material concentrations were also monitored to ensure that the reaction was still in its initial rate (<4% complete).

Each HPLC injection generated a text file that contained the time of injection, and a table of peak retention times and integrated peak areas, as well as other information. A series of output text files was read using a short script written with Perl[38] (Practical Extraction and Report Language) that reads the time of injection and peak area for a specified retention time and generates a text file that contains the relative time of injection and peak area in a format readable by the Kaleidegraph plotting program. Linear regressions were performed by Kaleidegraph, and slopes ($R > 0.992$) were calibrated on the basis of synthesized, characterized, and purified authentic products. Second-order rate constants ($M^{-1}\,min^{-1}$) were obtained from the calculated rate ($M\,min^{-1}$) divided by the initial concentrations of the reactants. Reactions were run in at least triplicate for each solvent system used, and all rate constants were reproducible to within at most 5%, usually 3−4%.

For all reactions monitored by HPLC, each kinetic method was calibrated with an authentic sample of the product as well as each of

the reactants. For a calibration, three stock solutions of a compound were separately prepared at a concentration comparable to the concentrations in the kinetic runs. Each sample was then injected into the HPLC three times and eluted with the same method used for the kinetics. Obtained peak areas were divided by the concentration of stock solutions, and all values were averaged to obtain a correction factor in units of M/area.

Solubilities. The solubilities of benzene and benzyl phenyl ether in water, 20% ethanol, and 20% DMSO were measured by HPLC. Three 2.0 mL samples of each solvent mixture were equilibrated with 50 mL (0.56 mmol) of benzene or 2.0 mg (0.011 mmol) of benzyl phenyl ether at 25 ± 0.2 °C for 24 h with slow stirring. The samples were then allowed to stand without stirring for an additional 24 h before being sampled with a needle. For benzene, 40.0 mL of solvent was drawn from underneath the benzene layer and diluted to 2.00 mL with ethanol and injected onto the HPLC three times. For benzyl phenyl ether, 0.500 mL of sample was drawn and injected directly into the HPLC three times. In each case, the HPLC peak areas were calibrated against three samples of the authentic compounds at known concentrations comparable to injected concentrations in pure ethanol. Benzene solubility in pure water was measured at 20.9 ± 1.0 mM as compared to the IUPAC value of 20.7 mM, confirming the accuracy of the measurements.

Computations. All ab initio calculations were performed with the Jaguar 2.5 or Jaguar 3.0 software packages[35] using the 6-31G** basis set. For calculations with water solvent, continuum solvent SCRF was used. Energies are calculated in hartrees, then converted to kcal/mol, where 1 hartree = 627.5 kcal/mol. Input structures were created with Macromodel[39] and minimized on the mm2* force field in the gas phase prior to export to Jaguar. The Macromodel files were converted to *xyz* and Jaguar *z*-matrix files with Babel.[41] Xmol[42] was used to view *xyz* input and output files and to measure coordinates of input structures in *xyz* format. Output files were searched and parsed with the aid of several scripts written in Perl[40] specifically for this series of calculations.

An ab initio computational method for estimating the effects of delocalized charge on the hydrophobicity of various aromatic surfaces was developed. For the calculations a molecule of ethane was used as a hydrophobic probe molecule, and it was brought into van der Waals contact with the surface of various aromatic substrates. Individual molecules (ethane and aromatic substrates) were first constructed with Macromodel and minimized on the MM2* force field in the gas phase. The coordinates were then converted to Jaguar format and minimized in water solution. The minimized coordinates for the aromatic substrates were then converted to a *z*-matrix text format. The *z*-matrix coordinates for ethane were then manually appended to the *z*-matrix coordinates of the aromatic solute. Six new *z*-matrix coordinates were then input to specify the relative orientation of the ethane molecule to the aromatic ring. The first coordinate is the distance from one of the ethane carbons to the carbon in the four position (arbitrarily chosen) of the monosubstituted benzene ring. The next two are the angle from the ethane carbon to the four and three carbons and the torsional (dihedral) angle from the ethane carbon to the four, three, and two carbons of the aromatic ring. The next two coordinates specify the angle and torsional angle from one of the hydrogens on the chosen ethane carbon through the ethane carbon to the four and three carbons of the aromatic ring. Finally, the last coordinate is the torsional angle from a second hydrogen on the ethane carbon, to the first hydrogen then to the ethane carbon and the four position of the aromatic ring.

The coordinates were obtained by maneuvering the molecules together to the desired relative orientation with Macromodel, converting the Macromodel file to *xyz* format and measuring the desired coordinates with Xmol. Once a set of input geometries was created, the orientation coordinates were cut and pasted into other input files for each of the different aromatic molecules. In this way, the initial orientations of the ethane to all model aromatic solutes were identical. Several geometries for interaction of ethane with the face of the benzene ring as well as parallel and perpendicular orientations of the ethane on the edge of the benzene ring were used. All other coordinates (i.e., all intramolecular coordinates) were constrained for the calculations of intermolecular interaction energies.

Output files were searched for the geometry with the lowest solution phase energy. Energy surfaces were generally rather flat, so geometric convergence was rare. Energetic convergence was obtained with good accuracy, however. To find the interaction energy, the sum of the calculated solution phase energies of the separate model aromatic solute and ethane was subtracted from the total solution phase energy calculated for the ethane and the model aromatic solute placed together. For the neutral aromatic molecules, including benzene, *N*-methylaniline, anilinium cation, benzaldehyde, 1,3-dinitrobenzene, and thiophenoxy and phenoxy radicals, the interactions on the face and edge were equivalent. For these molecules, results of all optimizations (corresponding to different input geometries) were averaged. For phenoxide and thiophenoxide anions and *N*-methylanilinium radical cation, however, the edge and face interactions were different and were therefore treated separately. The results are listed in Table 4.

Syntheses. 2,6-Diethylphenol.[43] Three grams (20 mmol) of 2,6-diethylaniline was dissolved in 60 mL of water and 40 mL of concentrated sulfuric acid in a 1 L round-bottom flask with a stir bar. Twenty-five grams of ice was added, and the solution was immersed in an ice bath. One and one-half grams (22 mmol) of sodium nitrite was dissolved in 40 mL of water with 10 g of ice, and the solution was transferred to an addition funnel attached to the 1 L reaction flask with the 2,6-diethylaniline solution. The sodium nitrite solution was added over about 15 s with vigorous stirring (note: the sodium nitrite solution can be added quickly only if the solutions are fairly dilute, as considerable heat is released and colored byproducts are formed if the solutions are more concentrated). The solution turned light orange in color, and bubbles of nitrogen were observed. The solution was transferred to a 1 L flask with 50 mL of 50% sulfuric acid that was heated to steaming (~50 °C), and the combined solution was heated to 90−100 °C for 15 min. The solution was then transferred to a 2 L separatory funnel, and the product was extracted with three 150 mL portions of methylene chloride. The methylene chloride was dried over sodium sulfate and evaporated. The resulting oil was placed in a sublimation apparatus with a 0° coldfinger at 0.25 mmHg and was heated at 40−50 °C. The product was collected as a white, crystalline solid on the coldfinger. A total of 1.6 g (53%) of product was collected from several distillations in the sublimation apparatus. ^{1}H NMR (CD_2Cl_2, 300 MHz): d 1.24 (t, J = 7.6 Hz, 6H), 2.64 (q, J = 7.6 Hz, 4H), 6.83 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 2H).

***p*-Carboxybenzyldimethylsulfonium Chloride 8.** *p*-Carboxybenzyl chloride **4** (1.7 g, 10 mmol) was dissolved in 20 mL (340 mmol) of dimethyl sulfide and 4 mL of ethanol in a 100 mL round-bottom flask with a stir bar and reflux condenser. The solution was stirred and immersed in an oil bath at 55−60 °C and refluxed for 7−10 days during which time a white precipitate formed. The solvent was evaporated, and the resulting solid was dissolved in 50 mL of hot ethanol. The ethanol was poured into a 500 mL beaker containing 250 mL of ethyl acetate resulting in the formation of bright, white crystals. The crystals were filtered and washed with three 25 mL portions of ethyl acetate and two 20 mL portions of hexanes and dried under vacuum yielding 2.0 g (86%) of pure product. ^{1}H NMR (DMSO-d_6, 300 MHz): d 2.89 (s, 6H), 4.90 (s, 2H), 7.61 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H), 13.2 (bs, 1H).

2,6-Dimethylphenoxide (10) Oxygen and Para Alkylation Products with 4. *p*-Carboxybenzyl chloride **4** (514 mg, 3.0 mmol) and 1.5

(40) Wall, L. *Perl*, 5th ed.; O'Reilly: Sebastopol, CA, 1994.
(41) Walters, P.; Stahl, M. *Babel*; University of Arizona: Tucson, Arizona, 1994.
(42) *Xmol*; Research Equipment, Inc., Minnesota Supercomputer Center, 1993.
(43) LeNoble, W. J. L.; Hayakawa, T.; Sen, A. K.; Tatsukami, Y. *J. Org. Chem.* **1971**, *36*, 193−196.

g (12 mmol) of 2,6-dimethylphenol were dissolved in 20 mL of absolute ethanol. Lithium hydroxide monohydrate (650 mg, 15 mmol) was dissolved in 80 mL of water freshly distilled under argon. The solutions were combined in a 250 mL round-bottom flask under argon and stirred at room temperature for 24 h. The solution was neutralized with 100 mL of 150 mM pH 7.2 phosphate buffer and extracted with three 100 mL portions of ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, and evaporated to an oily residue. Fifty milliliters of hexanes was added, and a white precipitate formed. The precipitate was filtered, washed with hexanes, and dried under vacuum to give 340 mg (44%) of a mixture of the oxygen and para alkylation products. The original aqueous layer was acidified to pH 3 with 1 M HCl and was again extracted with ethyl acetate as above yielding more product as well as starting material and hydrolysis product. The first extract containing only the two products was purified by reverse phase column chromatography eluting with 75:25:1 methanol:water:acetic acid.

Oxygen Alkylation Product 16. mp = 153−155 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.23 (s, 6H), 4.87 (s, 2H), 6.95 (t, J = 7.4 Hz, 1H), 7.05 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 12.95 (bs, 1H).

Para Carbon Alkylation Product 17. mp = 189−191 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.09 (s, 6H), 3.81 (s, 2H), 6.75 (s, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 8.02 (s, 1H), 12.71 (bs, 1H).

3,5-Dimethylphenoxide (13) Oxygen, Ortho and Para Alkylation Products with 4. *p*-Carboxybenzyl chloride **4** (1.7 g, 10 mmol) and 6.25 g (50 mmol) of 3,5-dimethylphenol were dissolved in 10 mL of absolute ethanol in a 250 mL round-bottom flask with a stir bar under argon. Lithium hydroxide monohydrate (2.6 g, 62 mmol) was dissolved in 100 mL of water freshly distilled under argon and added to the flask. The solution was stirred at room temperature for 24 h. About 3 mL of concentrated HCl was added to bring the solution to a pH of about 8−9. One-hundred milliliters of 140 mM pH 7.2 phosphate buffer was then added, and the solution was extracted with one 100 mL and three 50 mL portions of methylene chloride followed by one 100 mL and three 50 mL portions of ethyl acetate. The aqueous layer was then acidified with concentrated HCl to pH 2 and extracted again with ethyl acetate as above. Each set of extracts was combined, dried over sodium sulfate, and evaporated. The residue from the methylene chloride extracts, containing unreacted 3,5-dimethylphenol and the oxygen alkylation product, was triturated in 60 mL of hot hexanes, cooled, and the solid filtered resulting in about 400 mg (16%) of pure oxygen alkylation product. The residue from the first (neutral) ethyl acetate extract contained a mixture of all three products. Crude yield was high (>75%); however, separation of the ortho and para alkylation products was difficult, but small amounts of the pure products were finally obtained by reverse phase (RP-18) preparative HPLC (Dynamax 21.4 mm i.d., 250 mm L, 100 Å pore size, 5 mm particle size) eluting at 6 mL/min with a continuous gradient from 50:50 to 90:10 methanol/pH 3 25 mM phosphate buffer. From 150 mg of the mixture, about 35 mg (23%) of the ortho product and 16 mg (11%) of the para product were obtained pure off of the column.

Oxygen Alkylation Product 18. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.21 (s, 6H), 5.13 (s, 2H), 6.58 (s, 1H), 6.63 (s, 2H), 7.53 (d, J = 8.3, 2H), 7.94 (d, J = 8.3 Hz, 2H), 12.93 (bs, 1H).

Para Carbon Alkylation Product 19. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.07 (s, 6H), 3.94 (s, 2H), 6.46 (s, 2H), 7.08 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 9.05 (s, 1H), 12.7 (bs, 1H).

Ortho Carbon Alkylation Product 20. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.07 (s, 3H), 2.15 (s, 3H), 3.94 (s, 2H), 6.44 (s, 1H), 6.52 (s, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 9.22 (s, 1H), 12.70 (bs, 1H).

2,6-Diethylphenoxide (14) Oxygen, Ortho and Para Alkylation Products with 4. *p*-Carboxybenzyl chloride **4** (0.50 g, 3 mmol), 2.0 g (13 mmol) of 2,6-diethylphenol, and 0.56 g (13 mmol) of lithium hydroxide monohydrate were dissolved in 150 mL of water freshly distilled under argon in a 250 mL round-bottom flask with a stir bar. The solution was warmed to 90 °C for 2 h. The solution was extracted with two 100 mL portions of methylene chloride while still basic to remove unreacted phenol. The aqueous solution was then neutralized with 150 mL of 140 mM pH 7.2 phosphate buffer and extracted with three 100 mL portions of ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, and evaporated to a residue containing a mixture of the three products and some phenol. The residue was dissolved in 25 mL of methylene chloride and poured into 100 mL of hexanes upon which a white precipitate formed. The precipitated was filtered and washed with hexanes to yield 275 mg (32%) of a mixture of the three products (the rest of the products remained with the starting material and some hydrolysis product in the aqueous layer). The 275 mg (0.97 mmol) of product mixture was dissolved in 40 mL of freshly distilled methylene chloride in an oven-dried 250 mL round-bottom flask under argon. One gram (9.0 mmol) of *N*-hydroxysuccinimide and 575 mg (3 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and the previous product were stirred at room temperature for 4 h. The resulting hydroxysuccinimide esters were purified by silica gel chromatography eluting with methylene chloride with 2% ethyl acetate. The pure fractions were evaporated and then dissolved in 25 mL of 1 M sodium hydroxide, acidified with concentrated HCl, extracted with ethyl acetate, dried over sodium sulfate, and evaporated. The ether product and the para product were obtained pure by this procedure, but the ortho cyclohexadienone product had some impurity, presumably a decomposition product due the photosensitivity of cyclohexadienones. Final purification of the dienone was achieved by reverse phase column chromatography eluting with a gradient from 60:40 to 75:25 methanol:water with 1% acetic acid. The ortho product must be kept in the dark.

Oxygen Alkylation Product 21. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, J = 7.6 Hz, 6H), 2.70 (q, J = 7.6 Hz, 4H), 4.92 (s, 2H), 7.10 (m, 3H), 7.61 (d, J = 8.3 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H).

Para Carbon Alkylation Product 22. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.6 Hz, 6H), 2.59 (q, J = 7.6 Hz, 4H), 3.95 (s, 2H), 6.81 (s, 2H), 7.26 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H).

Ortho Carbon Alkylation Product 23. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.58 (dq, J = 5.6 Hz, 7.5 Hz, 1H), 2.09 (dq, J = 5.6 Hz, 7.5 Hz, 1H), 2.20 (q, J = 7.5 Hz, 2H), 2.75 (d, J = 12.7 Hz, 1H), 3.25 (d, J = 12.7 Hz, 1H), 6.20 (m, 2H), 6.56 (m, 1H), 7.10 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H).

2,6-Diisopropylphenoxide (15) Oxygen, Ortho and Para Alkylation Products with 4. *p*-Carboxybenzyl chloride (614 mg, 3.6 mmol), 2.0 mL (13 mmol) of 2,6-diisopropylphenol, and 606 mg (15 mmol) of lithium hydroxide monohydrate were dissolved in 150 mL of water freshly distilled under argon in a 250 mL round-bottom flask with a stir bar. The solution was warmed to 90 °C for 8 h. The solution was extracted with two 50 mL portions of ethyl acetate while still basic to remove unreacted 2,6-diisopropylphenol. The aqueous solution was then neutralized with 150 mL of 140 mM pH 7.2 phosphate buffer and extracted with three 50 mL portions of ethyl acetate. The neutral ethyl acetate extracts were combined, dried over sodium sulfate, and evaporated to give about 300 mg (27%) of a yellowish solid containing a mixture of the three products. The 275 mg (0.97 mmol) of product mixture was dissolved in 40 mL of freshly distilled methylene chloride in an oven-dried 250 mL round-bottom flask under argon. One gram (9.0 mmol) of *N*-hydroxysuccinimide and 500 mg (2.6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) were added, and the solution was stirred at room temperature for 4 h. The resulting hydroxysuccinimide esters were purified by silica gel chromatography eluting with methylene chloride. The pure fractions were evaporated and then dissolved in 25 mL of 1 M sodium hydroxide,

acidified with concentrated HCl, extracted with ethyl acetate, dried over sodium sulfate, and evaporated. Ninety-five milligrams (32%) of the ether product and 37 mg (12%) of the para product slightly impure with the ether were obtained. The dienone was not isolable by this method, but could be positively identified by its crude ^{1}H NMR spectrum.

Oxygen Alkylation Product 24. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (s, 6H), 1.18 (s, 6H), 3.27 (m, 2H), 4.85 (s, 2H), 7.13 (m, 3H), 7.60 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H), 12.9 (bs, 1H).

Para Carbon Alkylation Product 25. ^{1}H NMR (CD_3CN, 300 MHz): δ 1.15 (d, J = 6.8 Hz, 12H), 3.17 (m, 2H), 3.91 (s, 2H), 5.85 (bs, 1H), 6.91 (s, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H).

Ortho Carbon Alkylation Product 26. ^{1}H NMR (CD_3CN, 300 MHz): δ 0.69 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 2.20 (m, 1H), 2.75 (m, 1H), 3.02 (d, J = 12.4 Hz, 1H), 3.15 (d, J = 12.4 Hz, 1H), 6.25 (dd, J = 6.2 Hz, 9.6 Hz, 1H), 6.40 (d, J = 9.6 Hz, 1H), 6.49 (d, J = 6.2 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H).

Acknowledgment. We thank Professor Richard Friesner for making his computer programs and expertise available. Support of this work by the NIH, the NSF, and the EPA is gratefully acknowledged.

JA012293H