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MOLECULAR AGGREGATION AND ITS APPLICABILITY TO SYNTHESIS.

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Summary: The rates of intermolecular Diels-Alder reactions involving relatively hydrophobic dienes and dienophiles are significantly increased if these reactions are carried out in ethylene glycol. These rate enhancements are most easily understood in terms of aggregation phenomena

The rate of a bimolecular reaction is controlled by its specific rate constant and by the concentrations of the reacting species In practice, the specific rate constants for these reactions are rarely constant, but instead vary substantially with changes in temperature, pressure and/or solvent. Because of this, systematic variation of one or more of these parameters can oftentimes provide one with useful insight into the mechanism of the reaction under study For example, it is well-accepted that if increases in solvent polarity are accompanied by significant increases in the observed rate of a reaction, then the transition state probably possesses polar character Conversely, the absence of solvent effects in a reaction has been generally correlated with transition states in which no net charge develops (e g , most concerted reactions).

Perhaps the prototypical example of the latter situation is the Diels-Alder reaction. For instance, in the dimerization of cyclopentadiene, solvent variations over a series ranging in polarity from hexane to water alter the observed reaction rate only by a factor of four[1] As a consequence of this and other similar results, synthetic optimization studies of Diels-Alder reactions rarely include the solvent as one of their important variables However, some notable exceptions to this have been reported in recent years.

In a series of papers Breslow and co-workers reported that the rates of certain Diels-Alder reactions could

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be enhanced by as much as two hundred fold when carried out in water instead of acetonitrile[2] Based on their

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and his co-workers, the rates of Diels-Alder reactions involving dienes which possess carboxylic acid (or carboxylate) head groups were found to be significantly increased when the reactions were performed in an

[redacted]

Unfortunately, when we attempted to run the Diels-Alder reaction of carbonate diene 1 and 2,6-dimethylbenzoquinone, 2, in water, *not only was no rate enhancement observed relative to the same reaction performed in benzene, no reaction was observed!* This was presumably due to the total insolubility of 1 in water associated with disruptions to the hydrogen bonding network. Since each hydrogen bond contributes three to five kcal/mole in stabilization energy, it follows that, when molecular aggregates form, their volume will be kept to a minimum.

Extrapolation of this concept to the extreme, i.e., a two molecule aggregate consisting of one diene and one dienophile, although simplistic, is nonetheless instructive. As depicted in Figure 1, the volume of the π-stacked arrangements of dienophile and diene (particularly in its s-*cis* form) is smaller than the corresponding end-on arrangements. Since at least some of these π-stacked arrangements of diene and dienophile correspond to orientations suitable for reaction, the relative concentrations of productive arrangements of diene and dienophile are larger and, as a consequence, the observed rates of these reactions are higher. Studies which attempts to verify this hypothesis experimentally will be the subject of future reports.

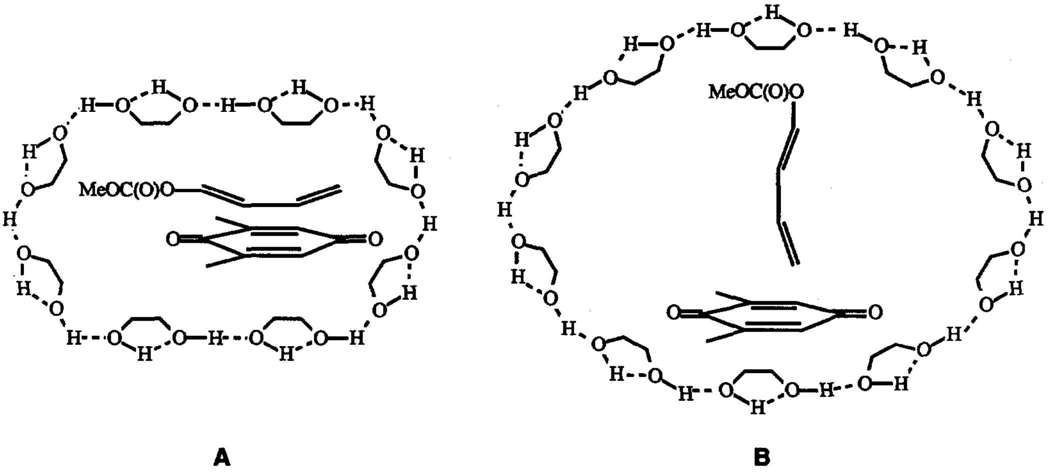

Figure 1. A. π-stacked arrangement; B. end-on arrangement.

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References and Notes

1. A. Wasserman, *Monatsh.*, **83**, 543 (1952).
2. (a) R. Breslow and D. Rideout, *J. Am. Chem. Soc.*, **102**, 7816 (1980).
   (b) R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, **24**, 1901 (1983).
   (c) R. Breslow and U. Maitra, *Tetrahedron Lett.*, **25**, 1239 (1984).
3. (a) P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, **48**, 3137 (1983).
   (b) P. A. Grieco, K. Yoshida and J. Huffman, *Tetrahedron Lett.*, **24**, 3087 (1983).
   (c) P. A. Grieco and K. Yoshida, *J. Org. Chem.*, **49**, 5257 (1984).
   (d) P. A. Grieco and S. D. Larsen, *J. Am. Chem. Soc.*, **107**, 1768 (1985).
   (e) P. A. Grieco, P. Galatsis and R. F. Spohn, *Tetrahedron,* **42**, 2847 (1986).
4. For some related studies, see:
   (a) X. K. Jiang, W. Fan and Y. Hui, *J. Am. Chem. Soc.*, **106**, 3839 (1984).
   (b) H. Schneider and N. K. Sangwan, *Angew. Chem. Internat. Ed. Engl.*, **26**, 896 (1987).
5. Most of the substrates in Table 2 are only sparingly soluble in ethylene glycol at 25°C, but soluble at reflux.
6. D. Liotta, M. Saindane and C. Barnum, *J. Am. Chem. Soc.*, **103**, 3224 (1981).
7. The lack of any obvious correlation with solvent dielectric constants only reinforces this belief.

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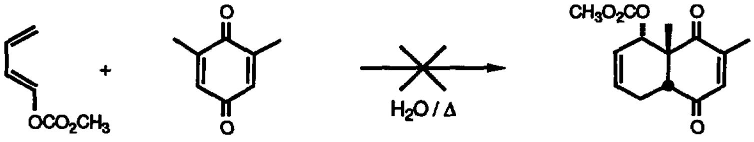
Attempts with a number of other hydrophobic diene/dienophile combinations in water also suffered the same fate. These results suggest that the success of the Grieco and Breslow procedures depends heavily on the condition that both the diene and the dienophile possess at least limited solubility in (hot) water.



1 **2** **3**

In an attempt to ascertain whether any other solvents might enhance the rates of hydrophobic Diels-Alder reactions, we examined the reaction of **1** with **2** in a variety of solvents. The results of this study are shown in Table 1. Clearly, performing this reaction in ethylene glycol provided a substantial rate enhancement (26.1) relative to benzene. In retrospect, this may not be surprising since this solvent possesses almost as extensive a hydrogen bonding network as water, as well as a small carbon backbone which could help solubilize hydrophobic dienes and dienophiles.[5]

Table 1

Solvent	**Dielectric Constant**	**Relative Rate**[A]
Benzene-d_6	2.3	1.0
Acetonitrile-d_3	36.2	1.8
Dimethylsulfoxide-d_6	46.6	3.1
Methanol-d_4	32.6	4.1
D_2O	78.0	no reaction
Ethylene glycol	37.7	26.1

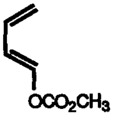
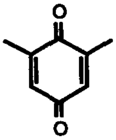
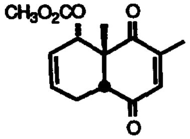
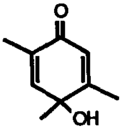
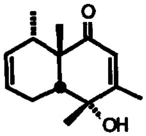
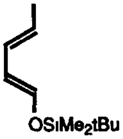
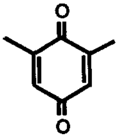
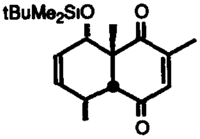
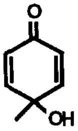
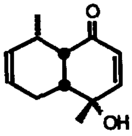
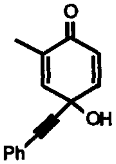
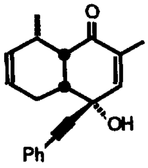
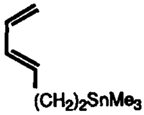
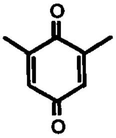
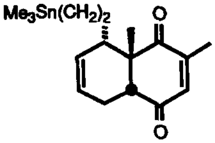
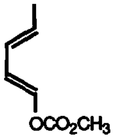
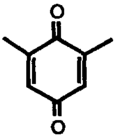
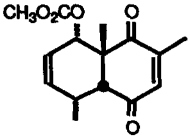
A. All reaction rates were determined by NMR.

A more extensive survey of the type of rate enhancements which are observed by performing Diels-Alder reactions of quinones and quinols[6] in ethylene glycol versus benzene is given in Table 2. In general, these rate enhancements range from one to several orders of magnitude. The only apparent exception to this is the reaction given in Entry 3. However, control experiments show that in refluxing ethylene glycol decomposition of the siloxydiene is competitive with the Diels-Alder reaction. Not surprisingly, when more solvolytically-labile dienes were employed (e.g., 1-ethoxy-1-trimethylsiloxy-2-methylbutadiene), diene decomposition became the exclusive reaction pathway.

Like the Breslow and Grieco groups, we feel that molecular aggregation is one of the important factors responsible for the observed rate acceleration.[7] However, if these accelerations were simply the result of an increase in the effective molarity of the reactants, then the rates of these reactions in ethylene glycol should not exceed the rates of corresponding reactions performed neat. Surprisingly, *the rate of the neat reaction of **1** with **2** is at least an order of magnitude slower that the rate observed in ethylene glycol*. This suggests that some other factor must be responsible for the rate enhancement. We believe that this factor is entropic in origin.

In principle, since hydrophobic molecules prefer to be solvated by other hydrophobic molecules, molecular aggregates of variable compositions and volumes could form. However, the stabilization energy associated with these favorable hydrophobic-hydrophobic interactions will be offset by the destabilization

Table 2

Entry	Diene	Dienophile	Temp (°C)	Time (hr)	Product	%Yield
1			100	0 50 0 50		$0^{A,C}$ $100^{B,C}$
2			150	5 75 5 75		$0^{A,C}$ $62^{B,E}$
3^{D}			95	7 7		$38^{A,E}$ $51^{B,E}$
4			140	3 3 22		$10^{A,C}$ $100^{B,C}$ $85^{A,E}$
5			150	6 6		$0^{A,C}$ $100^{B,C}$
6			100	2 2		$0^{A,C}$ $100^{B,C}$
7^{D}			95	93 22		$25^{A,E}$ $71^{B,E}$

A Reaction performed in benzene
B Reaction performed in ethylene glycol
C Yield determined by NMR
D Since the diene was an E/Z mixture, an appropriate excess was used
E Isolated yield