hydrolysis (trifluoracetic acid–water 60:40, 12 h, 25 °C) to give the aldehyde **9**. [^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1 H)], which was readily isomerised by triethylamine in $CHCl_3$ (15 min, 60 °C) to **10** [IR ($CHCl_3$) 3360, 1784, 1722, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.67 (s, 3 H), 1.84 (s, 3 H), 2.14 (s, 3 H), 5.08 (s, 2 H), 7.27 (s, 5 H), 7.3–8.0 (m, 5 H), 9.62 (s, 1 H); MS *m/e* 434 (M^+), 343, 315, 147, 104].

The most reasonable explanation of these results is that the sulfenic acid derived from **4** undergoes base-catalyzed ring opening to sulfine **8** which was isolated or alternatively isomerized to **11** and, after ring opening to **12**, underwent 1,3-dipolar cycloaddition to the isolated **5** (Scheme I). Attempts to effect isomerization of 8 to 12 with various bases merely led to a generalized decomposition.

We conclude that base-catalyzed ring opening of azetidinone sulfenic acids gives sulfines, which may be isolated or intercepted as their intramolecular 1,3-dipolar adducts.

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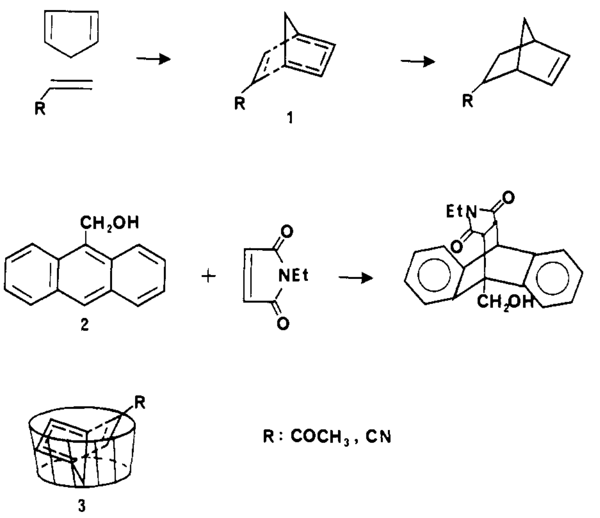
Hydrophobic Acceleration of Diels–Alder Reactions

Sir:

When substances with nonpolar regions are dissolved in water, they tend to associate so as to diminish the hydrocarbon–water interfacial area. This "hydrophobic effect"[1] is a principal contributor to substrate binding in enzymes and to the self-association of amphiphiles in micelles or membranes. Curiously, however, hydrophobic effects have not been reported, to our knowledge, for any typical bimolecular chemical reaction of small molecules in aqueous solution except for cases[2] in which long hydrocarbon chains are arbitrarily present to promote association. Since in the Diels–Alder reaction of, e.g., cyclopentadiene with butenone the transition state **1** brings together two nonpolar groups, one might expect that in water this reaction could be accelerated by hydrophobic interactions. We wish to report that this is indeed the case, both for simple hydrophobic binding and for mutual hydrophobic binding into a cyclodextrin cavity.

The reaction of cyclopentadiene (0.4 mM) with butenone (12.1 mM and 25.5 mM) was followed at 250 nm and 20.0 °C in water and showed first-order disappearance of cyclopentadiene over two half-lives. The pseudo-first-order rate constant was also first order in butenone, giving a second-order rate constant k_2 of $4.40 \pm 0.07 \times 10^{-2}\ M^{-1}\ s^{-1}$. This rate constant is listed in Table I along with the other rate constants determined for this reaction in other media and for the other Diels–Alder reactions we have examined. As this table shows, the reaction with butenone shows more than a 700-fold acceleration in water compared with the rate in 2,2,4-trimethylpentane. The rate in methanol is intermediate, but closer to that in the hydrocarbon solvent.

Lithium chloride is a salt which increases[3] the hydrophobic effect, i.e., it "salts out" nonpolar materials dissolved in water. As expected from this, we get an increase in the rate of the Diels–Alder reaction with 4.86 M LiCl over that in water alone. Guanidinium chloride is similar to urea in changing the water structure so that it normally decreases[3] hydrophobic interactions; i.e., it "salts in" nonpolar material. We find (Table I) that 4.86 M guanidinium chloride does not increase the Diels–Alder rate over that in water. The contrast with LiCl is as expected for a hydrophobic effect, although the absence of a rate decrease[4] with guanidinium was not expected.



The Diels–Alder reaction of cyclopentadiene with acrylonitrile (Table I) shows only a small rate increase on changing the solvent from hydrocarbon to methanol but a much larger increase with water. Again it seems likely that this large increase in water is not simply a polar effect in a reaction which shows little sensitivity to the polarity of the other two solvents but is a specific hydrophobic effect. The most striking evidence of this comes from our study (Table I) on the Diels–Alder reaction of anthracene-9-carbinol (**2**) with *N*-ethylmaleimide. This reaction is *slower* in polar solvents than it is in nonpolar hydrocarbon solution,[5] with the exception of water in which the rate is very fast. Only the hydrophobic effect seems capable of explaining this exceptional behavior of water.

Molecular models suggest that the transition states (**1**) for reaction of cyclopentadiene with butenone and acrylonitrile should be able to fit (cf. **3**) into the hydrophobic cavity of β-cyclodextrin (cycloheptaamylose) but not in the smaller cavity of α-cyclodextrin (cyclohexaamylose). The data in Table I indicate that this is correct. The two reactions are both even faster when 10 mM β-cyclodextrin is added to the water but slower with 5 or 10 mM α-cyclodextrin.[6] This inhibition by α-cyclodextrin is expected since cyclopentadiene can bind to it, but in this small cavity there is then no room for the dienophile. For the larger transition state in the anthracene-9-carbinol reaction, even β-cyclodextrin is unable to bind both diene and dienophile and is an inhibitor, not a catalyst.

The catalytic effect of β-cyclodextrin is even larger than is apparent from the data in Table I. The rates increase with increasing β-cyclodextrin concentration with no indication of kinetic saturation, so at 10 mM β-cyclodextrin we are far from V_{max}. Furthermore the hydrophobic binding of diene plus dienophile into a cyclodextrin cavity in water largely replaces the association because of hydrophobic interaction in water alone which we have already discussed earlier. Thus the catalysis of the Diels–Alder reactions of cyclopentadiene by mutual binding

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(1) For reviews, see: (a) Ben-Naim, A. "Hydrophobic Interactions"; Plenum Press: New York, 1980. (b) Tanford, C. "The Hydrophobic Effect", 2nd ed.; Wiley: New York, 1980.

(2) Reference 1a, p 97, and references therein.

(3) von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, *2*, 257.

(4) Urea at 5.38 M also gave at most a slight decrease in the rate.

(5) The decrease probably reflects hydrogen bonding between diene and dienophile in the transition state which is less effective in more polar solvents.

(6) One might in general expect some change in exo–endo product ratios for reactions which are hydrophobically accelerated by water or by cyclodextrin binding, but we have not yet seen large clear trends. Furthermore, reaction in a cyclodextrin cavity might induce chirality in the product. We do see some optical activity in the cyclopentadiene–butenone adducts, but it corresponds to only a few percent enantiomeric excess.

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Table I. Rate Constants for Diels-Alder Reactions

solvent	additional component	$k_2 \times 10^5$, $M^{-1}\ s^{-1}$[a]
(a) Cyclopentadiene + Butenone, 20 °C		
isooctane[b]		5.94 ± 0.3
MeOH		75.5
H_2O		4400 ± 70
H_2O	LiCl (4.86 M)	10800
H_2O	$C(NH_2)_3{}^+Cl^-$ (4.86 M)	4300
H_2O	β-cyclodextrin (10 mM)[c,f]	10900
H_2O	α-cyclodextrin (10 mM)[c,f]	2610
(b) Cyclopentadiene + Acrylonitrile, 30 °C		
isooctane[b]		1.9
MeOH		4.0
H_2O		59.3
H_2O	β-cyclodextrin (10 mM)[d,f]	537
H_2O	α-cyclodextrin (5 mM)[d,f]	47.9
(c) Anthracene-9-carbinol + *N*-Ethylmaleimide, 45 °C		
isooctane[b]		796 ± 71
1-butanol		666 ± 23
MeOH		344 ± 25
CH_3CN		107 ± 8
H_2O		22600 ± 700
H_2O	β-cyclodextrin (10 mM)[e]	13800

[a] Second-order rate constants. All data are the result of at least three runs at a given set of concentrations; error limits are given for cases in which triplicate runs were performed at more than one dienophile concentration. [b] 2,2,4-Trimethylpentane, >99% pure. [c] Initial conditions: cyclopentadiene (0.4 mM), butenone (10 mM). [d] Initial conditions; cyclopentadiene (0.4 mM), acrylonitrile (200 mM). [e] Initial conditions: anthracenecarbinol (0.03 mM), *N*-ethylmaleimide (1.0 mM). [f] The reactions were actually performed with 1 mol % of methanol and small amounts of HCl or formate buffer present; these had no effect on the reaction rate in pure water.

of reagents into a cyclodextrin cavity, compared with the reaction of *unassociated* molecules, is considerable.[7]

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(7) We acknowledge support of this work by the National Institutes of Health and an NSF Predoctoral Fellowship to D.C.R.

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Temperature and Matrix Effects on Migratory Aptitude and Stereochemistry in 1,2-Migration to a Divalent Carbon

Sir:

The 1,2-migration to divalent carbon generating an alkene has been of theoretical and synthetical interest, and hence considerable efforts[1] have been made to clarify the stereochemistry, migratory aptitude, and roles of multiplicity in the rearrangement. During the course of our studies[2] on the effect of temperature on carbene processes, we found that the migratory aptitude as well as the stereochemistry of a 1,2-H shift is highly sensitive to temperature and the reaction phase. The results provide important information concerning energetic and conformational controls in the carbenic rearrangement.

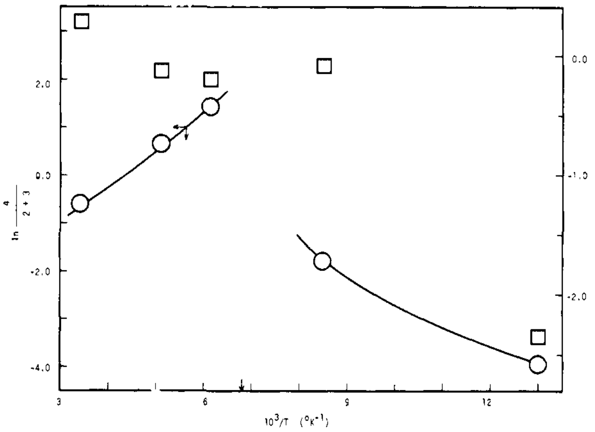
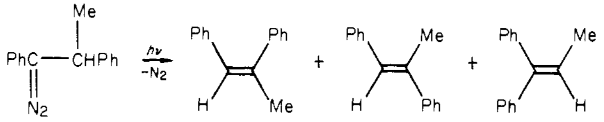


Figure 1. ln ([Ph migration product]/[H migration product]) (○) and ln {[(*E*)-olefin]/[(*Z*)-olefin]} (□) as a function of temperature in the photolysis of 1 in methylcyclohexane. Arrows show the freezing point of the solvent.

Direct irradiation of 1,2-diphenyl-1-diazopropane (**1**)[3] in methylcyclohexane in a sealed Pyrex tube was carried out with a 300-W high-pressure Hg lamp until all of the diazo compound was destroyed. A Corning CS-052 filter (**1**)[3] in cutoff at 350 nm was used in order to avoid product isomerization.[5] GC analysis of the reaction mixture showed that three olefins, i.e., 1,2-diphenylpropenes **2** and **3** and 1,1-diphenyl-1-propene (**4**), are formed in roughly equal amounts at ambient temperature along with α-phenylpropiophenone and its azine. Temperature studies



(1)

1 **2** **3** **4**

(+20 to −196 °C) revealed, however, that the relative amounts of olefins **2** and **3**, which result from H migration, and **4**, which results from phenyl migration, vary dramatically with temperature (Figure 1). Thus, as temperature decreases, phenyl migration product continues to increase as far as the solvent is fluid (81% at −110 °C), but its formation becomes remarkably suppressed once the environment becomes solid and is almost completely eliminated (<2%) at −196 °C.

Predominant Ph migration over H migration in a lower temperature liquid is quite interesting since the sequence of migratory aptitutde prevailing in ambient-temperature chemistry was given[6] as H > Ph > Me and since, moreover, it has often been assumed[1a,7] that 1,2-H migrations occur with essentially zero activation energy. Apparently, however, the phenomenon is interpretable as indicating that the activation energy for H migration marginally exceeds that for Ph migration. Drastic decrease in the formation of **4** in a low-temperature solid phase, in spite of the energetic advantage, is then ascribable not to a simple temperature effect but totally to a matrix effect (a change in environment). In a matrix environment, for example, in which molecular motions are known[8] to be severely restricted, migration of a larger group (Ph) becomes effectively suppressed, whereas migration of an extremely small particle (H) is still significant even at this low temperature.

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(1) For pertinent reviews, see: (a) Schaeffer, H. F., III. *Acc. Chem. Res.* **1979**, *12*, 288. (b) Moss, R. A.; Jones, M., Eds. "Carbenes"; Wiley: New York, 1973, 1975; Vol. I, II. (c) Kirmse, W., Ed. "Carbene Chemistry"; Academic Press: New York, 1971.

(2) (a) Tomioka, H.; Izawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 6128. (b) Tomioka, H. *Ibid*, **1979**, *101*, 256. (c) Tomioka, H.; Griffin, G. W.; Nishiyama, K. *Ibid.* **1979**, *101*, 6009. (d) Tomioka, H.; Inagaki, T.; Nakamura, S.; Izawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 130. (e) Tomioka, H.; Suzuki, S.; Izawa, Y. *Chem. Lett.* **1980**, 293. (f) Tomioka, H.; Miwa, T.; Suzuki, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753.

(3) All diazo compounds used in this study were prepared[4] by oxidation of the corresponding hydrazones and purified just before use. That no olefins were present before irradiation was easily shown by NMR.

(4) Pomerantz, M.; Witherup, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 5977.

(5) A control experiment indicated that the product olefins did not isomerize under these conditions.

(6) (a) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159. (b) Philp, B. H.; Keating, J. *Tetrahedron Lett.* **1961**, 523.

(7) This result is supported by MINDO calculations: Kyba, E. P. *J. Am. Chem. Soc.* 1977, *99*, 8330.

(8) See, for example: Wasserman, E.; Yager, W. A. *J. Phys. Chem.* **1967**, *71*, 201.

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