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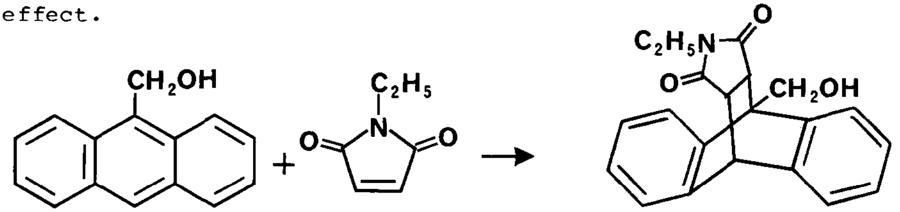
SELECTIVE DIELS-ALDER REACTIONS IN AQUEOUS SOLUTIONS AND SUSPENSIONS

Ronald Breslow*, Uday Maitra, and Darryl Rideout
Department of Chemistry, Columbia University, New York, NY 10027

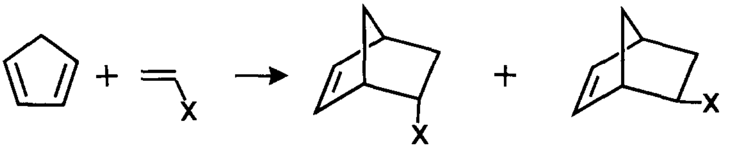
Diels-Alder reactions show high endo/exo selectivities in aqueous suspensions.

We have described[1] the very large rate accelerations which occur when some common Diels-Alder reactions are performed in water solution. The principal effect was ascribed to hydrophobic association of the diene with the dienophile. As further evidence for this, we find that the Diels-Alder reaction between N-ethylmaleimide and hydroxymethylanthracene (Scheme 1) at 45°C, whose second-order rate constant in water is over 200 times as large as that in acetonitrile,[1] shows the expected effects of dissolved salts. With 4.86 M lithium chloride the rate in water at 45°C is increased by 2.5 fold; lithium chloride is a solute which increases hydrophobic effects, decreasing the solubility of hydrocarbons in water.[2] By contrast, with 4.86 M guanidinium perchlorate in water the reaction of Scheme 1 at 45°C is 3.0 fold slower than in water. Guanidinium perchlorate as a solute decreases hydrophobic effects, increasing the water solubility of butane and of toluene.[3] Thus with the reaction of Scheme 1, for which polar solvents except for water slowed the rate, it seems clear that the special effect of water is due to the hydrophobic effect.



(1)

We have now examined the product ratios for several Diels-Alder reactions of cyclopentadiene, which can give endo or exo addition of dienophiles (Scheme 2). We find that some of them show large increases in the endo/exo ratio in water solution,[4] presumably related to the known effects[5] of polar media on such ratios and the need to minimize transition state surface area in water solution. Remarkably, these effects persist even with relatively insoluble systems, when two separate phases are present.



(2)

The data in Table 1 show that the reaction of cyclopentadiene with butenone shows an endo/exo ratio of only 3.85 in excess cyclopentadiene as solvent, but the ratio climbs to 21.4 when diene and dienophile are stirred at 0.15 M concentration in H_2O. This is only the formal concentration; butenone is completely soluble but cyclopentadiene has a solubility[6] of only ca. 0.01 M in water, so most of the cyclopentadiene is present as a second phase. The results are similar to the ratio (22.5) obtained at low (0.007 M) concentration with a true solution. Even more striking is the result with dimethyl maleate, which is poorly water soluble. Although the bulk of both diene and dienophile are present as a separate phase, the reaction in water suspension is quite selective. At higher concentrations the reaction in this separate phase begins to show up in a decreased ratio, but even at 0.48 M the selectivity with butenone is strikingly high.

A 1939 patent[7] reports that Diels-Alder reactions can be performed with yield advantage in aqueous detergent solutions. Accordingly, we have examined our reactions with the additions of sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB). As Table 1 shows, the detergent had little effect on the product ratios, and brought no advantage. Furthermore, rough rate studies on these stirred inhomogeneous reactions with 0.15 M cyclopentadiene and 0.15 M dienophile showed that 0.02 M SDS gave only a slight (ca. 15%) increase in velocity. Thus in our systems the addition of the detergent is pointless. It was also recently reported[8] that endo/exo ratios can be altered by performing Diels-Alder reactions in microemulsions: mixtures of water, toluene, and 2-propanol. In Table 1 we list the ratios in the three reported systems with and without detergents. These show poor selectivity compared with simple H_2O.

Even with a considerable layer of "neat" diene-dienophile solution the selectivities suggest that much of the reaction occurs in or at the water phase. This is consistent with our rough rate measurements. An undiluted equimolar mixture of cyclopentadiene and butenone at 20° is 50% reacted (loss of diene chromophore) in ca. 35-40 minutes, while in a well-stirred aqueous emulsion of 0.15 M of each component the 50% point is reached in 10-15 minutes. Since the thermodynamic activity of solute in water solution cannot

Table 1.

Endo/Exo Product Ratios[a] in Diels-Alder Reactions of Cyclopentadiene in Organic Media, in Water, in Aqueous Detergent Solutions, and in Microemulsions, at ca. 25°C.

	Medium	Formal Concentration of Diene and of Dienophile (M)	Dienophile			
			Butenone	Methyl Acrylate	Dimethyl Maleate	Methyl Methacrylate
1.	Cyclopentadiene[b]	Excess diene	3.85	2.9	2.8[i]	0.43
2.	Ethanol	0.15	8.5	5.2[c]	4.5	0.6(0.55[c])
3.	Water	0.15	21.4[d]	9.3	13.7[e]	1.4
4.	Water, SDS[f] (0.02 M)	0.15	19.5	8.9	10.2	1.1
5.	Water	0.30	18.6	5.9	--	--
6.	Water, SDS[f] (0.02 M)	0.30	16.0	6.2	--	--
7.	Water	0.45	17.2	--	--	--
8.	Water, SDS[f] (0.02 M)	0.48	15.0	--	--	--
9.	Water, CTAB[f] (0.02 M)	0.15	19.5	8.8	10.2	--
10.	Microemulsion[g]	0.15	7.9	4.7	--	0.58[h](0.53[i])
11.	" + SDS (0.02 M)	0.15	7.9	4.8	--	0.57[h]
12.	Small aggregates	0.15	8.1	4.9	--	0.58[h]
13.	" + SDS (0.02 M)	0.15	8.1	5.1	--	0.65[h]
14.	Ternary solution[g]	0.15	8.3	5.2	--	0.57[h]
15.	" + SDS (0.02 M)	0.15	8.3	5.2	--	0.87[h]
16.	" + CTAB (0.02 M)	0.15	8.1	--	--	0.85[h]

a. Determined by VPC analysis. Relative retention times and NMR spectra were consistent with known values. b. Data from ref. 9. c. From ref. 5. d. Yield over 80% after 3 hours. e. Yield 75% after 26 hours. f. SDS is sodium dodecyl sulfate, CTAB is cetyl trimethylammonium bromide. g. As described in ref. 8, H_2O(4.74g), 2-propanol (34.8g), and toluene (43.81g) make up the water in oil microemulsion; the solution of small aggregates is 4.95 g. water, 44.54 g. 2-propanol, and 33.00 g. toluene; the ternary solution is 5.25 g. water, 55.85 g. 2-propanol, and 20.11 g. toluene. In our reactions, 6 mmol each of diene and dienophile was added to 40 ml of the above solutions at room temperature, and analyzed after 2-5 hours. h. Data from ref. 8. i. Our value.

exceed that of the neat phase with which it is equilibrated, we ascribe the extra rate in this case to a polar solvent effect superimposed on an "effective concentation" in water equivalent to undiluted solute. In the systems we have examined, the result is that selectivities characteristic of aqueous media are observed at concentrations well above the solubility limit. Thus water as a medium for Diels-Alder reactions, and other processes, is of practical interest even with poorly soluble substrates.[10]

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