Tetrahedron Letters,Vol.24,No.18,pp 1897-1900,1983
Printed in Great Britain 0040-4039/83/181897-04$03.00/0

"MICELLAR" CATALYSIS IN THE AQUEOUS INTERMOLECULAR DIELS-ALDER REACTION: RATE ACCELERATION AND ENHANCED SELECTIVITY

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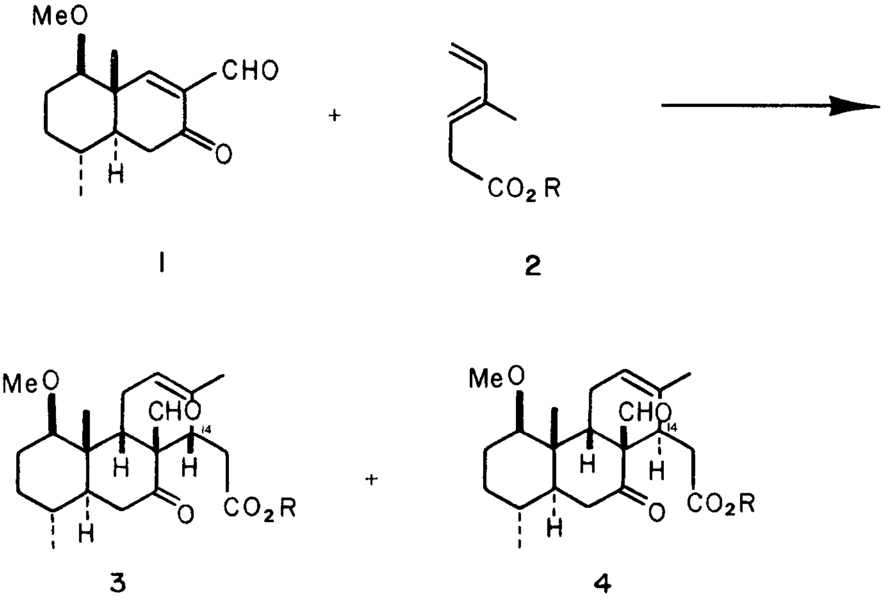
Summary: The intermolecular Diels-Alder reactions employing dienophiles 1 and 5 with diene 2 have been examined in water. The significantly enhanced rates, as well as the improved selectivity observed in water stand in sharp contrast to the results observed in hydrocarbon solvents.

As a consequence of our continuing interest in quassinoids,[1] we required substantial quantities of the Diels-Alder adduct (3). Intermolecular Diels-Alder reaction between dienophile 1[2] and diene 2 (R=Et)[3] proceeds in benzene at room temperature (see Table) giving after 288 h, a 52% yield of adducts 3 (R=Et), mp 129-130°C, and 4 (R=Et), mp 93.5-94.0°C, in a ratio of 1:1.2, along with a substantial amount of recovered dienophile.[4] In an attempt to shorten the reaction time and, more importantly, improve upon the isomer ratio, the reaction between 1 and 2 (R=Et) was examined in water.[5] The Table reveals that when the Diels-Alder reaction is carried out in water the rate of the reaction is more than doubled (288 h versus 168 h, entry 3). Also notable is the increase in the ratio of 14β-isomer 3 over the 14α-isomer 4 [0.85 (benzene) versus 1.3 (water)]. It is of



interest to note that the rate of the above aqueous reaction is not substantially different from the rate of reaction of 1 and 2 (R=Et) conducted in the absence of solvent (cf. Table, entries 2 and 3).

Diels-Alder reaction between dienophile 1 and diene acid 2 (R=H) in toluene at room temperature is sluggish (60% complete after 168 h, see Table, entry 4). On the other hand, use of water as solvent results in complete reaction after 17 h (see Table, entry 6). That the aqueous reaction [1 + 2 (R=H)] proceeds roughly twice as fast as the neat reaction (30 h, entry 5) and that water soluble cosolvents cause a five-fold reduction in rate (cf. entries 7 and 8) suggest that additional factors other than concentration may be involved.

The most dramatic results were observed during the reaction of 1 with the sodium salt of diene acid 2 (R=Na) in water at room temperature under vigorous stirring (entry 10).[6] The reaction was complete in 8h giving rise to an 83% yield of adducts 3 (R=H) and 4 (R=H) in a ratio of 2:1. The observed rate increase suggests that some type of micellar catalysis, resulting in mutual binding of reactants, is responsible for the enhanced rates.[7] Evidence in support of some sort of aggregation was obtained by varying the concentration of diene. When the reaction of 1 + 3 (R=Na) is conducted 2 M in diene the rate is approximately doubled (cf. entries 10 and 11). Of significance is the observed 3:1 ratio of adducts 3 and 4 which were obtained in quantitative yield (entry 11). A

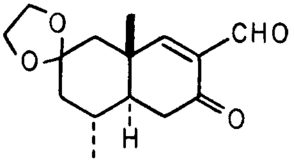
TABLE. Reaction of Dienophile 1 with Diene 2.

entry[a]	R	solvent	concentration of diene	time[b]	yield[c]	14βH/14αH[d]
1	Et	benzene	1.0 M	288 h	52%[e]	0.85
2	Et	neat	-----	144 h	69%	1.3
3	Et	water	1.0 M	168 h	82%	1.3
4	H	toluene	1.0 M	168 h	46%[e]	0.7
5	H	neat	-----	30 h	80%	1.4
6	H	water	1.0 M	17 h	85%	1.5
7	H	water-dioxane (1:1)	1.0 M	104 h	100%	0.8
8	H	water-MeOH (1:1)	1.0 M	97 h	99%	2.0
9	Na	water	0.1 M	120 h	46%[e]	0.9
10	Na	water	1.0 M	8 h	83%	2.0
11	Na	water	2.0 M	5 h	100%	3.0

[a] All reactions were run at room temperature employing a five-fold excess of diene over dineophile. [b] Reactions were judged to be complete by TLC analysis. [c] Yields reported are for chromatographically pure mixtures of C_{14} epimers. [d] Ratios were determined by NMR. [e] Starting dienophile was recovered: entry 1 (29%), entry 4 (40%), and entry 9 (14%).

greater than fifteen-fold decrease in rate accompanies the reaction that is 0.1 M in diene (compare entries 9 and 10).

Analogous results were obtained with dienophile 5.[8] Reaction of 5 with diene 2 (R=Et) [1.0 M in toluene] required heating at 100°C for 36 h to provide a 97% yield of 6 and 7 in a ratio of 1:1.1. In sharp contrast when the reaction was conducted in water (1.0 M) at room temperature employing diene 2 (R=Na), the reaction was complete in 4.5 h giving rise to a 90% yield of adducts 6 and 7 in a ratio of 3:1. Of significance once again is the change in the ratio of 6:7, 0.9 in the case of toluene as solvent versus 3.0 utilizing water.



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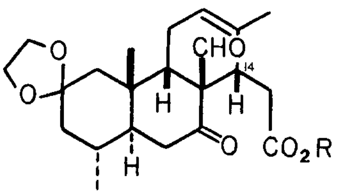

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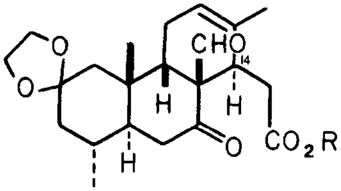

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The observed rate increases encountered above may be ascribed to the relative orientation of the reactants in a micelle, thus lowering the entropy requirements for the bimolecular reaction. We speculate that the observed increases in the 14βH/14αH ratios (compare entries 1 and 4 to 11 in the Table, and the above results with dienophile 5) might be explained in terms of transition state volume, wherein the transition state leading to formation of the 14βH isomer would occupy a smaller volume that that leading to the 14αH adduct, thus minimizing unfavorable hydrophobic interactions through more efficient aggregation (micellar packing).

Acknowledgements: This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute. We thank Professor F. Menger (Emory University) for come helpful suggestions.

References

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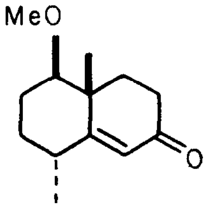
2. Enone 1, mp 101-103°C was prepared [(a) Li, NH_3, THF, t-BuOH; (b) NaH, DME, HCO_3Et; (c) DDQ, dioxane] from the known octalone i.[3]



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3. Grieco, P.A.; Vidari, G.; Ferriño, S. Tetrahedron Lett., 1980, 21, 1619.
4. The reaction of 1 and 2 (R=Et) in refluxing toluene goes to completion in ca. 40 h giving rise (90%) to adducts 3 and 4 in a ratio of 1:1.2.
5. For a recent study on the hydrophobic acceleration of an intermolecular Diels-Alder reaction in water and cyclodextrins, see: Rideout, D.C.; Breslow, R. J. Am. Chem. Soc., 1980, 102, 7816. Also see, Steinbach, D.D.; Rossana, D.M. ibid., 1982, 104, 5853.
6. Due to the heterogeneous nature of this system in water, vigorous stirring is essential. The reactions can be conducted with the aid of an ultrasonic bath giving rise to essentially identical results.
7. Cf. Fendler, J.H.; Fendler, E.J. "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, 1975. Menger, F.M. Acc. Chem. Res., 1979, 12, 111.
8. Details for the preparation of 5 will be published in the full account of this work.

(Received in USA 27 January 1983)