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ON THE ORIGIN OF PRODUCT SELECTIVITY IN AQUEOUS DIELS-ALDER REACTIONS

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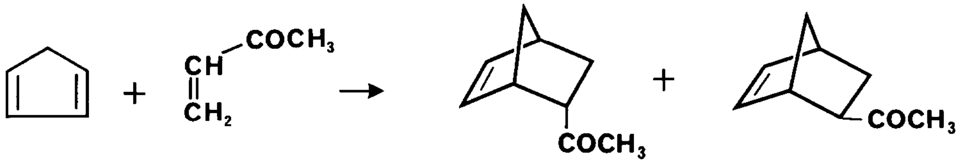
Abstract: The high endo/exo product ratio in the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone in water does not reflect aggregation, but the ratio is affected by salts which change the hydrophobicity of the medium.

Our discovery[1] that Diels-Alder reactions can be strikingly accelerated when water is the solvent has prompted us[2] and Grieco[3,4] to examine the selectivity of such aqueous reactions. As we have reported[2], striking effects are seen in the addition of cyclopentadiene to methyl vinyl ketone. In the absence of solvent, or in solution in most solvents, a modest four-fold or so preference for endo addition is seen; the endo/exo ratio climbs to over 20/1 in water solution. The results with suspensions of diene (0.15-0.45 M) were also striking, although the ratios were not as high as that with a true solution of cyclopentadiene (0.007 M) and methyl vinyl ketone in water.



We suggested that this preference for endo attack in water was the result of two factors: a polar medium increases the charge transfer interaction which results from "secondary orbital overlap" in the endo transition state, and hydrophobic effects in water favor the more compact endo transition state. Grieco has suggested[3,4] instead that the increased selectivity he observes in Diels-Alder reactions of more complex substrates reflects micellar aggregation. We have now performed experiments to distinguish among these possibilities for the cyclopentadiene reaction with methyl vinyl ketone.

Cyclopentadiene is soluble in water at 10 mM, so we have examined the products of reaction at room temperature with 10 mM methyl vinyl ketone over a cyclopentadiene range of 1 mM to 10 mM. At 1 mM and 2 mM the endo/exo ratio is 25.0 ± 0.5, at 4 mM and 8 mM it is 24.5 ± 0.4, and at 10 mM it is 24.0 ± 0.3. The change is negligible, but if anything the selectivity is less at higher concentrations at which multimolecular aggregation might occur. Thus we conclude that micellar or pre-micellar aggregation is not the cause of our selectivity.

To look for hydrophobic effects, we have examined the reaction with 1 mM cyclopentadiene and 10 mM methyl vinyl ketone in 4.86 M aqueous LiCl and in 4.86 M aqueous guanidinium chloride. As we have described[2], the well-known increased hydrophobic character of aqueous LiCl increases the rate of one of our aqueous Diels-Alder reactions, while the well-known decreased hydrophobic character of aqueous guanidinium chloride decreases the rate. In the present study the 25.0 ± 0.5 endo/exo ratio in water increased to 28 ± 0.4 in aqueous LiCl, and decreased to 22 ± 0.8 in aqueous guanidinium chloride. This is as expected if hydrophobic effects favor the endo transition state, with its smaller exposed non-polar surface. Of course these experiments do not exclude the operation of polar effects as well.

Thus we conclude that hydrophobic packing of diene and dienophile in a simple one-to-one transition state is at least part of the reason for the remarkably high product selectivity of this Diels-Alder reaction. Furthermore, our studies exclude a contribution to this high selectivity from multimolecular aggregation, as in a micelle.

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