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Hydrophobic effects in a simple Diels–Alder reaction in water

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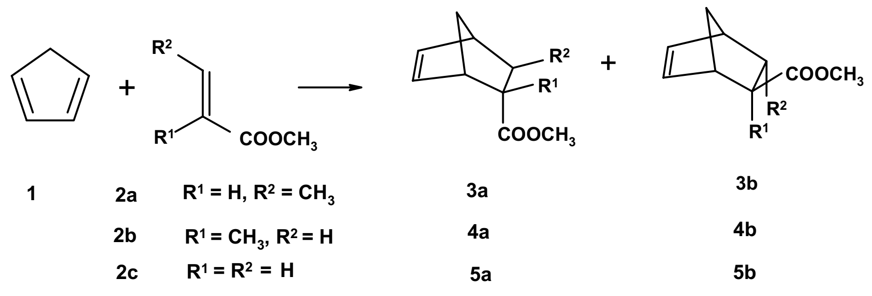
Abstract—The *endo*/*exo* ratio for a simple Diels–Alder reaction carried out in water has been used to argue that hydrophobic effects can dominate the geometries of the transition states.

In this letter, we report the stereoselectivities of a simple Diels–Alder (DA) reaction in water to demonstrate that hydrophobic packing effects can dominate the geometries of transition states. The simple explanation of stereoselectivities in DA reactions on the basis of secondary orbital interactions (SOI)[1,2] has been questioned.[3] A combination of solvent effects, steric interactions, hydrogen bonds, electrostatic interactions, etc. can be used in their place. The pioneering work of Rideout and Breslow[4] on the special role of water in DA reactions suggested that both diene and dienophile dislike water and tend to come closer (the hydrophobic effect) in order to realize the reaction at a faster rate than in the absence of water. Because of the hydrophobic packing of diene and dienophile, the *endo* stereoisomer is preferred over the *exo* one.[5] In order to demonstrate the role of hydrophobic effects we measured the *endo*/*exo* ratios for the DA reaction of cyclopentadiene **1** and methyl *trans*-crotonate **2a** (Scheme 1) in water and in other organic solvents. In the past, this reaction has been reported in organic solvents to show *endo*/*exo* ratios of 1:1.[6,7] For this reaction, the convention *endo*/*exo* refers to $endo_{\text{carboxy}}/exo_{\text{carboxy}}$.

The $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratios[8] for the reaction of **1** with **2a** (Table 1) show that the $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratio obtained in water is lower than those obtained in other solvents. The reaction of **1** with **2a** in water was expected to give a higher $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratio, similar to that of the reaction of **1** with **2c** or other DA reactions discussed elsewhere.[5] In general, DA reactions in water offer higher *endo*/*exo* ratios as compared to those in conventional organic solvents, but this was not the case for the reaction of **1** with **2a**. This reaction, in *n*-heptane (a nonpolar solvent) gave an $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratio lower than that in water. The highest $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratio of 2.57, a twofold increase as compared to that in water was obtained when the reaction was carried out in the highly polar solvent, *N*-methylformamide. The $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ value



Scheme 1. Diels–Alder reactions.

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Table 1. $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ Ratios[a,b] for the reaction of **1** with **2a** in different solvents and for the reactions of **1** with **2b** and **2c** in water alone

Solvent	$endo_{\text{carboxy}}/exo_{\text{carboxy}}$	Isolated yield %	Solvent	$endo_{\text{carboxy}}/exo_{\text{carboxy}}$	Isolated yield (%)
Water	1.28	78	DMSO	2.29	62
Methanol	2.09	60	Nitrobenzene	1.73	49
Ethanol	1.85	58	Formamide	2.09	69
Propan-1-ol	1.78	55	*N*-Methylformamide	2.57	65
Butan-1-ol	1.84	50	Ethylene glycol	2.14	68
Ethylene carbonate	1.95	50	*n*-Heptane	0.97	35
Reaction **1** + **2b** in water	0.40[c]	60	Reaction **1** + **2c** in water	1.97[d]	85

[a] Also implies the same as $exo_{\text{mt}}/endo_{\text{mt}}$.

[b] An average of triplicate data with a standard deviation of 0.03.

[c] From Ref. 9.

[d] From Ref. 10.

in propan-1-ol, butan-1-ol, ethanol, ethylene carbonate, methanol, formamide, ethylene glycol and DMSO increases by 35%, 39%, 44%, 44%, 52%, 63%, 67% and 68%, respectively, as compared to that in water alone.

The methyl group is more hydrophobic than the carboxylate group, so the hydrophobic packing of the methyl group in the transition state would lead to more $endo_{\text{mt}}$, corresponding to more exo_{carboxy}. This is exactly what one finds in this water-mediated reaction of **1** with **2a**. This suggests that hydrophobic effects influence the stabilization of the geometry of the transition states. A similar change in the $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ selectivity was observed for the *exo*-selective reaction of **1** with methyl methacrylate **2b** (Scheme 1) in water[9] (Table 1) and organic solvents.[6,7] In the absence of methyl group substitution, as in the reaction of **1** with methyl acrylate, **2c** (Scheme 1), hydrophobic interactions become less important and SOIs direct the reaction to be $endo_{\text{carboxy}}$ selective leading to a higher $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ ratio in water (Table 1).[6,10]

The $endo_{\text{carboxy}}/exo_{\text{carboxy}}$ values in water were checked after every 30 min before the completion of the reaction to yield the ratio as 1.28 ± 0.08 (an average of six readings) indicating that selective decomposition of either *endo* or *exo*-product did not take place. Also the separated *endo* and *exo* products were kept in water for the same time without any change suggesting that the *endo* product (56%) did not convert into the *exo* isomer (44%) and vice versa.

In summary, it is possible to invoke the role of hydrophobic packing to explain the stereoselectivity of a Diels–Alder reaction in water.

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8. Compound **1** was freshly cracked from its dimer just before its use. Compound **2a** was prepared by heating freshly crystallized *trans*-crotonic acid with methanol and sulfuric acid for 18 h using the procedure given elsewhere.[7] Deionized water was used for carrying out the reactions. The organic solvents (purity > 99+%, spectrophotometric grade) were used in the investigation. In a typical run, 0.6 mL (7.24 mmol) of freshly cracked **1** was transferred into 5 mL of solvent. Then 0.6 mL (6.44 mmol) of **2a** was dissolved in 5 mL of the solvent. The solution containing **1** was added to the solution containing **2a**. The reaction mixture was magnetically stirred at 27 °C for about 12 h. The stereochemical assignments were made by condensing crotonic acid with **1** and the resultant *endo* and *exo* bicylic acids separated by iodolactonization as described by Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256; The ^{1}H NMR spectrum of the *endo* ester is also reported by Ikota, N. *Chem. Pharm. Bull.* **1989**, *37*, 2219–2221, The products were analyzed by gas chromatography using a CP SIL 5CB column. The retention times for the *endo* and *exo* products were 8.411 and 8.278 min, respectively. GC analyses of the individual isomers were found to be 8.633 min for the *endo* and 8.249 min for the *exo* ester. GC and NMR were also used to check the dimerization of **1**, which was found to be negligible.
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