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Comment

Rate enhancement of Diels–Alder reactions in aqueous solutions

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ABSTRACT: It is shown that the concept of internal pressure cannot be used to explain the strong rate enhancement of Diels–Alder reactions when carried out in water with respect to common organic solvents. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: Diels–Alder reaction; hydrophobic interactions; work of cavity creation; internal pressure

In a recent article, Kumar and Deshpande[1] claimed that the correlation proposed by Kodaka[2] between the internal pressure P_{int} and the work of cavity creation ΔG_{c} provides support for a quantitative understanding of the rate enhancement of Diels–Alder reactions in water and aqueous salt solutions with respect to organic solvents. They explicitly wrote that 'the hydrophobic packing of diene and dienophile is greatly facilitated by the internal pressure of water'. It is simple to show that the claim by Kumar and Deshpande is not correct. The values of P_{int} at 25 °C for the solvent media in which the reaction of anthracene-9-carbinol with *N*-ethylmaleimide has been investigated are reported in Table 1, together with those of the second-order rate constant.[3] The P_{int} values are calculated by means of the thermodynamic relationship $P_{\mathrm{int}} \approx \alpha T/\beta$, where α is the thermal expansion coefficient and β is the isothermal compressibility of the liquid.[4–7] All the P_{int} values for aqueous salt solutions were directly calculated by Kumar.[7]

What is immediately evident is that P_{int} of water is smaller than that of isooctane, methanol, 1-butanol and acetonitrile. This fundamental point was completely neglected by Kumar and Deshpande, but is of central importance. In fact, even though the trend of the P_{int} values for water and aqueous salt solutions correlates with the trend of the rate constants, the correlation does not exist when non-aqueous solvents are considered. According to the data in Table 1, on passing from acetonitrile to water k_2 increases 200-fold, whereas P_{int} decreases 2-fold. In addition, the reaction shows the lowest k_2 value in acetonitrile, even though this solvent has the largest P_{int} even considering the aqueous salt solutions.

Such a result is not restricted to the specific Diels–Alder reaction selected, but is of general validity. Compare, for instance, the k_2 values for the reaction of cyclopentadiene with 5-methoxy-1,4-naphthoquinone[8] in different solvents with the respective values of P_{int} reported in Table 2. In addition, there is rate enhancement also at the temperature of maximum density of water

Table 1. Second-order rate constants for the Diels–Alder reaction of antracene-9-carbinol with *N*-ethylmaleimide in various media at 45 °C[3] and the respective values of the internal pressure, P_{int},[4–7] at 25 °C[a]

	$k_2 \times 10^3$ ($M^{-1}\,s^{-1}$)	P_{int} (atm)
Isooctane	8.0 ± 0.7	2326
Methanol	3.4 ± 0.3	2780
1-Butanol	6.7 ± 0.2	2961
Acetonitrile	1.1 ± 0.8	3841
Water	230 ± 2	1655
NaCl–water	308 ± 6	3756
NaBr–water	298 ± 5	3692
$NaBF_4$–water	224 ± 2	2231
$NaClO_4$–water	205 ± 2	1530
$NaPF_6$–water	190 ± 2	1441
$NaAsF_6$–water	179 ± 5	1373
GdmCl–water	129 ± 6	1426
GdmBr–water	116 ± 2	1402
$GdmBF_4$–water	92 ± 4	1230
$GdmClO_4$–water	86 ± 4	1146

[a] All the aqueous salt solutions have a 2 M concentration. Gdm^+ stands for guanidinium ion.

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Table 2. Second-order rate constants for the reaction of cyclopentadiene with 5-methoxy-1,4-naphthoquinone at 25 °C in different solvents[8] and the respective values of the internal pressure at 25 °C[4]

	$k_2 \times 10^3$ ($M^{-1} s^{-1}$)	P_{int} (atm)
Hexane	0.77	2578
Carbon tetrachloride	1.43	3381
Benzene	1.52	3773
Acetone	1.73	3585
Dimethyl sulfoxide	7.88	4932
Ethanol	14.5	2816
Methanol	17.9	2780
Ethylene glycol	133	5243
Water	5260	1655

where P_{int} is zero, in striking contrast with the claim by Kumar and Deshpande.

Therefore, it is not true that a higher internal pressure of the liquid medium implies higher reaction rates for Diels–Alder reactions. The internal pressure concept cannot explain the strong rate enhancement of Diels–Alder reactions when carried out in water with respect to common organic solvents, as already pointed out by Blokzijl and Engberts.[9] This is a general conclusion that should be widely recognized.

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