

Diels–Alder Reactions in Hydrophobic Cavities: a Quantitative Correlation with Solvophobicity and Rate Enhancements by Macrocycles¹

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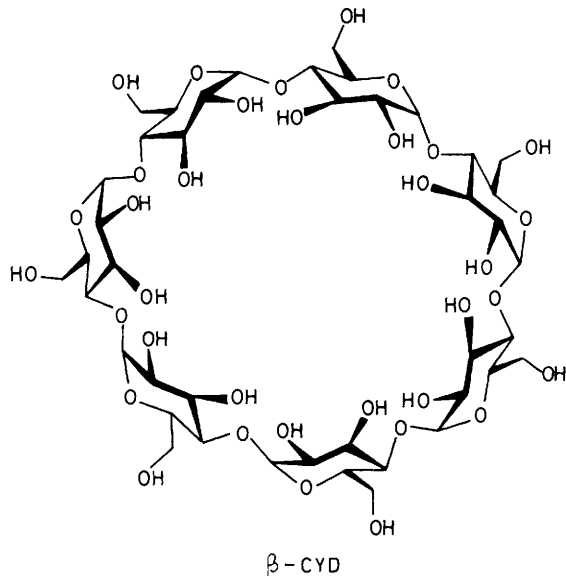
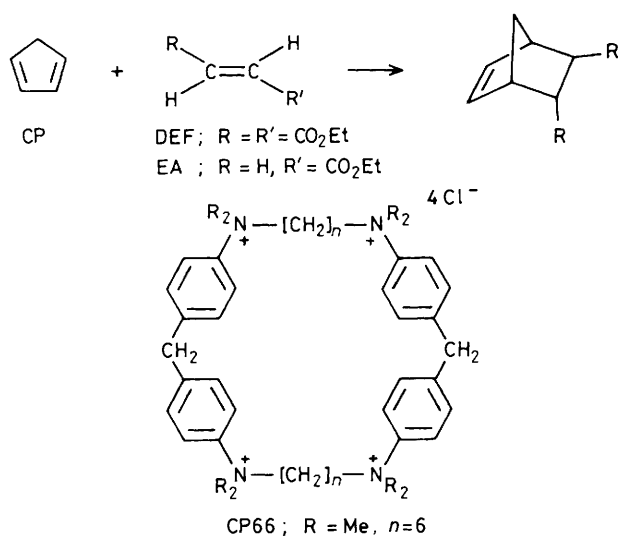
Based on the reaction of cyclopentadiene with diethyl fumarate a linear correlation of $\log k$ vs. solvophobicity parameters is reported as well as saturation kinetics showing up to 70-fold rate increase by complexation in β -cyclodextrin.

Through the work of Breslow,² Grieco,³ Lubineau,⁴ and others⁵ it has become apparent that the course of Diels–Alder cycloadditions can be remarkably influenced by the use of aqueous solvents^{2a,b,3–5} as well as by the presence of cyclodextrins.^{2c} The common origin of the observed accelerations must be seen in the association between diene and dienophile driven either by hydrophobic forces in aqueous solvents or/and by an intracavity inclusion in a macrocycle.^{2–5}

After the recent kinetic characterization of ternary complexes in acyl transfer reactions with a macrocyclic azacyclopentane derivative⁶ we became interested in the possible use of this and other host compounds for processes requiring the complexation of substrate and cosubstrate. This demanded a simultaneous study of related solvent effects in view of (i) the parallel features of hydrophobic effects and intracavity inclusion as cited above, (ii) the necessity to measure kinetics in solvents of different hydrophobicity, and (iii) the pronounced dependence of related host–guest complexation constants on solvent hydrophobicity or lipophilicity.⁷

The only quantitative correlation of Diels–Alder cycloaddition rates with solvent properties known so far is restricted to *polar* effects.⁸ The rates of reaction between cyclopentadiene (CP) and diethyl fumarate (DEF)†, which have been used in this study, indeed correlated well with medium polarity parameters as long as we stayed within binary aqueous mixtures. Thus, a plot of $\log k$ vs. Y-polarity parameters¹⁰ in 11 methanol–water and dioxane–water mixtures shows a very

† Rates were followed by the u.v. absorbance decrease at $\lambda = 239$ nm (λ_{max} of cyclopentadiene) for up to 70% conversion at 20.0 ± 0.05 °C; for fast reactions ($k > 19.5 \times 10^{-3}$ dm³ mol⁻¹ s⁻¹), continuous measurement using automatic data collection and processing was used; for slower reactions and those performed in dioxane, 5–10 samples were analysed after appropriate dilution with 50% methanol–water. All reactions followed clean second order kinetics with linear correlation coefficients of $r > 0.998$. The only comparable literature value (for dimethyl fumarate with cyclopentadiene in dioxane⁹) agrees to within $\pm 1.5\%$.



linear correlation (not shown) ($r = 0.995$; $\psi = 1.25\%$). However, as already suggested by the observations of earlier workers,²⁻⁵ the effect of pure water is too large in comparison to other polar, yet lipophilic solvents. In fact, there is no correlation between the observed rates and polarity parameters of selected pure solvents (Figure 1).

In spite of the large number of empirical solvent parameters¹⁰ there has been no reliable measure available for hydrophobicity or lipophilicity of solvents until now. Recently Abraham¹¹ has developed a corresponding solvophobicity parameter set Sp ^{11c} which is based on the linearly correlated standard free energies ΔG_s° of noble gases, alkanes *etc.* for the transfer from gas to a given solvent.¹¹ We found earlier that free complexation energies $\Delta G_{\text{complex}}^\circ$ between an azacyclophane and naphthalene derivatives show excellent correlation with ΔG_s° values obtained with, *e.g.*, tetramethyltin transfer from methanol-water mixtures.^{7,11} If we now compare the Diels-Alder reaction rates with Sp values in 13 different media including pure solvents a linear correlation ($r = 0.978$, $\psi = 5.0\%$, Figure 2) is obtained. To our knowledge this represents the first quantitative description of chemical rates as a function of solvophobicity.

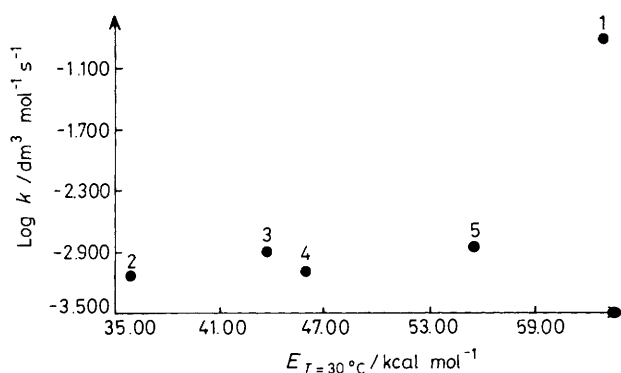


Figure 1. $\log k_2$ of the reaction DEF + CP (20.0°C) vs. solvent polarity parameters E_T (1 kcal = 4.184 kJ). 1: H₂O; 2: dioxane; 3: dimethylformamide (DMF); 4: MeCN; 5: MeOH.

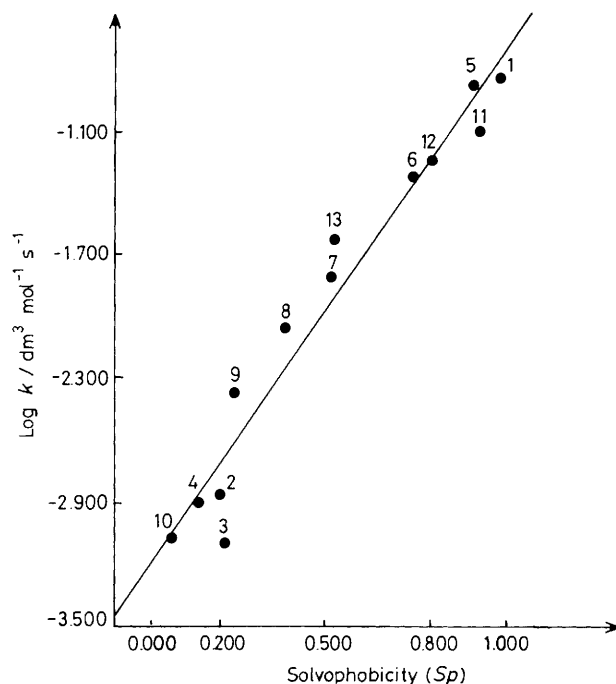


Figure 2. $\log k_2$ of the reaction DEF + CP (20.0°C) vs. solvophobicity parameters Sp .¹¹ 1: H₂O; 2: MeOH; 3: MeCN; 4: DMF; 5-10: 10, 30, 50, 60, 70, 90% dioxane-H₂O; 11-13: 10, 30, 60% MeOH-H₂O (aqueous mixtures in % vol. + vol.).

The azacyclophane CP66^{7,12a} provides a lipophilic cavity of at least ~ 6.5 Å internal width, and in addition positive charges which could contribute to rate accelerations with suitably bound dienophiles such as fumarate esters by an electrostatic decrease of electron density at the olefinic bond. DEF and CP showed moderate rate accelerations upon addition of CP66. Thus, rate constants k_2 in 50% dioxane-water increased from 15.8×10^{-3} dm³ mol⁻¹ s⁻¹ to 24×10^{-3} dm³ mol⁻¹ s⁻¹ with 0.07 M CP66. In 10% dioxane the complexation constants increase,⁷ in line with an observed rate increase from 0.137 to approximately 0.40 dm³ mol⁻¹ s⁻¹ with [CP66] = 0.10 M. (Owing to heavily overlapping CP66 absorptions these rates were less accurate than those without the host.)

In contrast with these results, addition of β -cyclodextrin (β -CYD) promoted the cycloaddition of DEF to CP to an extraordinary degree (Figure 3). This is also the first observa-

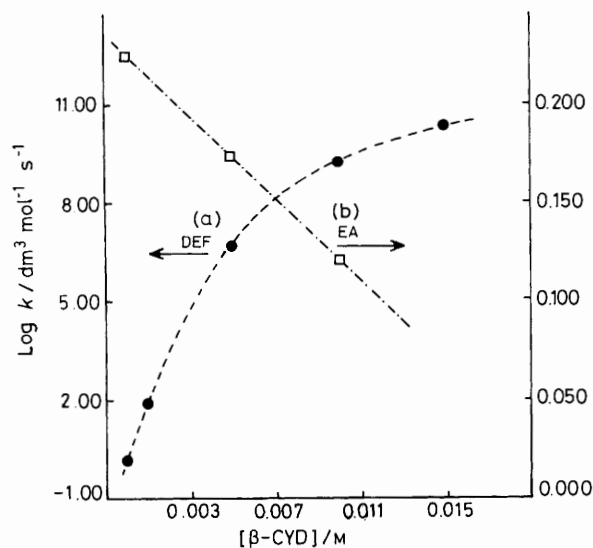


Figure 3. Rate constants k_2 of the reaction (a) DEF + CP, (b) EA + CP (all at 20.0°C, in water, 0.1 vol % dioxane) vs. $[\beta\text{-CYD}]$ in $\text{mol}^{-1} \text{dm}^{-3}$.

tion of enzyme-analogue saturation kinetics with a Diels-Alder reaction, indicating the formation of ternary complexes. A full kinetic analysis must await an evaluation of the additional ternary and possibly also binary complexation constants between the host and diene as well as dienophile alone. Based on our experience with a related complex system,⁶ these constants cannot be extracted from saturation kinetics alone but require independent measurements by spectroscopic methods. If one takes an association constant for the ternary complex $[\beta\text{-CYD}\cdot\text{DEF}\cdot\text{CP}]$ of $K \sim 10^4 \text{ dm}^3 \text{ mol}^{-1}$ from comparison with related cyclodextrins¹³ as a conservative limit, the observed rates (Figure 3) would indicate a catalysed reaction with at least $k_{\text{cat}} \sim 10^{-1} \text{ s}^{-1}$.[‡]

The reaction between ethyl acrylate (EA) and cyclopentadiene in the presence of β -cyclodextrin strikingly shows a rate

[‡] This estimate is derived from the assumption that with 0.15 M β -CYD the uncatalysed reaction is negligible (see Figure 3). The initial rate with $[\beta\text{-CYD}] = 0.15 \text{ M}$ and $[\text{DEF}] = [\text{CP}] = 10^{-4} \text{ M}$ is $v = [\text{DEF}]_0[\text{CP}]_0 k_{\text{obs}} = 10^{-7}$ which is also equal to $v: k_{\text{cat}}[\text{Tern}] = v = 10^{-7}$. The concentration of the ternary complex $[\text{Tern}]$ at the concentrations given above is 10^{-7} M with $K = 10^4$ and, e.g., 10^3 (by mass law), which gives k_{cat} values of 10^{-1} s^{-1} or 1 s^{-1} , respectively.

decrease (Figure 3), reminiscent of some earlier observations.^{2c,5a} Such a behaviour could be attributed to a preferred binding of two molecules of either diene or dienophile. The results demonstrate the delicate geometric requirements to be fulfilled when a macrocycle is used to bind two different substrates within the cavity.

Financial support by the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt, is gratefully acknowledged. N. K. S. acknowledges a leave of absence granted by the Haryana Agricultural University, Hissar, India.

Received, 7th July 1986; Com. 929

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