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CORRELATIONS OF RATE AND SELECTIVITY OF A DIELS–ALDER REACTION WITH S_p PARAMETERS

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The rate and *endo/exo* selectivity of the Diels–Alder reaction between cyclopentadiene and methyl (*E*)-α-cyanocinnamate at 25 °C, in several acetone–water and 1,4-dioxane–water mixtures, were measured. The linear correlations of log *k* and log(*endo/exo*) vs solvophobicity are reported. Correlations for selectivity are considerably improved when the results obtained in acetone–water and 1,4-dioxane–water are taken as separate series.

Cycloaliphatic amino acids, such as those with a norbornane skeleton, are of interest because of their biological activity.[1] We have recently developed[2] a synthetic route for the preparation of the four *dl* pairs of 2-amino-3-phenylnorbornane-2-carboxylic acid, the key step being the Diels–Alder reaction between cyclopentadiene (**1**) and methyl (*E*)-α-cyanocinnamate (**2**).[3] The rate of this reaction is noticeably increased by the use of aqueous solvents, but the *endo/exo* selectivity is only slightly modified.

Breslow and co-workers,[4] Grieco and co-workers[5] and Lubineau and Queneau[6] have reported that the rate of intermolecular Diels–Alder reactions can be greatly increased by the use of aqueous solvents. The origin of these accelerations was attributed to the association between diene and dienophile driven by hydrophobic forces in aqueous solvents.[4–6] Further, increased *endo/exo* selectivity has been observed in several intermolecular Diels–Alder reactions.[4b,c,5a,b,6] This selectivity is probably not a consequence of the relatively high polarity of water. In fact, although a correlation between solvent polarity and stereoselectivities of Diels–Alder reactions has been reported with non-polar substrates in several solvents,[7] with water and other hydroxylated solvents no correlation was observed with any function of the dielectric constant.[8]

In spite of the importance of the solvophobic effect in several areas, only recently have Abraham and co-workers[9] developed a quantitative scale of solvophobic power (S_p) that could be applied to pure solvents and especially to aqueous–organic mixed solvents.[9b]

This parameter set was used earlier by Schneider and Sangwan,[10a] who found a linear correlation between the log *k* of the Diels–Alder reaction of diethyl fumarate with cyclopentadiene and S_p values. They also studied the increase in the proportion of the *endo* adducts obtained by the use of water in reactions of cyclopentadiene with maleic acid derivatives.[10b] They found a correlation between the log(*endo/exo*) values, obtained from the reaction of monoethyl maleate, and solvophobicity parameters S_p, which supported the hydrophobic effect being responsible for the changes in selectivity. They carried out a multiple correlation for the same system including $E_T(30)$ values and the results obtained showed that the inclusion of polarity parameters was of no significance. To our knowledge, these are the only descriptions of chemical rates and selectivities as a function of solvophobicity.

We agree with Abraham *et al.*[9b] that further investigation to test the general applicability of the S_p scale is necessary, so we have compared the rates and *endo/exo* selectivities of the Diels–Alder reactions between cyclopentadiene (**1**) and methyl (*E*)-α-cyanocinnamate (**2**) in several reaction media with S_p values.[9b]

Table 1 shows the results obtained in this Diels–Alder reaction (Figure 1) at 25 °C in several reaction media. As can be seen, the reaction rate is noticeably increased when the percentage of the water increases, whereas the *endo/exo* selectivity is only slightly increased.

Figure 2 shows the existence of a linear correlation

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Table 1. Second-order constants[a] and *endo*/*exo* ratios[a] for the Diels–Alder reaction of **1** and **2** at 25 °C

Entry	Organic solvent	Water concentration (%)	$R \times 10^3$ ($dm^3\,mol^{-1}\,s^{-1}$)	**3a**: **3b** *endo*/*exo* ratio
1	1,4-Dioxane	20[b]	3·5	1·35
2	1,4-Dioxane	30	6.2	1.44
3	1,4-Dioxane	40	12.6	1.52
4	1,4-Dioxane	50	24.9	1.59
5	1,4-Dioxane	60	47.0	1.77
6	1,4-Dioxane	70[c]	76.1	1.86
7	Acetone	20[b]	3.8	1.48
8	Acetone	30	6.9	1.54
9	Acetone	40	10.7	1.60
10	Acetone	50	18.1	1.66
11	Acetone	60	45.4	1.72
12	Acetone	70[c]	95.1	2.03

[a] Determined by HPLC (see Experimental).

[b] With less water the reaction is too slow to allow an accurate determination of *k*.

[c] With more water **2** is not soluble.

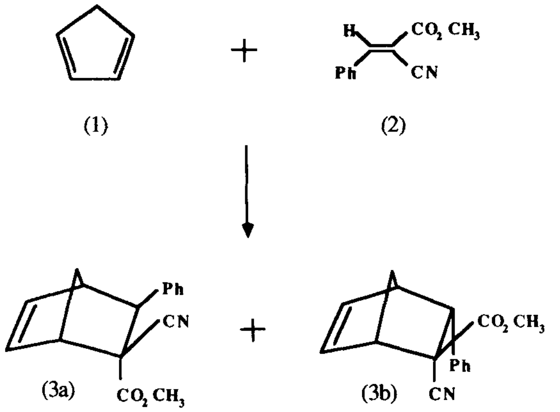

Figure 1. Diels–Alder reaction between cyclopentadiene and methyl (*E*)-α-cyanociannamate.

between log *k* and S_p values;[9b] this correlation is only slightly improved when the reactions carried out in 1,4-dioxane–water and acetone–water are taken as separate series (Figure 3). The change from one to two series is just within the limit of statistical significance and does not justify using S_p values[9b] in separate series, as a function of the organic solvent, instead of a complete series of solvophobicity values.

Figure 4 shows the linear correlation between log(*endo*/*exo*) and S_p values;[9b] this correlation is noticeably improved when the results obtained in 1,4-dioxane–water and in acetone–water are taken as separate series (Figure 5). This improvement has a statistical significance of over 99·9%. Since small differences in *endo*/*exo* selectivity exist, the interpretation of these results requires caution. However, the results indicate that the *endo*/*exo* selectivity data are better explained using the S_p values within each series of organic solvent–water mixtures.

Breslow *et al.*[4b] suggested that the increase in *endo*/*exo* selectivity in aqueous solvents are related to the well known effects of polar media and the need to minimize transition-state surface area in aqueous solution. Taking this into account, it seems logical to obtain different correlations as a function of the polarity of the organic solvent present in the mixture. In our case, large *endo*/*exo* ratios cannot be expected because of the presence of electron-withdrawing groups attached to both sides of the double bond. However, the selectivity obtained is in accordance with the larger *endo*-directing tendency of the methoxycarbonyl group in comparison with the cyano group.[11] This tendency is more favoured by acetone–water than 1,4-dioxane–water mixtures [$E_T(30)_{\mathrm{acetone}} = 42{\cdot}2\ \mathrm{k\,cal\,mol^{-1}}$; $E_T(30)_{\mathrm{1,4\text{-}dioxane}} = 36{\cdot}0\ \mathrm{k\,cal\,mol^{-1}}$].[12] We agree with Schneider and Sangwan that the hydrophobic effect is the main factor responsible for the changes in selectivity, but in contrast with their results, the polarity of the solvent may play a significant role.

In conclusion, both our results and Schneider and Sangwan's show the usefulness of S_p values[9b] to explain the rates and selectivities of intermolecular Diels–Alder reactions. However, the use of separate series of S_p values[9b] for each kind of organic solvent–water mixture may be advisable in order to explain the differences in *endo*/*exo* selectivity. However, further investigations, using Diels–Alder reactions whose *endo*/*exo* selectivity

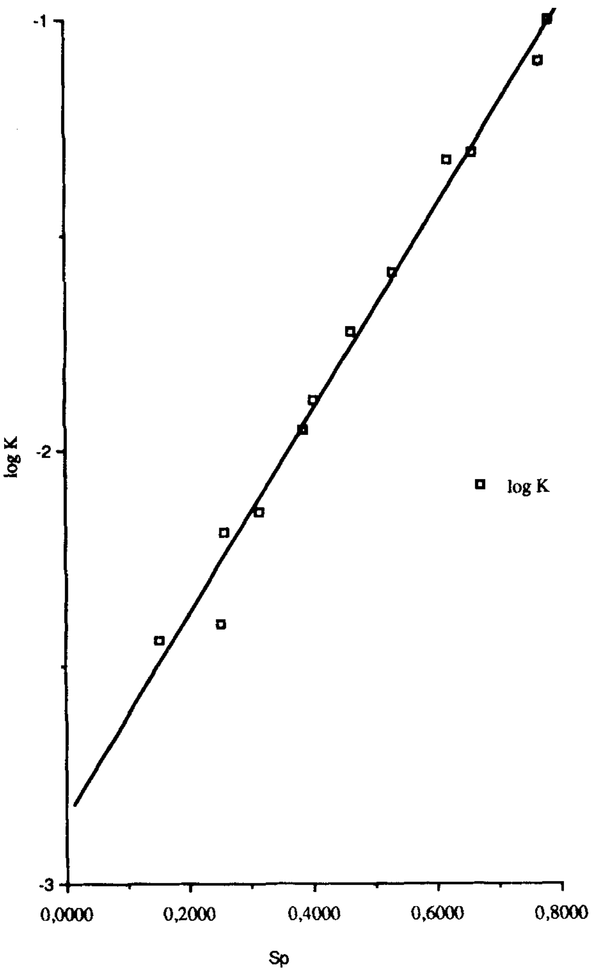

Figure 2. Log *k* of the reaction of **1** + **2** at 25 °C vs solvophobicity values (S_P).[9b] $y = -2 \cdot 8374 + 2 \cdot 3516\ (\pm 0 \cdot 1974)x$; $r = 0 \cdot 9939$; $s = 0 \cdot 0613$; $F = 704 \cdot 8622\ (F_{1,10;0 \cdot 95} = 4 \cdot 96)$.

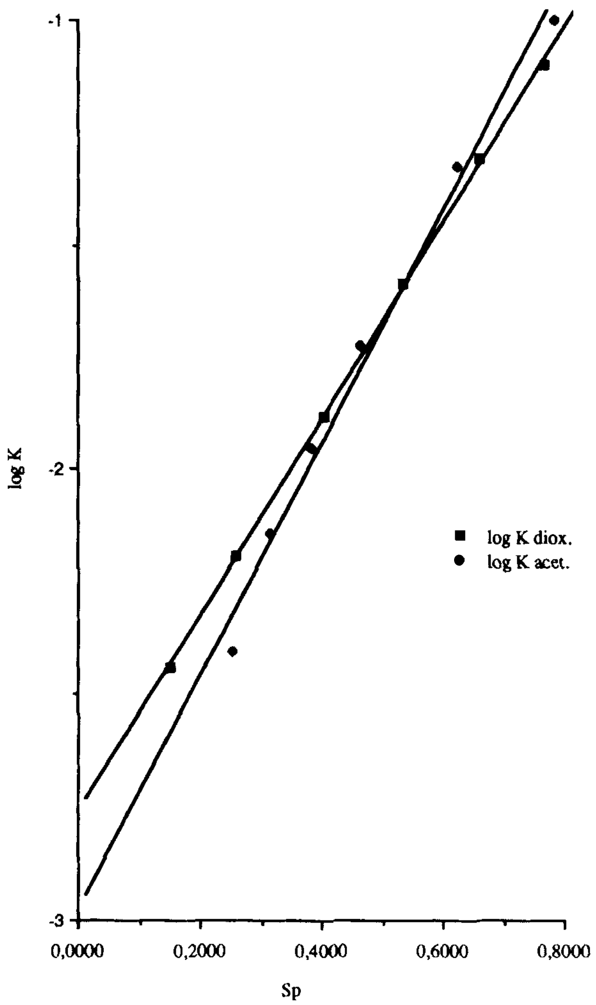

Figure 3. Log k of the reaction of **1** + **2** at 25 °C vs solvophobicity values (S_P),[9b] taking 1,4-dioxane–water and acetone–water as separate series. Acetone–water: $y = -2 \cdot 9601 + 2 \cdot 5935\ (\pm 0 \cdot 3836)x$; $r = 0 \cdot 9944$; $s = 0 \cdot 0618$; $F = 325 \cdot 0113\ (F_{1,4;0 \cdot 95} = 7 \cdot 71)$. 1,4-Dioxane–water: $y = -2 \cdot 7448 + 2 \cdot 1803\ (\pm 0 \cdot 0661)x$; $r = 0 \cdot 9998$; $s = 0 \cdot 0126$; $F = 8389 \cdot 6923\ (F_{1,4;0 \cdot 95} = 7 \cdot 71)$.

is more sensitive to the percentage of water in the mixture, are necessary.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XL-200 instrument. Microanalyses were carried out with a Perkin-Elmer 240-C microanalyzer. HPLC analyses were carried out with an HP-1090 chromatograph equipped with a diode-array detector. Data were analysed by the Statwork 1·1 and Cricket Graph 1·0 programs, distributed by Cricket Software for an Apple Macintosh computer.

Material. Dioxane was distilled from sodium under a nitrogen atmosphere and stored before use over molecular sieves 4Å. Commercial acetone was used without further purification. Water was deionized and doubly distilled in all-glass apparatus.

Methyl (*E*)-α-cyanocinnamate (**2**)[3] and cycloadducts (**3a**, **3b**)[2] were prepared according to previously described methods and identified by their ^{1}H NMR spectra and elemental analyses.

Kinetic procedure. A 330-mg (5-mmol) amount of freshly distilled cyclopentadiene dissolved in the corresponding aqueous mixture (5 cm^3 for entries 1–5 and

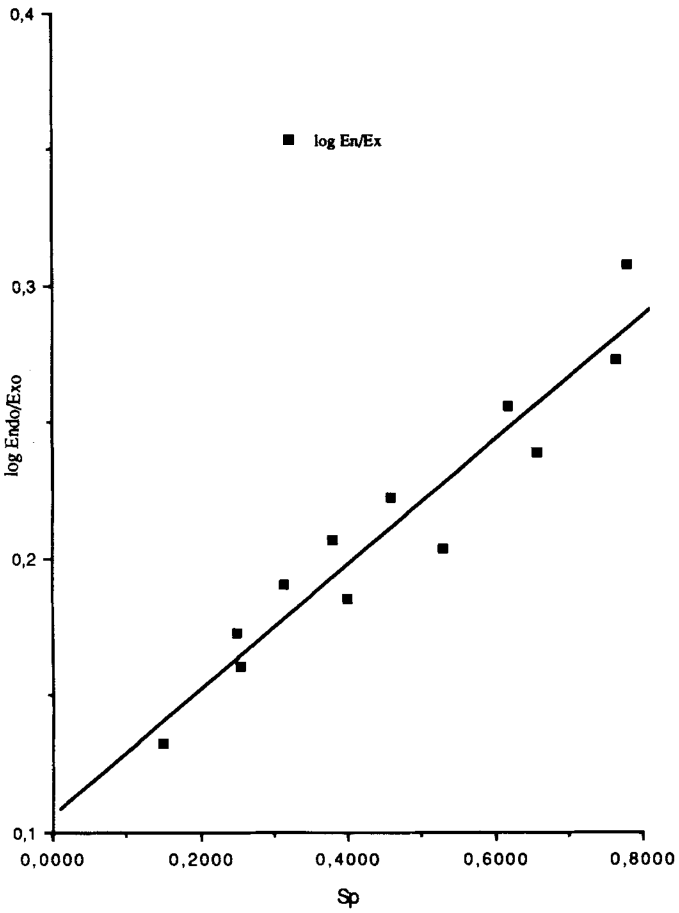

Figure 4. Log (*endo*/*exo*) of the reaction of **1** + **2** at 25 °C vs solvophobicity values (S_p).[9b] $y = 0{\cdot}1063 + 0{\cdot}2284\ (\pm 0{\cdot}0495)x$; $r = 0{\cdot}9557$; $s = 0{\cdot}0154$; $F = 105{\cdot}5298$ ($F_{1,10;0{\cdot}95} = 4{\cdot}96$).

7–11 and 20 cm^3 for entries 6 and 12, in Table 1) were added to a thermostated (25 ± 0·1 °C) solution of 187 mg (1 mmol) of methyl (*E*)-α-cyanocinnamate (**2**) in the same mixture (45 cm^3 for entries 1–4 and 7–10, 60 cm^3 for entries 5 and 11 and 180 ml for entries 6 and 12 in Table 1) and the solution obtained was stirred magnetically (the volume of solvent depends on the solubility of **2** in the mixture). Reaction rates were determined by HPLC analyses of aliquots of the reaction mixtures, following the formation of cycloadducts **3a** and **3b**. All reaction followed second-order kinetics.

Chromatographic analyses. Reaction mixtures were analysed using a Hypersil MOS (C_8) column (5 μm; 100 mm × 4·6 mm i.d.) and methanol–water as the mobile phase with a linear gradient from 55:45 to 75:25 (v/v) in 2 min at a flow-rate of 1·7 ml min^{-1}. Detection

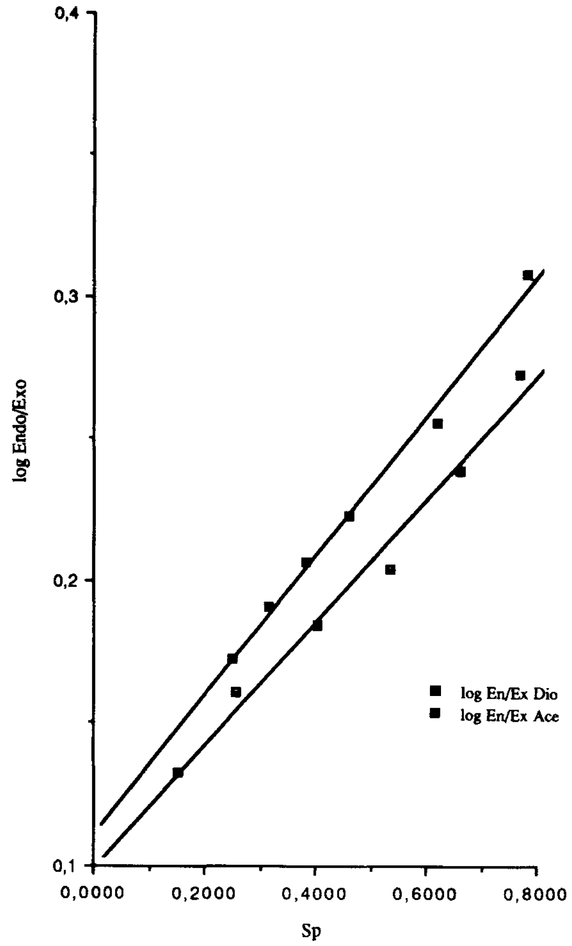

Figure 5. Log (*endo*/*exo* of the reaction of **1** + **2** at 25 °C vs solvophobicity values (S_p),[9b] taking 1,4-dioxane–water and acetone–water as separate series. Acetone–water: $y = 0{\cdot}1117 + 0{\cdot}2445\ (\pm 0{\cdot}0297)x$; $r = 0{\cdot}9962$; $s = 0{\cdot}0048$; $F = 526{\cdot}3438$ ($F_{1,4;0{\cdot}95} = 7{\cdot}71$). 1,4-Dioxane–water: $y = 0{\cdot}0996 + 0{\cdot}2149\ (\pm 0{\cdot}0389)x$; $r = 0{\cdot}9916$; $s = 0{\cdot}0074$; $F = 235{\cdot}5660$ ($F_{1,4;0{\cdot}95} = 7{\cdot}71$).

was performed at 210 nm; $\varepsilon_2{:}\varepsilon_{3a}{:}\varepsilon_{3b} = 1217{:}1000{:}1137$. In kinetic runs the products were identified by comparing their retention times with those of reference compounds: **2**, 2·28 min; **3a**, 2.90 min, **3b**, 3·08 min.

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