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DEVELOPMENT OF A MODEL TO EXPLAIN THE INFLUENCE OF THE SOLVENT ON THE RATE AND SELECTIVITY OF DIELS–ALDER REACTIONS

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Solvophobic and polarity parameters are used to explain the *endo/exo* selectivity of the reaction between cyclopentadiene and methyl acrylate. A good linear regression model with *Sp* and $E_T{}^N$ is obtained. The existence of an intrinsic correlation between the *Sp* and $E_T{}^N$ values, which makes the interpretation of the results difficult, is shown. A comparison of the results with other previously reported showed that the relative influence of *Sp* and $E_T{}^N$ on selectivity depends on the nature of the reagents.

INTRODUCTION

It has been reported that the rate and *endo/exo* selectivity of intermolecular Diels–Alder reactions can be greatly increased by the use of aqueous solvents.[1] The origin of this behaviour was attributed to the association between diene and dienophile driven by hydrophobic forces. In fact, Schneider and Sangwan[2] found a linear correlation between log *k* of the Diels–Alder reaction of diethyl fumarate with cyclopentadiene and *Sp* values of solvophobic power,[3] and have recently extended the study to several other dienophiles.[4]

Although a correlation between solvent polarity and the stereoselectivity of Diels–Alder reactions had been reported,[5] Schneider and Sangwan found a correlation between log(*endo/exo*) values, obtained from the reaction between monoethyl maleate and cyclopentadiene, and the solvophobicity parameter *Sp*.[6] Further, they carried out a multiple correlation for the same system and showed that the inclusion of $E_T(30)$ polarity values was of no significance.

Recently we have studied the Diels–Alder reaction of (*E*)-methyl α-cyanocinnamate with cyclopentadiene in several aqueous acetone and 1,4-dioxane mixtures.[7] We observed the existence of a linear correlation between log *k* and *Sp* values. There is also a linear correlation between log(*endo/exo*) and *Sp*, but this correlation is noticeably improved when the results obtained in aqueous acetone and in aqueous 1,4-dioxane are taken as separate series. This result is in accordance with those of Schneider and Sangwan inasmuch as the changes in selectivity are mainly caused by the solvophobic effect. However, in our case polarity seems to play a significant role.

Unfortunately, (*E*)-methyl α-cyanocinnamate is too complex a dienophile to allow an easy interpretation of the results obtained. Therefore, in this work we have studied the reaction between methyl acrylate and cyclopentadiene in several reaction media, including pure solvents and aqueous–organic mixtures, in order to clarify the influence of solvent polarity and solvophobicity on Diels–Alder reactions.

RESULTS AND DISCUSSION

As we tried to cover a broad range of solvents, they were selected according to their *Sp* (ref. 3) and normalized $E_T{}^N$ (Ref. 8) values. Table 1 shows the results obtained in the Diels–Alder reaction between cyclopentadiene (**1**) and methyl acrylate (**2**) (Scheme 1) at 25 °C in the different reaction media.

In order to analyse the influence of solvophobicity and polarity on the reaction rate, we tested the linear correlation of log *k* with *Sp* and $E_T{}^N$. Figure 1 plots the experimental values of log *k* versus those calculated

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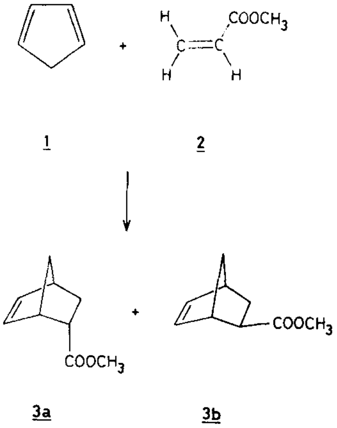
Table 1. Rates and *endo*/*exo* selectivity of the Diels–Alder reaction between methyl acrylate and cyclopentadiene in several pure solvents and organic solvent–aqueous mixtures[a]

Entry	Reaction medium	Sp	E_T^N	Log k	Log k_{endo}	Log k_{exo}	Log(k_{endo}/k_{exo})
1	100% methanol	0·1998	0·7623	−2·263(±0·054)	−2·320	−3·177	0·857(±0·011)
2	90% methanol	0·2729	0·7840	−1·990(±0·025)	−2·043	−2·934	0·892(±0·035)
3	80% methanol	0·3543	0·7994	−1·740(±0·019)	−1·790	−2·699	0·908(±0·023)
4	70% methanol	0·4459	0·8179	−1·488(±0·018)	−1·532	−2·501	0·968(±0·011)
5	60% methanol	0·5306	0·8364	−1·348(±0·013)	−1·388	−2·409	1·021(±0·018)
6	50% methanol	0·6312	0·8519	−1·210(±0·015)	−1·247	−2·296	1·049(±0·018)
7	100% acetone	0·1267	0·3549	−2·801(±0·101)	−2·887	−3·547	0·660(±0·027)
8	80% acetone	0·2389	0·6636	−2·266(±0·023)	−2·333	−3·108	0·774(±0·006)
9	60% acetone	0·3699	0·7436	−1·777(±0·014)	−1·839	−2·656	0·817(±0·018)
10	50% acetone	0·4491	0·7623	−1·413(±0·011)	−1·466	−2·351	0·885(±0·022)
11	100% dioxane	0·0794	0·1636	−2·774(±0·045)	−2·883	−3·427	0·544(±0·014)
12	90% dioxane	0·0624	0·4938	−2·413(±0·023)	−2·494	−3·184	0·690(±0·012)
13	80% dioxane	0·1392	0·5648	−2·156(±0·020)	−2·225	−2·988	0·763(±0·039)
14	70% dioxane	0·2449	0·6235	−1·877(±0·016)	−1·939	−2·752	0·813(±0·021)
15	60% dioxane	0·3899	0·6667	−1·647(±0·018)	−1·701	−2·576	0·875(±0·012)
16	50% dioxane	0·5206	0·7068	−1·408(±0·015)	−1·461	−2·353	0·892(±0·012)
17	100% acetonitrile	0·2167	0·4599	−2·755(±0·026)	−2·829	−3·560	0·731(±0·028)
18	100% ethanol	0·1440	0·6543	−2·347(±0·034)	−2·423	−3·142	0·719(±0·021)
19	100% formamide	0·3863	0·7994	−1·701(±0·040)	−1·754	−2·644	0·890(±0·023)

[a] Log k_{endo} and log k_{exo} were calculated from the corresponding log k and log(k_{endo}/k_{exo}) values.



Scheme 1

from the following model:

$$\log k = -3{\cdot}195 + 2{\cdot}075(\pm 0{\cdot}824)Sp + 0{\cdot}904(\pm 0{\cdot}746)E_T^N \quad (1)$$

$$N = 19;\ r = 0{\cdot}942;\ s = 0{\cdot}180;\ F_{1,16} = 62{\cdot}81$$

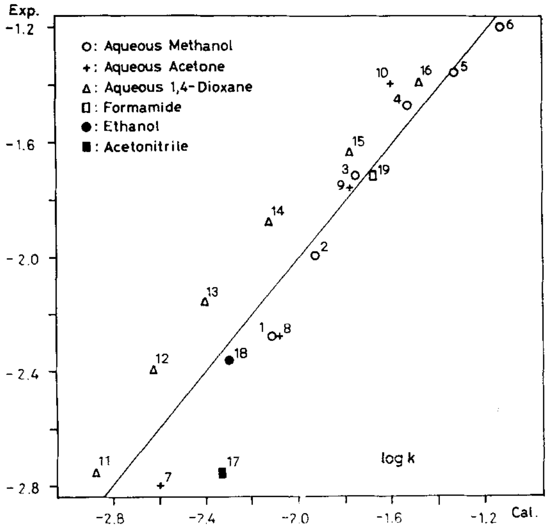


Figure 1. Experimental log k values vs values calculated with equation (1)

The model fits the experimental results well and is highly significant. Although both the Sp and E_T^N coefficients are significant at the 95% level of probability, Sp plays a more important role in determining the reaction rate. In fact, a good model for log k can be obtained with only Sp($r = 0{\cdot}918$), which agrees with the results presented by Schneider and Sangwan.[2,4] However, the inclusion of a polarity term may be important, even determinant, in explaining the reaction rates observed in some systems. Examples of such models have been described by Desimoni and co-workers,[9] who used the Gutmann AN parameter.[10]

The reaction studied shows high *endo*/*exo* selectivity; as a consequence, log $k \approx$ log k_{endo} and the relationship of the latter with Sp and E_T^N is represented by almost the same linear regression model:

$$\log k_{endo} = -3\cdot316 + 2\cdot108(\pm 0\cdot831)Sp + 0\cdot977(\pm 0\cdot752)E_T^N \quad (2)$$

$$N = 19;\ r = 0\cdot945;\ s = 0\cdot182;\ F_{1,16} = 66\cdot25$$

However, when a similar correlation was tried for $\log k_{exo}$, a different model with no significance of the E_T^N coefficient was obtained:

$$\log k_{exo} = -3\cdot770 + 1\cdot754(\pm 0\cdot833)Sp + 0\cdot573(\pm 0\cdot754)E_T^N \quad (3)$$

$$N = 19;\ r = 0\cdot908;\ s = 0\cdot182;\ F_{1,16} = 37\cdot55$$

Similarly, a good correlation of the *endo*/*exo* selectivity with Sp and E_T^N was found. Figure 2 plots experimental versus calculated values of $\log(k_{endo}/k_{exo})$ corresponding to the following linear regression model:

$$\log(k_{endo}/k_{exo}) = 0\cdot457 + 0\cdot356(\pm 0\cdot149)Sp + 0\cdot399(\pm 0\cdot135)E_T^N \quad (4)$$

$$N = 19;\ r = 0\cdot970;\ s = 0\cdot033;\ F_{1,16} = 126\cdot75$$

This dual-parameter model represents a significant improvement with regard to the single-parameter models ($r = 0\cdot892$ only with Sp and $r = 0\cdot920$ only with E_T^N). In this case the Sp and E_T^N coefficients are significant and they also show a similar importance of the solvophobicity and polarity effects, E_T^N having the larger coefficient. An easy interpretation of this result can be obtained by taking into account that the model in equation (4) is the difference between those models in equations (2) and (3). Therefore, there is a partial cancellation of the Sp coefficients, but given that a large value appears in the model of $\log k_{endo}$, the increase in the Sp value increases the selectivity. On the other hand, as E_T^N has no significant influence on $\log k_{exo}$, its effect on selectivity is determined only by its influence on $\log k_{endo}$. As a consequence, the difference between the models in equations (2) and (3) results in an increase in the relative importance of E_T^N.

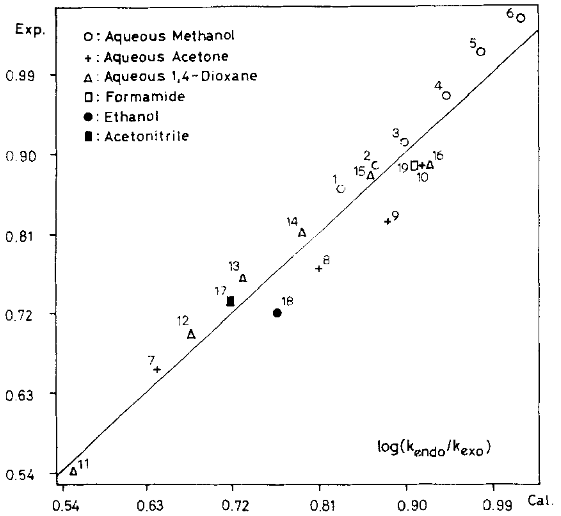


Figure 2. Experimental $\log(k_{endo}/k_{exo})$ values vs values calculated with equation (4)

The correlation that accounts for the *endo*/*exo* selectivity seems to contrast with the results obtained by Schneider and Sangwan[6] in the reaction between monoethyl maleate and cyclopentadiene. However, a thorough analysis of both reactions may explain the differences.

First it is important to take into account that, though Schneider and Sangwan found a better correlation of log(*endo*/*exo*) with $Sp(r = 0\cdot9835)$, the correlation with $E_T(30)$ was not bad ($r = 0\cdot9177$). The lack of significance of $E_T(30)$ in the multiple regression analysis can be explained by the good linear correlation between the Sp and $E_T(30)$ values for the seven solvents and solvent mixtures used in his study ($r = 0\cdot815$). In our case, there is a slightly poorer linear correlation between Sp and E_T^N values ($r = 0\cdot747$) which, taken with the larger number of points included in the correlation, makes our model more reliable.

The correlation between the Sp and E_T values is intrinsic, because the most solvophobic solvents are also the most polar, and therefore cannot be avoided by selecting a different set of solvents. This makes it difficult to interpret the results. In fact, it would be interesting to be able to distinguish between the solvent–solvent interactions, which increase Sp, and the dipolar solute–solvent interactions, which may lead to a different stabilization of *endo* and *exo* activated complexes.

In spite of this, a qualitative physico-chemical justification of these models can be obtained from the nature and differences in the transition states leading to *endo* and *exo* cycloadducts and from the influence of the reaction media on the activation parameters.

The differences between monoethyl maleate and methyl acrylate must be considered. The former gives better *endo*/*exo* selectivity (Table 2), which may well be explained by the existence of two secondary orbital interactions. This would lead to a larger difference in compactness between the *endo* and the *exo* activated

Table 2. *Endo*/*exo* ratios of the reaction of monoethyl maleate (**4**) and methyl acrylate (**2**) with cyclopentadiene

Aqueous solvent	Dienophile 2[a]	Dienophile 4[b]
90% dioxane	4·9	21·2
70% methanol	9·3	30·2
50% methanol	11·2	36·3

[a] Values determined by HPLC.

[b] Values calculated from the correlation of Schneider and Sangwan of log(*endo*/*exo*) vs *Sp*.

complexes[11] and would consequently increase the influence of solvophobic interactions on the *endo*/*exo* selectivity.

On the other hand, it has been shown[12] that the reaction of asymmetric dienophiles proceeds via an unsymmetric transition state and is not synchronous. The degree of synchronicity, with the more symmetrical dienophile used by Schneider and Sangwan, must be higher, which may lead to a minor influence of the polar solute–solvent interactions on the *endo*/*exo* selectivity. The differences in relative compactness and synchronicity between the two reactions studied could explain the larger relative influence of *Sp* on the reaction of monoethyl maleate with cyclopentadiene.

With regard to the rates of the reactions studied in this work, similar arguments can be used. As expected for reactions with a large negative activation volume, both log k_{endo} and log k_{exo} increase when the solvophobicity is increased, but this effect is slightly greater with the former owing to the greater compactness of the corresponding transition state. On the other hand, the polarity effect seems only to affect the *endo* transition state, according to its greater dipole moment, as explained by Berson *et al.*[5]

As $\log k = \log(k_{endo} + k_{exo})$, an increase in solvophobicity globally increases the rate of the reaction, the polarity effect being less important. On the other hand, as $\log(k_{endo}/k_{exo}) = \log k_{endo} - \log k_{exo}$, only the differential solvophobic effect on both transition states is important, and hence the relative importance of polarity in determining selectivity increases.

CONCLUSIONS

A dual model with *Sp* and $E_T{}^N$ accounts for the rates and *endo*/*exo* selectivity of intermolecular Diels–Alder reactions. Unfortunately, the intrinsic correlation between both parameters makes a clear physicochemical explanation of the results difficult because the effect of dipolar solute–solvent interactions may be included in the *Sp* term. The relative influence of solvophobicity and polarity on reaction rates and *endo*/*exo* selectivity seems to depend on the nature of the reagents used.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XL-200 instrument. Microanalyses were carried out on a Perkin-Elmer 240-C Microanalyzer. High-performance liquid chromatographic (HPLC) analyses were carried out with a Hewlett-Packard HP-1090 M system equipped with a diode-array detector.

Materials. All organic solvents were dried and purified according to standard procedures. Water was deionized and doubly distilled in all-glass apparatus. Methyl acrylate was purchased from Merck and was used without further purification. The cycloadducts (**3a**, **3b**) were prepared according procedures described in the literature.[13]

Kinetic procedure. A 0·990 g (15 mmol) amount of freshly distilled cyclopentadiene dissolved in the corresponding organic solvent or organic–aqueous mixture (10 ml) was added to a thermostated (25 ± 0·1 °C) solution of 0·430 g (5 mmol) of methyl acrylate in the same solvent (70 ml) and the solution obtained was stirred magnetically. Reaction rates were determined by HPLC analyses of aliquots of the reaction mixtures, following the formation of cycloadducts (**3a**, **3b**). All reactions followed second-order kinetics.

Chromatographic analyses. Reaction mixtures were analysed using a Nucleosil 120-C$_{18}$ (5 μm) column (125 mm × 40 mm i.d.) and methanol–water as the mobile phase with a linear gradient from 60 : 40 (v/v) to 70 : 30 (v/v) methanol–water in 2 min and a flow-rate of 2·0 ml min^{-1} Detection was effected at 200 nm. $\varepsilon_{3a} : \varepsilon_{3b} = 100000 : 126908$. In kinetic runs products were identified by comparing their retention times with those of reference compounds (**3a**, **3b**);

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