

Modelling of Solvent Effects on the Diels–Alder Reaction

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1 Introduction

Since the pioneering work of Menshutkin in 1890, it is well known that a change of solvent can considerably alter the rate and selectivities of homogeneous phase chemical reactions,¹ owing to the different effect on the Gibbs free energy of the reaction components by differential solvation of the reactants and of the different activated complexes.

Reactions involving isopolar activated complexes, such as the Diels–Alder reaction, normally exhibit small solvent effects and, consequently, studies on this topic have traditionally been scarce. However, interest in the role of the solvent in Diels–Alder reactions has increased over the last few years because of the noticeable improvement in these reactions achieved by the use of water or aqueous solvent mixtures.² As a consequence, there have been many papers recently dealing with the elucidation of the physico-chemical causes of the variations in rate and in the different selectivities, induced by a change of the medium in which the reactions are carried out. Two main approaches have been used to achieve this goal. Firstly, an empirical approach considers some experimental values of the reaction studied, such as the rate or several types of selectivity, which are subsequently related to empirical solvent parameters used to model the different properties of the solvents. Secondly, in a theoretical approach, the solvent effect is assessed by means of different theoretical models, using quantum chemical or classical intermolecular potential calculations.

In this review we wish to present the most relevant papers concerning this work. For the sake of conciseness, non-quantitative studies are not included. In 1980, Sauer and Sustmann³ published a review dealing with the influence of the solvent on the Diels–Alder reaction. However, most of the quantitative empirical

studies and all of the theoretical work in this field have been published since then.

2 Empirical Models

Chemical reactions can be affected by the solvent through several kinds of interactions. For this reason, the role of the different solvation mechanisms influencing a particular reaction cannot be deduced from purely qualitative data. Instead, studies on solvent effects are generally carried out by means of relationships between reactivity properties, *i.e.* reaction rate or several types of selectivity, and empirical parameters representing different kinds of solute–solvent interaction mechanisms.

These parameters are usually derived from measurements on equilibrium, kinetic or spectroscopic properties.¹ As a consequence, it is not reasonable to expect high correlations when empirical models based on these kinds of parameters are used to study reactions or properties very different from those used to determine their values. However, sometimes such high correlations are indeed obtained, which indicates that there are some intrinsic solvation features that are transferable from one property to another. In any case, of more relevance than high determination coefficients (r), the statistical significance of the regression coefficients must be tested in order to get some insight into the solvation mechanisms that influence a particular reaction result.

2.1 Solvent Effects on Reaction Rates

The first correlation of Diels–Alder reaction rates with empirical solvent parameters appeared in 1974.⁴ In this work, the kinetic rate

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José Ignacio García was born in Zaragoza in 1959. He obtained a PhD in 1986 at the University of Zaragoza. After postdoctoral research at the Institut de Topologie et de Dynamique des Systèmes of the CNRS–Université de Paris VII he joined the Instituto de Ciencia de Materiales de Aragón, where he has a permanent post of scientific researcher. His main research interest is in molecular aspects of stereoselective organic reactions, with particular emphasis on heterogeneous catalysis and solvent effects.

Luis Salvatella was born in Girona in 1967. He received his PhD degree in 1994 at the University of Zaragoza, having worked on experimental and theoretical modelling of solvent effects on Diels–Alder reactions. In the same year he was appointed to the post of Assistant Professor at the University of Zaragoza. In October 1996 he will start postdoctoral research work at the University of Nancy 1 (France), with Professor M. F. Ruiz-López. His present interests are the modelling of Diels–Alder reactions and the heterogeneous catalysis, as well as the history of chemistry.



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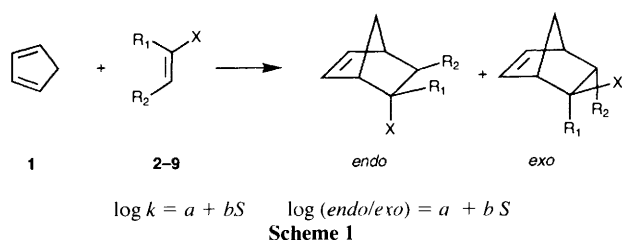


Table 1 Correlations of rates and selectivities of several Diels–Alder reactions (Scheme 1) with Brownstein's S^o solvent polarity parameter (see ref 4 for details)

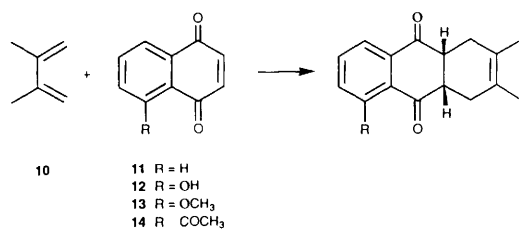
Dienophile	R ₁	R ₂	X	a	b	r	a	b	r
1	—	—	—	-5.38	0.55	0.46	—	—	—
2	H	H	CHO	-3.03	3.83	0.84	0.64	0.64	0.81
3	CH ₃	H	CHO	-3.22	3.52	0.90	-0.79	-0.04	0.77
4	H	H	CO ₂ CH ₃	-3.57	1.70	0.85	0.80	1.31	0.96
5	H	CH ₃	CHO	-3.95	1.13	0.53	0.43	0.72	0.80
6	CH ₃	H	CO ₂ CH ₃	—	—	—	-0.22	0.90	0.94
7	H	CH ₃	CO ₂ CH ₃	—	—	—	0.26	0.99	0.88
8	H	H	CN	—	—	—	0.25	0.16	0.42
9	H	H	COCH ₃	—	—	—	0.81	0.67	0.85

More polar solvents have higher S^o values

constants, k , of the Diels–Alder reactions of cyclopentadiene **1** with acrolein **2**, methacrolein **3**, methyl acrylate **4** and crotonaldehyde **5** (Scheme 1), were measured in a series of solvents, covering a wide range of polarities (from CCl₄ to ethanol-water, 80/20). For the first three reactions, $\log k$ showed significant linear correlations ($r \geq 0.84$) with the empirical parameter of solvent polarity, Brownstein's S^o , which indicates that reaction rates increase with solvent polarity (Table 1). For the reaction with crotonaldehyde the same tendency was observed, but with a worse correlation coefficient. It was shown that the dimerisation of cyclopentadiene **1** also followed the same trend, but with even worse correlation.

However, previous knowledge about the Diels–Alder reaction suggested that a quantitative treatment of the reaction rate on the basis of the whole solvent polarity is a crude approach. In fact, many Diels–Alder reactions are catalysed by Lewis acids, and this makes it logical to study the influence of the solvent 'acidity' on the rate of these reactions.

The influence of the electron pair acceptor (EPA) properties of the solvent on the rates of Diels–Alder reactions was first recognised⁵ in the reaction of 2,3-dimethylbutadiene **10** with 1,4-naphthoquinone **11** (Scheme 2), whose kinetic rate constant was measured in a series of 17 solvents, with polarities ranging from that of cyclohexane to acetic acid. These values did not show suitable linear correlations with classical polarity parameters, such as Reichardt's $E_T(30)$ or Kosower's Z^+ . However, when $\log k$ values were plotted against the Gutmann's AN (Acceptor Number) parameter,¹ a smooth hyperbolic correlation was obtained. Given that this reaction belongs to the normal electron-demand type, *i.e.* it is HOMO_{diene}–LUMO_{dienophile} controlled, the coordination of the EPA solvent at the carbonyl oxygen atom of the naphthoquinone would lower its LUMO energy, increasing the reaction rate. The reaction of the same diene **10** with several 5-substituted-1,4-naphthoquinones **11–14** also showed the abovementioned



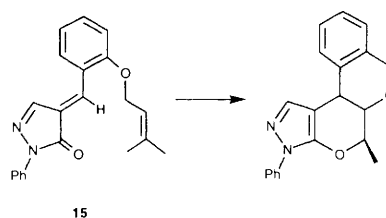
$$\log k = A[(1 - B \times AN)/(1 - C \times AN)]$$

Scheme 2

thoquinone **11** (Scheme 2), whose kinetic rate constant was measured in a series of 17 solvents, with polarities ranging from that of cyclohexane to acetic acid. These values did not show suitable linear correlations with classical polarity parameters, such as Reichardt's $E_T(30)$ or Kosower's Z^+ . However, when $\log k$ values were plotted against the Gutmann's AN (Acceptor Number) parameter,¹ a smooth hyperbolic correlation was obtained. Given that this reaction belongs to the normal electron-demand type, *i.e.* it is HOMO_{diene}–LUMO_{dienophile} controlled, the coordination of the EPA solvent at the carbonyl oxygen atom of the naphthoquinone would lower its LUMO energy, increasing the reaction rate. The reaction of the same diene **10** with several 5-substituted-1,4-naphthoquinones **11–14** also showed the abovementioned

Table 2 Correlations of the rate of the reaction between **10** and dienophiles **11–14** (Scheme 2) with the AN parameter (see ref 6 for details)

Dienophile	R	A	B	C	r
11	H	-4.08	-0.004	-0.170	0.985
12	OH	-5.71	-0.102	-0.280	0.985
13	OCH ₃	-3.79	-0.003	-0.015	0.963
14	COCH ₃	-3.83	-0.002	-0.016	0.962



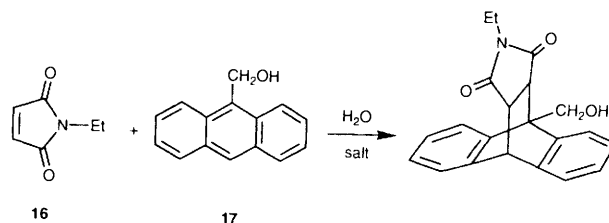
Scheme 3

hyperbolic correlation between $\log k$ and AN (Table 2). Furthermore, the nature of the substituent had a small influence on the solvent effect observed for these Diels–Alder reactions.⁶

The intramolecular Diels–Alder reaction of 1-phenyl-4-[2-(3-methylbut-2-enyloxy)phenylmethylene]pyrazol-5-one **15** (Scheme 3) was studied in several solvents and benzene solutions with varying amounts of acetic and haloacetic acids.⁷ The kinetic data for non-acid and acid solvents plotted against the AN parameter fell on the same hyperbolic curve, which allowed the authors to conclude that solvent effect and acid catalysis follow the same mechanism, increasing the reaction rate by coordination with the α,β -unsaturated heterocycle moiety, whose LUMO energy is lowered.

Although these studies clearly showed the importance of the acidic properties of the solvent, they did not fully account for the dramatic increase in rates observed in several Diels–Alder reactions carried out in water or organic solvent–aqueous mixtures. It has been suggested that the cavitation term of the solvation energy is responsible for this behaviour.

Thus, internal pressure has been invoked to explain the changes in reaction rates for the reaction between *N*-ethylmaleimide **16** and 9-anthrylmethanol **17**, caused by several aqueous salt solutions (Scheme 4).



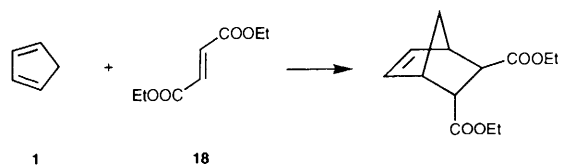
$$\text{Sodium salts } k = 0.11849 + 0.48788 \times 10^{-4}P$$

$$\text{Guandinium salts } k = -8.2767 \times 10^{-2} + 1.4306 \times 10^{-4}P$$

Scheme 4

4)⁸ The reaction rate was higher in media with higher internal pressure, which is consistent with the changes in hydrophobic effects, such that a simple bulk property can account for these changes.

The development by Abraham and coworkers of a quantitative scale of solvophobic power (Sp),¹ that can be applied to pure solvents and to aqueous–organic mixed solvents, allowed the use of this solvent feature as a variable in quantitative studies. Even prior to this publication, Sp values were used to study the solvent effects on the rate of the reaction between diethyl fumarate **18** and cyclopentadiene **1** (Scheme 5).⁹ When the reaction was carried out in binary water–methanol and water–1,4-dioxane mixtures, $\log k$ showed a linear correlation with the solvent polarity parameter $E_T(30)$, but this correlation disappeared when water and other pure solvents were included in the analysis. However, $\log k$ measured in 13 reaction media, including pure solvents and aqueous mixtures, showed a linear correlation with Sp values.

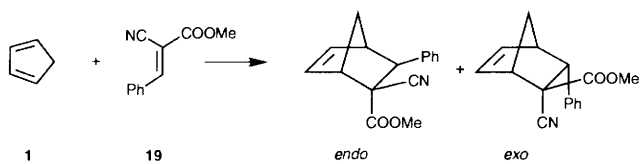


$$\log k = -40(\pm 1.0) + 2.2(\pm 0.4)Sp + 0.2(\pm 0.02)E_T(30) \quad (r = 0.9761)$$

Scheme 5

After this quantitative study of reaction rates as a function of solvophobicity, the same parameter was used in further work. Thus, a variety of Diels–Alder reactions with several dienes and dienophiles were studied in a very much narrower set of solvents: water, methanol, and two aqueous mixtures. The sensitivity of the reaction to solvent solvophobicity was shown to depend on the nature of the reagents and, unexpectedly, it decreased with solvent hydrophobicity in a series of acrylates.¹⁰ This result indicates that the self-association between molecules of the dienophile, driven by the solvent hydrophobicity, can be counter-productive.

The positive influence of solvophobicity, which is expected in processes with a negative activation volume, was further shown in other Diels–Alder reactions, such as those of methyl (*E*)-2-cyanocinnamate¹¹ **19** (Scheme 6), methyl acrylate¹² **4**, and (*1R,2S,5R*) menthyl acrylate¹³ **20** (Scheme 7) with cyclopentadiene.



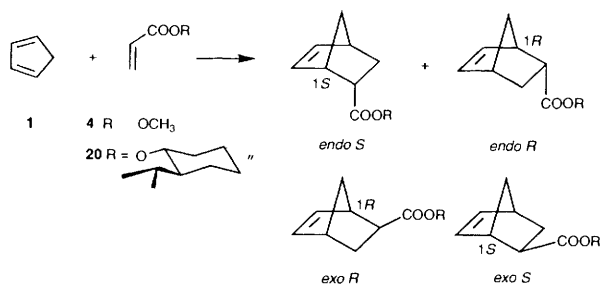
$$\log k = -2.8374 + 2.3516(\pm 0.1974)Sp \quad (r = 0.994)$$

$$\log (endo/exo) = 0.1063 + 0.2284(\pm 0.0459)Sp \quad (r = 0.956, n = 12)$$

$$\log (endo/exo)_{\text{acetone-water}} = 0.1117 + 0.2445(\pm 0.0297)Sp \quad (r = 0.996, n = 6)$$

$$\log (endo/exo)_{\text{dioxane-water}} = 0.0996 + 0.2149(\pm 0.0389)Sp \quad (r = 0.992, n = 6)$$

Scheme 6



$$\log k(\mathbf{4}) = -3.195 + 2.075(\pm 0.824)Sp + 0.904(\pm 0.746)E_T^N \quad (r = 0.942)$$

$$\log k(\mathbf{20}) = -4.646 + 1.354(\pm 0.590)Sp + 0.520(\pm 0.243)E_T^N \quad (r = 0.912)$$

$$\log k(\mathbf{20}) = -4.489 + 0.446(\pm 0.042)\alpha \quad (r = 0.947)$$

$$\log (endo/exo)(\mathbf{4}) = 0.457 + 0.356(\pm 0.149)Sp + 0.399(\pm 0.135)E_T^N \quad (r = 0.970)$$

$$\log (endo/exo)(\mathbf{20}) = 0.415 + 0.432(\pm 0.069)Sp + 0.320(\pm 0.040)E_T^N \quad (r = 0.986)$$

$$\log (endo/exo)(\mathbf{20}) = 0.345 + 0.367(\pm 0.061)\pi^* - 0.121(\pm 0.038)\delta + 0.163(\pm 0.028)\alpha \quad (r = 0.957)$$

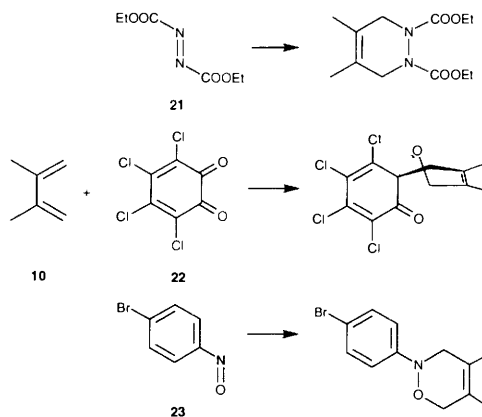
$$\log (endo_R/endo_S)(\mathbf{20}) = 0.053 + 0.099(\pm 0.020)E_T^N \quad (r = 0.758)$$

$$\log (endo_R/endo_S)(\mathbf{20}) = 0.103 + 0.060(\pm 0.006)\alpha \quad (r = 0.832)$$

Scheme 7

1 However, the results obtained with acrylates indicated that the inclusion of a polarity term, represented by the E_T^N parameter [a normalised $E_T(30)$ parameter],¹ may be important in explaining the influence of the solvent on the rate of some Diels–Alder reactions. A comparison of these results with those obtained with mono- and di-ethyl fumarates, and fumaric and maleic acids,¹⁰ indicates that the relative importance of solvent polarity and solvent solvophobicity depends on the nature of the dienophile. The influence of solvent polarity is greater for the more unsymmetrical dienophiles, namely

methyl **4** and (*1R,2S,5R*)-menthyl **20** acrylates, which can be accounted for by a more asynchronous reaction mechanism. Furthermore, the influence of the solvent solvophobicity is expected to be greater for the reactions with a more negative activation volume ($\Delta V^\ddagger = -32.7 \text{ cm}^3 \text{ mol}^{-1}$ for the reaction of dimethyl fumarate with cyclopentadiene, and $\Delta V^\ddagger = -30.1 \text{ cm}^3 \text{ mol}^{-1}$ for the reaction of methyl acrylate with cyclopentadiene).



Scheme 8

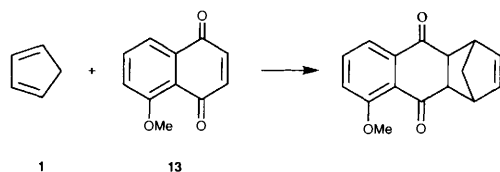
These papers showed that the nature of the reagents has a great influence on the dependence of the rate of different Diels–Alder reactions on the solvent properties. This fact was also clearly shown¹⁴ for the reactions of three different heterodienophiles, namely diethyl azodicarboxylate **21**, tetrachloro-*o*-benzoquinone **22**, and *p*-bromonitrosobenzene **23** with 2,3-dimethylbuta-1,3-diene **10** (Scheme 8). In the first reaction the rate was increased by solvents with electron acceptor properties, *i.e.* high ΔN values. This case is representative of those reactions for which the interaction of the diene or the dienophile with an electrophilic solvent lowers its LUMO energy. The second reaction was disfavoured by solvents with electron donor properties, as quantified by the D_π values.¹ This second case is representative of those reactions for which the reaction rate decreases owing to the increase of the dienophile LUMO energy, caused by interaction with nucleophilic solvents. In the third reaction, the variation in the reaction rate was mainly accounted for by the changes in solvent cohesive energy, as represented by Hildebrand's δ_H^\dagger values.¹

It is important to note that the interpretation of the results obtained from these studies is not straightforward because of the correlations that exist between pairs of empirical solvent parameters. Thus, it is known that E_T is a blend of dipolarity and hydrogen bond donor (HBD) properties of the solvent.¹ Furthermore, Sp and E_T parameters show an intrinsic correlation, since the most solvophobic media are also the most polar ones.¹² As a consequence, the existence of good correlations with only one of these parameters does not mean that the rate of the reactions only depends on one term of the solvation energy.

In view of this, it is advisable to use multiparameter approaches. The Abboud–Abraham–Kamlet–Taft (AAKT) model¹ has been used to study the effect of the solvent on the reaction between cyclopentadiene **1** and (*1R,2S,5R*)-menthyl acrylate **20** (Scheme 7). When applied to changes in the reaction rate, expressed as $\log k$, the results indicated that the HBD ability (represented by the α parameter) is the only solvent feature with a statistically significant regression coefficient.¹³ However, the α and Sp solvent parameter values are strongly correlated, and some of this influence may be due to the solvent solvophobicity. Indeed, a reasonable regression model is obtained using the Sp and E_T^N parameters, and the reaction is faster in the most solvophobic solvents (aqueous mixtures), rather than in those with the best HBD properties (fluorinated alcohols).

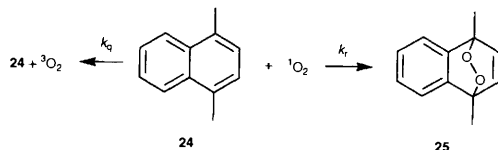
The relevant role of hydrogen-bonding and solvophobicity (represented by the cohesive energy density) on the rate of Diels–Alder reactions has also been shown¹⁵ in the reaction of cyclopentadiene **1** with 5-methoxy-1,4-naphthoquinone **13** (Scheme 9), using the Kirkwood–Onsager–Parker–Marcus–Hildebrand (KOPMH) equation.

Very recently, the AAKT model has been used to study solvent



$$\log k = -3.27 + 31.08\alpha - 14.53\delta_{\text{H}}^2 \quad (r = 0.977)$$

Scheme 9



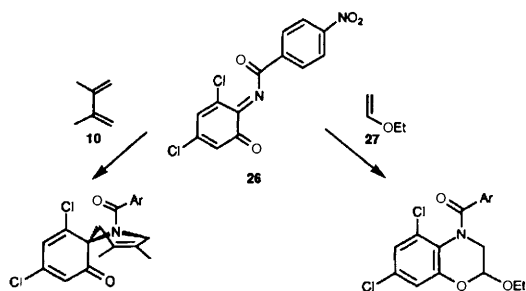
$$\log(k_r + k_q) = 2.62 + 0.07\delta_{\text{H}} + 1.18\pi^* \quad \text{Scheme 10}$$

effects on the quenching of singlet oxygen by 1,4-dimethylnaphthalene **24** (Scheme 10) for 28 solvents¹⁶. Again, cohesive energy density plays a relevant role, but in this case, the solvent dipolarity is also important, which is accounted for by a two-step mechanism. The first step involves the reversible formation of an exciplex with a charge transfer character. In the second step, the solvated exciplex yields the endoperoxide **25** or intact 1,4-dimethylnaphthalene **24** and oxygen in the ground state.

The results described so far indicate that solvent solvophobicity has a great (and not unexpected) influence on the rate of Diels–Alder reactions, and that the HBD ability of the solvent is very important in many cases. The influence of the solvent dipolarity is not so clear, and some of the above results can be ascribed to a positive influence of this solvent feature on the reaction rate.

However, the use of the AAKT multiparameter model has shown¹⁷ that the solvent dipolarity–polarisability (represented by the π^* parameter) has a negative influence on the rate of the reactions of the *o*-quinone imine **26** with 2,3-dimethylbuta-1,3-diene **10**, and with ethyl vinyl ether **27** (Scheme 11). These are the only known examples for which a negative influence of solvent dipolarity–polarisability has been experimentally found. In the same reactions a negative influence of the solvent electron donor ability (represented by the β parameter) was reported.

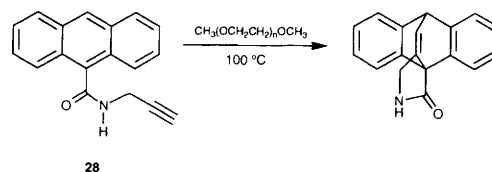
Finally, a particular point, namely the relationship between solvent viscosity or solvent density and the rate of some intramolecular Diels–Alder reactions, deserves some comments. The vibrational activation theory states that bond-making reactions are promoted by



$$3 + \log k = 1.80 - 0.63\pi^* + 0.04\delta - 1.57\beta \quad (r = 0.90)$$

$$3 + \log k = 2.73 - 0.97\pi^* + 0.23\delta - 1.16\beta \quad (r = 0.92)$$

Scheme 11



$$k_{\text{in}}/k_1 = 0.66 + 0.37(\eta_{\text{n}}/\eta_1) \quad (r = 0.984)$$

Scheme 12

vibrational energy in the reactants and that high translational energy is detrimental to the reaction. As a consequence, high solvent viscosity should promote bond making reactions. For bimolecular reactions, reactants cannot locate each other if the viscosity is too high, because of diffusional problems, so the effect of viscosity has only been studied for intramolecular reactions for which, in principle, solvent polarity has a small influence. An example of such a reaction is the Diels–Alder reaction of *N*-prop-2-ynylantracene-9-carboxamide **28** (Scheme 12)¹⁸. The reaction was carried out in a series of glymes in order to have a set of solvents of similar structure (and hence polarity), but different viscosity. A significant correlation between the relative rate and the relative viscosity was found. Although it would be better to use microviscosity instead of the macroscopic property, the results show that viscosity can be considered as one of the external factors controlling the rates of intramolecular Diels–Alder reactions.

The same reaction was carried out at 100 °C in several mixtures of tetraglyme with poly(ethylene glycol) monomethyl ethers¹⁹. Although the reaction rates increased with viscosity, the increase was smaller than that observed for the series of glymes, and it was not regular. However, the relative rate increased linearly with solvent density (Fig. 1). The density increase was attributed to a more efficient

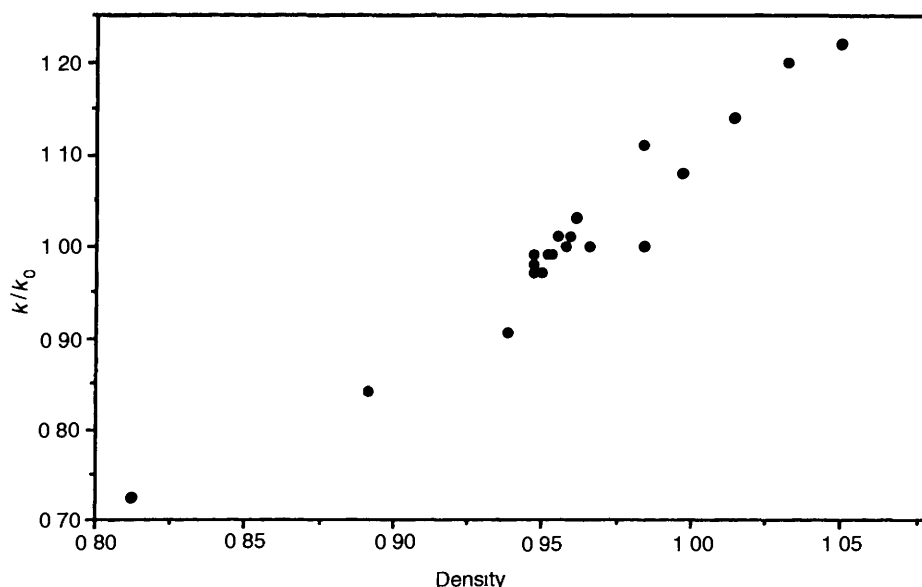


Figure 1 Relationship between relative kinetic rate constants and density of the medium for the intramolecular Diels–Alder reaction of *N*-prop-2-ynylantracene-9-carboxamide, carried out in several mixtures of tetraglyme with poly(ethylene glycol) monomethyl ethers (see ref. 19 for details)

packing of the solvent chains, and these closely packed zones favour the reaction because they hinder the translation of the two reactive parts of the molecule. Thus, density was proposed as a new reactivity index not subject to the drawbacks of macroscopic viscosity.

2.2 Solvent Effects on Selectivities

2.2.1 *endo/exo* Selectivity

In 1962, Berson *et al.* published²⁰ a pioneering work dealing with solvent effects on the *endo/exo* selectivities of several reactions of α,β -unsaturated esters with cyclopentadiene **1**. The reactions were carried out in 12 different solvents, with polarities ranging from that of decalin to methanol and acetic acid. At that time, water or aqueous mixtures could not be included owing to the low sensitivity of the gas chromatographic analyses and the low solubility of cyclopentadiene. Berson and coworkers found that the *endo/exo* selectivities of all reactions were co-linear. In fact, they defined a new solvent polarity parameter, the so-called Ω_t parameter (where t denotes temperature), as the logarithm of the *endo/exo* ratio for the reaction of cyclopentadiene **1** with methyl acrylate **4**. Ω_t was shown to correlate with several other polarity parameters, such as Kosower's Z^1 ($r = 0.972$) or $\log k_{\text{ion}}^1$ ($r = 0.936$), as well as with solvent dielectric functions, such as $[(\epsilon - 1)/(2\epsilon + 1)] \times (\rho/M)$ ($r = 0.957$), in the case of aprotic solvents. Given that these solvent polarity scales cover very different ranges (from 0.5 kcal mol⁻¹ in the case of Ω_t , to 24 kcal mol⁻¹ in the case of Z^1 , 1 cal = 4.184 J) the authors concluded that 'a set of solvents behaves as an elephant, which can lift a log or a peanut with equal dexterity'.²⁰ With regard to the origin of these solvent effects, the authors of this work invoked the greater dipole moment of the *endo* over the *exo* transition state (Fig. 2). The preferential solvation of the former in polar solvents leads to enhanced *endo/exo* ratios.

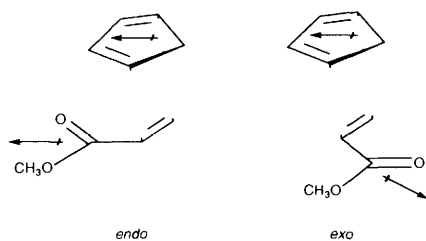
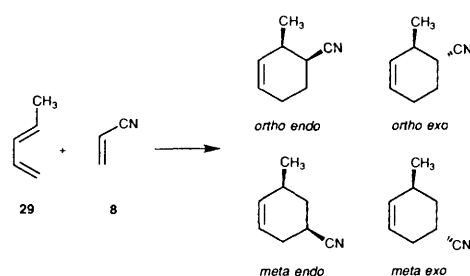


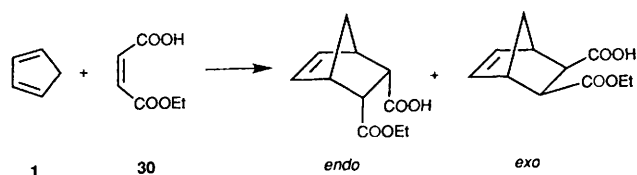
Figure 2 Berson's justification of why the *endo* transition state of the reaction between cyclopentadiene and methyl acrylate has a higher dipole moment than the corresponding *exo* one (see ref. 20 for details).

As a further extension of this work, the *endo/exo* selectivity of the reactions of cyclopentadiene **1** with eight different dienophiles (Scheme 1), was measured in 17 solvents, with polarities ranging from that of *n*-hexane to ethanol–water (80/20) and formic acid.⁵ In most cases, fairly good correlations ($r \geq 0.77$) were found between $\log(\textit{endo/exo})$ and Brownstein's S , which is in turn closely related to Kosower's Z^1 . The worst result corresponded to the reaction of cyclopentadiene **1** with acrylonitrile, for which a correlation coefficient of 0.42 was reported (Table 1).

However, changes in *endo/exo* selectivity for the reactions of cyclopentadiene **1** with methyl acrylate **4** and acrylonitrile **8**, carried out in a set of 13 solvents with polarities ranging from that of *n*-hexane to methanol, can be explained in a different way.²¹ In fact, good correlations were found between $\log(\textit{endo/exo})$ and the molar refractivity, R_D , of the solvent. Good correlations between these parameters were also found when using acetone–hexane and methanol–benzene mixtures as reaction media. The correlation with R_D indicates that dispersion forces play a role. Further studies carried out for the reaction of (*E*)-penta-1,3-diene **29** with acrylonitrile **8**²² in five solvents (Scheme 13) also showed a linear correlation between $\log(\textit{endo/exo})$ and R_D . Steric effects and dipole–dipole interactions were discarded as causes of the change in selectivity observed owing to the particular features of the diene concerned. Thus, the authors concluded that solvent polarisability plays a role in determining *endo/exo* selectivities.



Scheme 13



$$\log(\textit{endo/exo}) = 1.30(\pm 0.024) + 0.414(\pm 0.038)Sp \quad (r = 0.9835)$$

$$\log(\textit{endo/exo}) = 1.304(\pm 0.322) + 0.364(\pm 0.101)Sp + 0.0035(\pm 0.0065)E_T(30) \quad (r = 0.9850)$$

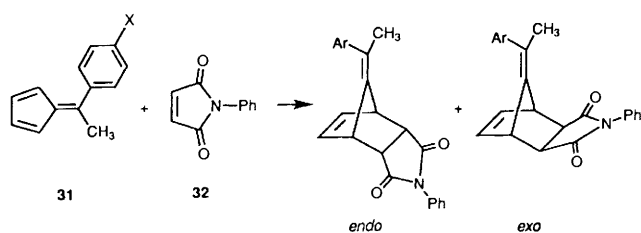
Scheme 14

The role of water and aqueous mixtures on the *endo/exo* selectivity of Diels–Alder reactions suggests that solvent solvophobicity can be important. The influence of this factor was first explored by Schneider and Sangwan²³ for the reaction of cyclopentadiene **1** with ethyl maleate **30** (Scheme 14). Two possible effects were considered, namely solvent polarity [as represented by $E_T(30)$] and solvophobicity (as represented by Sp). A good regression line was obtained between $\log(\textit{endo/exo})$ and Sp , whereas the fit was not so good with $E_T(30)$. Furthermore, a multiparameter $Sp/E_T(30)$ regression model did not improve the fit compared with the monoparameter Sp fit. These results seem to indicate that the hydrophobic effect is the main factor determining the *endo/exo* selectivity of this reaction.

The idea of solvophobicity as the main solvent characteristic controlling changes in *endo/exo* selectivity is very attractive and it was used in a study of the reaction of cyclopentadiene **1** with methyl (*E*)-2-cyanocinnamate **19** (Scheme 6) in 12 water–dioxane and water–acetone mixtures.¹¹ A fairly good correlation was found between $\log(\textit{endo/exo})$ and Sp , but in this case, the regression fit significantly improved when each solvent series was taken separately. This result indicates that solvent polarity also plays an additional role in explaining the changes in *endo/exo* selectivity induced by the reaction medium. This point was further explored by studying the reaction of cyclopentadiene **1** with methyl acrylate **4** in 19 organic solvents and aqueous mixtures.¹² The *endo/exo* selectivity results were accounted for by means of a two-parameter Sp/E_T^1 model (Scheme 7). Unlike Schneider's results,²³ both solvophobic and polar contributions had significant coefficients, and both showed similar relative importance. These differences were ascribed to the different nature of the dienophiles used. Thus, methyl acrylate leads to more asynchronous, unsymmetrical transition states, which would explain the greater influence of polar effects. On the other hand, the difference in compactness between the *endo* and the *exo* transition states of the ethyl maleate–cyclopentadiene reaction ($\Delta\Delta V^\ddagger = 0.82 \text{ cm}^3 \text{ mol}^{-1}$) is greater than that for the corresponding reaction between cyclopentadiene **1** and methyl acrylate **4** ($\Delta\Delta V^\ddagger = 0.62 \text{ cm}^3 \text{ mol}^{-1}$), which would explain the larger relative influence of Sp on the former reaction.

(1*R*,2*S*,5*R*)-Methyl acrylate **20** displays a behaviour similar to that observed for methyl acrylate **4**.¹³ The regression analyses again showed that both Sp and E_T^1 are necessary to explain the changes observed in *endo/exo* selectivity. Furthermore, both parameters have similar relative weights. The comparison of results indicates that, as happens with the reaction rate, there is a close relationship between the nature of the reagents and the effect of the solvent on the *endo/exo* selectivity.

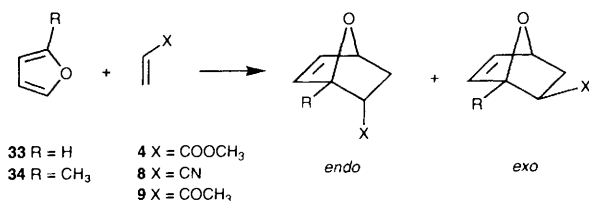
The subtle dependence of solvent influence on the nature of the reagents has also been shown²⁴ in a study dealing with the effect of



Scheme 15

the solvent on the *endo/exo* selectivity of the reaction between *para*-substituted 6-methyl 6-phenylfulvenes **31** and *N*-phenylmaleimide **32** (Scheme 15). Solvent effects changed as a function of the substituent in the aryl group of the diene. Thus, when this substituent was the CN group, an increase in the *endo/exo* ratio with the relative permittivity of the solvent was observed. On the other hand, solvent effects were negligible when the substituent was the $N(CH_3)_2$ group. However, owing to the extremely small set of solvents considered in this work (benzene, acetone and dimethyl sulfoxide), we should take these conclusions with some caution.

The same effect, namely the influence of the solvent on the *endo/exo* selectivity depending strongly on the reagents, was observed when comparing several reactions of furan **33** and 2-methylfuran **34** with methyl vinyl ketone **9**, methyl acrylate **4**, and acrylonitrile **8** (Scheme 16), carried out in seven different reaction



Scheme 16

media.²⁵ Thus, the solvent hardly modified the *endo/exo* ratios observed for the reactions of furan **33** with acrylonitrile **8** and 2-methylfuran **34** with methyl acrylate **4**. On the other hand, for the reaction between furan **33** and methyl vinyl ketone **9**, there was a significant variation in the selectivity with the reaction medium. This variation is, however, difficult to rationalise, since water always behaves differently from the rest of the reaction media. Excluding water from the analysis, the *endo/exo* selectivity seemed to be linearly correlated with the cohesive energy density of the medium.

A point of caution should be expressed regarding the conclusions drawn from these empirical models, owing to the high cross-correlations between solvent scales representing different solvent properties. It seems clear that a single solvent parameter does not account for the changes in *endo/exo* selectivity, which led to the use of multiparameter models.

Thus, the AAKT model has been used to analyse the results of the reaction between cyclopentadiene **1** and (1*R*,2*S*,5*R*)-methyl acrylate **20**.¹³ Both dipolarity–polarisability (as represented by the couple π^*/δ) and HBD ability (as expressed by α) are important in explaining the solvent effects observed, both having similar relative importance (Scheme 7).

A different kind of multiparameter model, namely the KOPMH one, was used¹⁵ to analyse Berson's results²⁰ for the reaction between cyclopentadiene **1** with methyl acrylate **4**. The application of the KOPMH equation to ten sets of experimental data indicated that both the cohesive energy density and the HBD ability of the solvent increase the *endo* selectivity. These results are essentially identical to those obtained using the AAKT model, and they are in full agreement with the conclusions previously reported.¹² If 2,2,2-trifluoroethanol (TFE) was included in the analysis, the relative importance of the HBD ability with regard to the cohesive energy density increased, hence showing that the results obtained from the data analysis depend on the solvent set considered.

The importance of solvophobic effects on the *endo/exo* selectivity has been shown further in a recent study²⁶ concerning the reac-

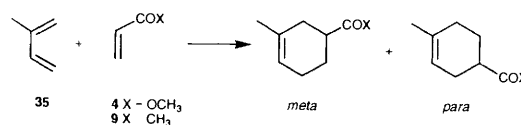
tions of cyclopentadiene **1** with methyl acrylate **4** and methyl vinyl ketone **9** in 18 different organic solvents and aqueous mixtures, with a wide range of solvent properties. The experimental *endo/exo* selectivities were analysed by means of the AAKT model, augmented with an *Sp*-dependent term, in order to account for solvophobic effects. The results obtained from regression analyses showed that for both reactions solvophobicity and HBD ability were the main factors responsible for the changes in selectivity observed. In the case of the reactions of methyl acrylate **4**, the dipolarity–polarisability also played a significant role, which indicates that the nature of the dienophile also determines the solvent effects. It is worth noting that high co-linearities were observed between *Sp* and π^* , and between *Sp* and α . However, the highest *endo* selectivities are always obtained for the reactions carried out in water or aqueous mixtures, which is more consistent with the dominance of the solvophobic, rather than the dipolar or HBD, term.

Experimental results show that solvent solvophobicity, dipolarity and HBD ability influence the *endo/exo* selectivity of Diels–Alder reactions, but the relative importance of these factors depends on the nature of the reagents.

2.2.2 Regioselectivity

The effect of the solvent on the regioselectivities of Diels–Alder reactions has received far less attention than its effect on the *endo/exo* stereoselectivity, probably owing to the lower sensitivity of the former towards changes in the reaction medium.

The solvent effect on the *ortho/meta* regioselectivity of the reaction of (*E*)-penta-1,3-diene **29** with acrylonitrile **8** (Scheme 13) was studied by Nakagawa *et al.*²² in five solvents (methanol, ethanol, acetone, tetrahydrofuran and benzene). The regioselectivity results were correlated with the molar refractivity, R_D , of the corresponding solvents. This correlation prompted the authors to conclude that solvent polarisability may play a role in determining the regioselectivity of this reaction.



$$\log(\textit{para/meta})(\mathbf{4}) = 0.350 + 0.167(\pm 0.010)\alpha \quad (r = 0.977, \text{ with fluorinated alcohols})$$

$$\log(\textit{para/meta})(\mathbf{4}) = 0.350 + 0.167(\pm 0.014)\alpha \quad (r = 0.961, \text{ without fluorinated alcohols})$$

$$\log(\textit{para/meta})(\mathbf{9}) = 0.301 + 0.222(\pm 0.034)\alpha \quad (r = 0.867, \text{ with fluorinated alcohols})$$

$$\log(\textit{para/meta})(\mathbf{9}) = 0.347 + 0.082(\pm 0.015)\alpha \quad (r = 0.844, \text{ without fluorinated alcohols})$$

Scheme 17

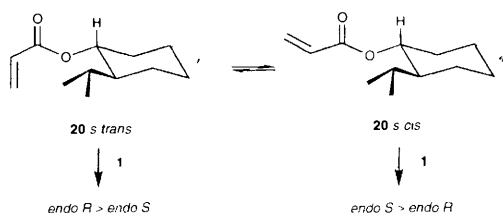
Much more recently,²⁶ the reactions of 2-methylbuta-1,3-diene (isoprene) **35** with methyl acrylate **4** and methyl vinyl ketone **9** (Scheme 17) were studied for 18 solvents, with polarities ranging from that of *n*-hexane to HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) and water. The results obtained were analysed by means of the AAKT model. For both reactions, it was found that the HBD ability of the solvent was the only significant factor influencing the *para/meta* regioselectivity. However, the behaviour of both dienophiles in fluorinated alcohols was different. Thus, whereas the exclusion of TFE and HFIP from the regression analysis did not change the coefficient of α in the case of methyl acrylate, this coefficient dramatically decreased in the case of methyl vinyl ketone. Such results indicate that in the former case the same solvation mechanism accounts for results in all the solvents considered, whereas in the latter case fluorinated alcohols display a different behaviour. IR spectroscopic studies of the interactions between HBD solvents and dienophiles showed that, in the case of methyl vinyl ketone, fluorinated alcohols (but not methanol) are able to form two simultaneous hydrogen bonds with the carbonyl oxygen atom. This does not happen in the case of the less basic methyl acrylate, which would explain its different behaviour.

The HBD ability of the solvent increases the regioselectivity of

normal electronic demand Diels–Alder reactions, but the magnitude of this effect depends on the nature of the reagents. It is also worth noting that a correct choice of the solvent set to use for the experimental study is crucial, given that in most cases solvent effects are noticeable only for solvents with very high HBD ability, such as fluorinated alcohols.

2.2.3 Diastereofacial Selectivity

The only systematic study on the influence of the solvent on asymmetric induction is that of Cativiola *et al.*,¹³ who studied the reaction between cyclopentadiene **1** and (1*R*,2*S*,5*R*)-menthyl acrylate **20** (Scheme 7) in 20 solvents and aqueous mixtures, covering a wide range of solvent properties. The results of diastereofacial selectivity of the major *endo* cycloadducts were analysed by means of two different multiparameter regression models. Only moderate, though significant, correlations were found between the experimental results and E_N^\ddagger and α parameters. This points to the HBD ability of the solvent as the main factor in determining the asymmetric induction, which is in turn related to the *s-cis/s-trans* conformational equilibrium of the dienophile (Scheme 18). In this respect, the



Scheme 18

authors concluded that HBD solvents, and in particular fluorinated alcohols, behave as mild Lewis acids. It is worth noting that if fluorinated alcohols were excluded from the regression equation, the variation in diastereofacial selectivity was better described by the π^* parameter, which indicates that dipolarity, which also influences the abovementioned conformational equilibrium, plays a role. The influence of the dipolarity is thus obscured by the effect of the highly HBD fluorinated alcohols.

3 Theoretical Models

Real solutions are composed of a huge number of at least two kinds of molecules in motion interacting by means of very complex potentials. For this reason, theoretical calculations on chemical systems in solution are more sophisticated than those in the gas phase. In a typical study, reactivity properties (activation barriers and several kinds of selectivity) are compared between the 'gas phase' calculations of reactants and transition structures (TSs) by means of common theoretical methods and those in which solute–solvent interactions are considered explicitly. Of course, the reliability of such a study depends strongly on two main features, namely the theoretical level and the solvent model used.

Both semiempirical and *ab initio* methods have been used to study solvent effects on the Diels–Alder reaction.

Several solvent models can be proposed depending on the properties that one wishes to describe in a more realistic manner. Three of these have been applied to the Diels–Alder reaction, SCRF, Monte Carlo and supermolecule.

The self-consistent reaction field (SCRF, also called cavity or continuum) model represents the solvent as an infinite polarisable continuum, characterised by its relative permittivity, ϵ , surrounding a variable shaped cavity, in which the solute is placed. This is a convenient model for describing electrostatic interactions due to the solvent polarity. However, short-range interactions are not correctly represented by this method. Spherical as well as ellipsoidal cavity shapes have been used for the studies of Diels–Alder reactions. The ellipsoidal cavity produces a more realistic model than the spherical one because of its better fit to the solute shape. In addition to the difference in the cavity shape, there is a second consideration concerning the quality of the SCRF model, depending on the formula

used for the solvation energy. In general, the free energy of solvation is composed of a number of multipole–multipole interactions. If only dipole–dipole terms are considered, and a spherical cavity is taken into account, the Onsager model is obtained.

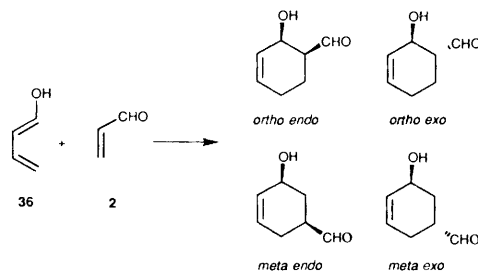
Another kind of solvent model is that obtained by means of Monte Carlo simulations, which represent the solvent as a set of discrete molecules interacting through simple pairwise additive potentials. Through stochastic numerical integration techniques, it is possible to obtain ensemble averages, which can be used for computing properties of liquids and solutions. Both the canonical (NVT) and the isothermal–isobaric (NPT) ensembles are usually used in these simulations, and the Metropolis importance sampling algorithm has become a standard. An advantage of the Monte Carlo simulations is that they account not only for solute–solvent interactions, but also for solvent–solvent interactions, which can be extremely important in the case of highly self-organised solvents, like water.

Finally, in the supermolecule model, the solvent is considered as a single molecule (or a small set of them) coordinated to the solute. Obviously, this method cannot take into account most of the solute–solvent interactions. However, it is useful for describing accurately specific short-range interactions, such as hydrogen bonds, by means of quantum mechanical calculations.

As in the case of empirical methods, these solvent models have been applied to the study of four different kinds of effects in the Diels–Alder cycloadditions: reaction rate, and *endo/exo*, regio-, and diastereofacial selectivities.

3.1 Solvent Effects on Reaction Rates

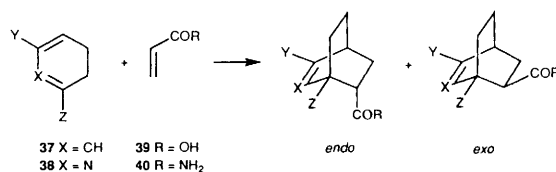
The pioneering work of Bertran²⁷ and coworkers studied solvent effects on the reaction of (*E*)-buta-1,3-dien-1-ol **36** with acrolein **2** (Scheme 19) by means of the SCRF model. The results obtained from MINDO/3 calculations indicated that an increase in solvent polarity produced a decrease in the activation barrier.



Scheme 19

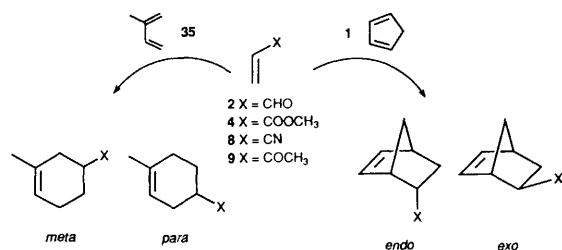
It is well known nowadays that MINDO/3 predicts extremely unsymmetrical transition structures for Diels–Alder reactions. This fault can be overcome by using AM1 and PM3 semiempirical methods, which generally predict concerted mechanisms with geometries for the transition structures similar to those obtained by means of *ab initio* calculations.

The SCRF model with PM3 calculations was used to study the reactions of several cyclohexadienes **37** and 6-silyloxy-4,5-dihydropyridine **38** with acrylic acid **39** and acrylamide **40** (Scheme 20).²⁸ Two kinds of mechanisms, concerted or two-step, were calculated as a function of the diene. In both cases, the solvent stabilises preferentially the structure with the higher dipole moment, which in the stepwise mechanism increases the barrier of the second step.



Scheme 20

A comprehensive study was carried out for the reactions of cyclopentadiene **1** and isoprene **35** with four dienophiles by means of

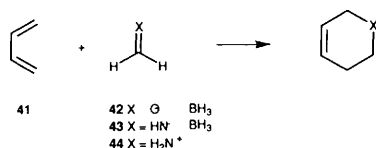


Scheme 21

PM3 and AM1 methods using the SCRF model (Scheme 21)²⁹ The activation barrier was found to decrease for the reactions of acrolein **2** and acrylonitrile **8** and to increase for the reactions of methyl vinyl ketone **9** and methyl acrylate **4**. The supermolecule model, considering the effect of a single water molecule coordinated to the carbonyl or to the nitrile groups with the PM3 method, predicted a decrease in the activation barrier for all the reactions studied. However, both methods have some intrinsic weaknesses, which make the interpretation of some of their results difficult.²⁹

Ab initio calculations have also been used³⁰ to study the influence of the solvent on the rate of the reaction between methyl acrylate **4** and cyclopentadiene **1** using the SCRF model, as well as the supermolecule model, coordinating a single water molecule to the oxygen atom of the carbonyl group. As happened with semiempirical calculations, the SCRF model predicted that the solvent polarity increases the activation energy whereas solvent coordination decreases it.

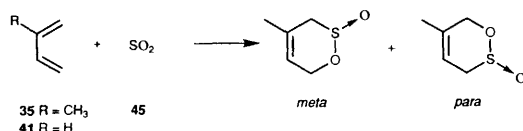
Ab initio calculations in combination with continuum models have also been used to predict the effect of the solvent on Diels–Alder reactions with heterodienophiles. The reactions of buta-1,3-diene **41** with both borane-coordinated formaldehyde **42** and formalimine **43** as well as with the formaldiminium ion **44** were studied³¹ by means of the Onsager model (Scheme 22). The



Scheme 22

results depended on the model used. Thus, 3-21G and 6-31G*//3-21G results showed a non-systematic behaviour, whereas MP2/6-31G*//3-21G calculations predicted an increase in the activation barrier (2.0–2.5 kcal mol⁻¹) due to electrostatic interactions in all the reactions studied. Owing to the neglect of charge terms in the Onsager model, the results obtained for the formaldiminium ion may not be reliable.

For the hetero-Diels–Alder reaction of isoprene **35** and buta-1,3-diene **41** with sulfur dioxide **45** (Scheme 23), the results for the SCRF model depended on whether catalysis was considered or not. Thus, RHF/3-21G* level calculations indicated that solvent polarity raises the activation barrier for the non-catalysed reaction, whereas it decreases it for the borane-catalysed process.³²



Scheme 23

The reaction between cyclopentadiene **1** and methyl vinyl ketone **9** was studied by means of the Monte Carlo model³³ 6-31G*//3-21G calculations on the *endo*-*s-cis* TS, as well as on the reactants, were carried out by considering the solvent models propane, methanol and water. The methodology used was as follows. The reaction path was first calculated in the gas phase, starting from a well characterised TS, and then a number of structures on this reaction path were

'immersed' in the solvent. The solvation effects thus calculated were used in conjunction with the free energy perturbation theory to calculate the solvent effect on the free energy profile of this reaction. The results indicated that water produces an important decrease in the activation barrier (4.2 kcal mol⁻¹), whereas a smaller effect was calculated for methanol, and a very slight variation in the reaction rate was predicted for propane. Analysis of the results indicated that acceleration in the aqueous medium contains a significant non-hydrophobic component stemming from an enhanced polarisation of the TS that leads to stronger hydrogen bonds at the carbonyl oxygen.

A later re-evaluation³⁴ of this reaction has been carried out, as well as a study of the dimerisation of cyclopentadiene. In this work, some technical changes were introduced. 6-31G* geometries were considered (not 3-21G) and 6-31G* CHELPG (not 6-31G* Mulliken) charges were used. Nevertheless, conclusions on the reaction of methyl vinyl ketone were similar to those obtained in the former study. For the dimerisation of cyclopentadiene, only minor changes in the reaction rate induced by the solvent were found.

The influence of solvent solvophobicity has also been evaluated¹³ using the scaled particle theory (SPT) model for the reaction of cyclopentadiene **1** with methyl acrylate **4** and the results obtained agreed with an increase in the reaction rate due to this effect.

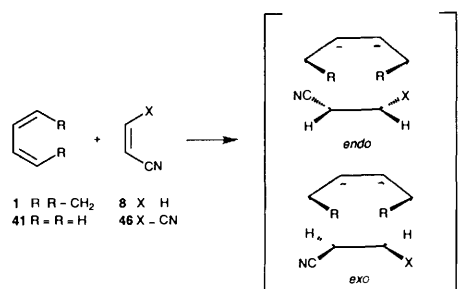
3.2 Solvent Effects on Selectivities

3.2.1 *endo/exo* Selectivity

For the reaction between (*E*)-buta-1,3-dien-1-ol **36** and acrolein **2** (Scheme 19), MINDO/3 SCRF results indicated that electrostatic solvent interactions produce a differential solvation of the *endo* TSs over those of the corresponding *exo* TSs. This effect was attributed to the greater dipole moments and the larger charge transfer between the reactants calculated for the *endo* TSs.²⁷

In the study of the reactions of substituted cyclohexadienes **37** and 6-silyloxy-4,5-dihydropyridine **38** with acrylic acid **39** and acrylamide **40** (Scheme 20) by means of the PM3 method, *endo/exo* selectivity was also found to increase with solvent polarity, according to the SCRF model.²⁸ In fact, this selectivity inverts on passing from the gas phase to continuum model calculations. This effect may again be explained through the dipole moments of the TSs. Reoptimisation of intermediates using the continuum model showed that the solvent effect is underestimated when gas phase geometries are used.

An increase in the *endo* preference with an increase in solvent polarity was also calculated for the reactions of cyclopentadiene **1** and buta-1,3-diene **41** with acrylonitrile **8** and maleonitrile **4b** (Scheme 24).³⁵ In particular, the major product of the reaction



Scheme 24

between cyclopentadiene **1** and acrylonitrile **8** changed from *exo* to *endo* by considering the solvent interactions by means of the continuum model and PM3 energies. For this reason, the authors proposed that the *endo/exo* selectivity experimentally found for this reaction is due to the solvent polarity, secondary orbital interactions being unable to explain the *exo* preference calculated for the gas phase reaction, and experimentally observed in the least polar solvents.

For the reaction of cyclopentadiene **1** with acrylonitrile **8**, acrolein **2**, methyl vinyl ketone **9** and methyl acrylate **4** (Scheme 21), SCRF results predicted an increase in the *endo/exo* selectivity

at both AM1 and PM3 levels. The coordination of a water molecule, calculated by means of the PM3 semiempirical method, hardly modified the *endo/exo* selectivity in the reaction of acrylonitrile, but increased this selectivity in the reactions of the other three dienophiles.²⁹

For the reaction of cyclopentadiene **1** with methyl acrylate **4**, the continuum model predicted a greater stabilisation for the *endo* TSs than for the corresponding *exo* ones¹⁶ by using *ab initio* methods.^{13–30} The examination of the multipole terms showed that the Onsager model is not adequate for this reaction because of the importance of other contributions than the dipole terms. Supermolecule results followed an identical pattern to the SCRf model, although differential stabilisations were smaller.³⁰

For the reactions of buta-1,3-diene **41** with both BH₃-coordinated formaldehyde **42** and formalimine **43** (Scheme 22), the influence of the position of the catalyst (*endo* or *exo*) on the solvation of the TSs was studied by means of the Onsager model.³¹ Calculations indicated that selectivity varies only slightly by taking account of the solvent. This result may be explained by the similarity of the dipole moments calculated for the TSs.

For the hetero-Diels–Alder reaction between isoprene **35** and sulfur dioxide **45** (Scheme 23), the results indicated that the *endo* approach is favoured by more polar solvents.³² As in Bertrán's work,²⁷ a greater solvation effect was predicted for TS's in which charge transfer is larger.

3.2.2 Regioselectivity

Regioselectivity was also studied for the reaction of (*E*)-buta-1,3-dien-1-ol **36** with acrolein **2** (Scheme 19) by means of MINDO/3 and the continuum model. The results indicated that an increase in the solvent polarity increases the *ortho/meta* selectivity.²⁷

For the reactions of isoprene **35** with acrylonitrile **8**, acrolein **2**, methyl vinyl ketone **9** and methyl acrylate **4** (Scheme 21), very small variations in regioselectivity were predicted by means of both SCRf and supermolecule models (considering a single water molecule coordinated to the carbonyl or nitrile groups) with semiempirical AM1 and PM3 calculations.²⁹

para/meta Selectivity also increased with an increase in the solvent polarity for the reaction between isoprene **35** and sulfur dioxide **45** (Scheme 23).³²

3.2.3 Diastereofacial Selectivity

From a rigorous point of view, no theoretical work has been published on the effect of the solvent on the diastereofacial selectivity of Diels–Alder reactions because chiral reactants have not been considered by research groups. However, an achiral reactant can be used as a model for a chiral compound when the variation in asymmetric induction of the reaction is governed by the conformational equilibrium of this molecule. Typical examples are α,β -unsaturated carbonyl compounds, frequently used as dienophiles in Diels–Alder reactions. Unfortunately, the possibility of *s-cis/s-trans* isomerism in the TSs is generally disregarded for this type of compounds.^{27, 28, 33, 34}

The only Diels–Alder reaction explicitly considered as a model for a chiral cycloaddition in a theoretical study of solvent effects was that of cyclopentadiene **1** with methyl acrylate **4** (Scheme 25).^{13–30, 36} In this case, the latter reactant can be used to model the

behaviour of (*1R,2S,5R*)-menthyl acrylate **20**. For the model reaction between cyclopentadiene and methyl acrylate, the *endo s-cis* TS was calculated to be more stable than the *endo s-trans* at both semiempirical^{13, 29} and *ab initio* levels,^{30–36} which disagrees with the experimental results obtained in the asymmetric reaction, where the major product (*endo R*) arises from the attack of the diene on the less-hindered face of the *s-trans* conformation (Scheme 18). Both SCRf and supermolecule models predicted a differential stabilisation of the *s-trans* TSs, but this stabilisation was not enough to produce an inversion in the *s-cis/s-trans* stability through semiempirical and low level *ab initio* calculations. Reoptimisation of the TSs in the electrostatic continuum caused an additional stabilisation of *s-trans* transition structures, but the geometry must be optimised at a high theoretical level (RHF/6-31G**) to make the *endo s-trans* TS more stable than the *endo s-cis*, and thus reproduce the experimental observations.³⁶

4 Conclusions

Experimental studies of solvent effects on Diels–Alder reactions have shown the importance of correctly selecting solvents to represent a wide range of solvent properties and to avoid cross correlations between pairs of empirical parameters.

Both theoretical and experimental results indicate that, in Diels–Alder reactions of the normal type with dienophiles possessing coordinating groups, the electron pair acceptor properties of the solvent are the main factor in increasing the rate and the three kinds, *endo/exo*, regio- and diastereofacial, of selectivity.

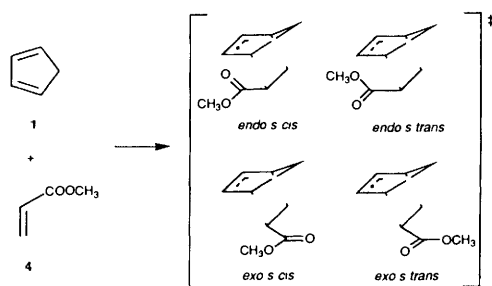
Experimental studies show that solvent polarity has only a marginal influence on the rate of some Diels–Alder reactions, whereas theoretical results indicate that the activation barrier increases or decreases as a function of the dienophile. However, solvent polarity increases *endo/exo* selectivity, and, in agreement with SCRf theoretical calculations, the diastereofacial selectivity.

In general, the donor properties of the solvent are not very important, although in some reactions a solvent with a high donor ability decreases the reaction rate.

Finally, solvent solvophobicity is the main factor influencing reaction rate, which accounts for the acceleration in aqueous media, and also the *endo/exo* selectivity of some reactions, but it has no influence on regio- and diastereofacial selectivities.

Theoretical results depend on the model used to represent the solvent and on the theoretical level at which calculations are carried out. Continuum or reaction field models are adequate to represent the electrostatic solvation, which may be important in explaining changes in selectivity, but usually they have little influence on activation barriers, and hence on reaction rates. On the other hand, Monte Carlo models are adequate to model the hydrophobic effect, which seems to be fundamental in explaining the effect of solvent on reaction rates with water or aqueous mixtures as reaction media. However, they do not allow us to consider the electronic and nuclear relaxation induced by the solvent, which has been shown to be important in explaining some of the experimental results, such as the diastereofacial selectivity. Finally, supermolecule models, based on quantum mechanical calculations, are the best way to account for hydrogen-bonding effects. In the future, mixed theoretical models, such as Monte Carlo with mixed quantum mechanics–molecular mechanics intermolecular potentials will be able to overcome the individual limitations of the abovementioned models, although the huge computational resources necessary to achieve good representation levels will undoubtedly limit their use.

Both semiempirical and *ab initio* implementations of the Hartree–Fock theory have been used in the modelling of solvent effects on the Diels–Alder reaction. Although the *ab initio* approach is conceptually preferable, it has the drawback of the limited size of the systems which can be envisaged to be studied. In fact, to date, solvent effects studies based on *ab initio* calculations have been performed only on small systems, at the Hartree–Fock level, *ie* without considering correlation energy corrections, and with basis sets of small or medium size. An interesting alternative lies in the use of density functional theory, which allows, in principle, systems of greater size and correlation energy to be considered to some



Scheme 25

Table 3 Comparison between the conclusions reached by using empirical and theoretical models to study solvent effects on the Diels–Alder reaction

Experimental response	Solvation mechanism	Empirical models	Theoretical models
Reaction rate	Solvophobicity	YES	YES
	HBD ability	YES	YES
	Dipolarity	Depends on the reagents	Depends on the reagents
Endo/exo selectivity	Solvophobicity	YES	Not studied
	HBD ability	YES	YES
	Dipolarity	YES	YES
Regioselectivity	Solvophobicity	NO	Not studied
	HBD ability	YES (only for strong HBD solvents)	NO or little influence
	Dipolarity	NO	NO
Diastereofacial selectivity	Solvophobicity	NO	Not studied
	HBD ability	YES	YES
	Dipolarity	YES	YES

extent Several studies have recently appeared dealing with Diels–Alder reactions in the gas phase, and also with the solvation of small hydrogen-bonded species A combination of both for modelling solvent effects on the Diels–Alder reaction is undoubtedly only a matter of time

Is there a moral to this story? If there was one, it should be that empirical and theoretical models are complementary and not competitive Although extensive and systematic studies of modelling of solvent effects have not been carried out for the same reaction using all the approaches, some general trends can be drawn from the published data They are summarised in Table 3 As can be seen, there is an almost perfect coincidence in the conclusions reached by both empirical and theoretical approaches Empirical models have the advantage of being applicable to very complex systems and of being able, at least in principle, to consider every solvation mechanism in a single equation, provided the solvent set used is well designed On the other hand, the cross-correlations between empirical solvent parameters often makes the interpretation of the results difficult Theoretical models are much more specialised than empirical ones, *i e* there is not a single theoretical model which accounts simultaneously for all the possible solvation mechanisms However, their combined use allows a better understanding of the relative importance of each particular solvation energy term on the whole solvent effect

5 References

- C Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 1988
- R Breslow, *Acc Chem Res*, 1991, **24**, 159
- J Sauer and R Sustmann, *Angew Chem, Int Ed Engl*, 1980, **19**, 779
- V B Blankenburg, H Fiedler, M Hampel, H G Hauthal, G Just, K Kahlert, J Korn, K H Muller, W Pritzkow, V Reinhold, M Rollig, E Sauer, D Schnurpfeil and G Zimmermann, *J Prakt Chem*, 1974, **316**, 804
- A Corsico Coda, G Desimoni, E Ferrari, P P Righetti and G Tacconi, *Tetrahedron*, 1984, **40**, 1611
- G Desimoni, G Faita, P P Righetti, N Tornaletti and M Visgalli, *J Chem Soc Perkin Trans 2*, 1989, 437
- A Corsico Coda, G Desimoni, G Faita, P P Righetti and G Tacconi, *Tetrahedron*, 1989, **45**, 775
- A Kumar, *J Org Chem*, 1994, **59**, 230
- H J Schneider and N K Sangwan, *J Chem Soc Chem Commun*, 1986, 1787
- N K Sangwan and H J Schneider, *J Chem Soc Perkin Trans 2*, 1989, 1223
- C Cativiela, J A Mayoral, A Avenoza, J M Peregrina and M A Roy, *J Phys Org Chem*, 1990, **3**, 414
- C Cativiela, J I Garcia, J A Mayoral, A Avenoza, J M Peregrina and M A Roy, *J Phys Org Chem*, 1991, **4**, 48
- C Cativiela, J I Garcia, J A Mayoral, A J Royo, L Salvatella, X Assfeld and M F Ruiz Lopez, *J Phys Org Chem*, 1992, **5**, 230
- G Desimoni, G Faita and P P Righetti, *Tetrahedron*, 1991, **47**, 5857
- J J Gajewski, *J Org Chem*, 1992, **57**, 5500
- J M Aubry, B Mandard Cazin, M Rougee and R V Bensasson, *J Am Chem Soc*, 1995, **117**, 9159
- G Desimoni, G Faita and P P Righetti, *Tetrahedron*, 1991, **47**, 5857
- R A Firestone and M A Vitale, *J Org Chem*, 1981, **46**, 2160
- R A Firestone and S G Saffer, *J Org Chem*, 1983, **48**, 4783
- J A Berson, Z Hamlet and W A Mueller, *J Am Chem Soc*, 1962, **84**, 297
- K Nakagawa, Y Ishii and M Ogawa, *Tetrahedron*, 1976, **32**, 1427
- K Nakagawa, S Iwase, Y Ishii, S Hamanaka and M Ogawa, *Rev Roum Chim*, 1979, **24**, 613
- H J Schneider and N K Sangwan, *Angew Chem Int Ed Engl*, 1987, **26**, 896
- M M Gugelchuk, P C M Chang and T J Sprules, *J Org Chem*, 1994, **59**, 7723
- G Jenner, *Tetrahedron Lett*, 1994, **35**, 1189
- C Cativiela, J I Garcia, J A Mayoral and L Salvatella, *J Chem Soc Perkin Trans 2*, 1994, 847
- L Pardo, V Branchadell, A Oliva and J Bertran, *J Mol Struct (THEOCHEM)*, 1983, **93**, 256
- R Sustmann and W Sicking, *Tetrahedron*, 1992, **48**, 10293
- C Cativiela, V Dillet, J I Garcia, J A Mayoral, M F Ruiz Lopez and L Salvatella, *J Mol Struct (THEOCHEM)*, 1995, **331**, 37
- M F Ruiz Lopez, X Assfeld, J I Garcia, J A Mayoral and L Salvatella, *J Am Chem Soc*, 1993, **115**, 8780
- M A McCarrick, Y D Wu and K N Houk, *J Org Chem*, 1993, **58**, 3330
- D Suarez, X Assfeld, J Gonzalez, M F Ruiz Lopez, T L Sordo and J A Sordo, *J Chem Soc Chem Commun*, 1994, 1683
- J F Blake and W L Jorgensen, *J Am Chem Soc*, 1991, **113**, 7430
- W L Jorgensen, J F Blake, D Lim and D L Severance, *J Chem Soc Faraday Trans*, 1994, **90**, 1727
- T Karcher, W Sicking, J Sauer and R Sustmann, *Tetrahedron Lett*, 1992, **33**, 8027
- X Assfeld, M F Ruiz Lopez, J I Garcia, J A Mayoral and L Salvatella, *J Chem Soc Chem Commun*, 1995, 1371