

## Solvent Effects on *endo/exo*- and Regio-selectivities of Diels–Alder Reactions of Carbonyl-containing Dienophiles

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The selectivity of Diels–Alder reactions of methyl vinyl ketone and methyl acrylate, with cyclopentadiene and isoprene, have been studied in 18 pure solvents and aqueous mixtures. The results obtained have been analysed by means of regression models, using empirical solvent parameters. The *endo/exo* selectivity mainly depends on the solvophobic ( $S_p$ ) and hydrogen bond donor ( $\alpha$ ) properties of the solvent. The influence of the dipolarity ( $\pi^*$ ) is only observed in the reactions with methyl acrylate. Regioselectivity almost exclusively depends on the hydrogen bond donor ability of the solvent. The double coordination observed with highly hydrogen bond donating solvents in the case of methyl vinyl ketone greatly increases the *para/meta* isomer ratio.

In the last few years, several experimental<sup>1–3</sup> and theoretical<sup>3c,4</sup> works dealing with the effect of the solvent on intermolecular Diels–Alder reactions have been published. Most of these papers are only concerned with the effect of the solvent on reaction rates.<sup>1</sup> With regard to selectivity, in spite of the pioneering work of Berson and co-workers,<sup>5</sup> there is surprisingly little work, which deals almost exclusively with the effect of the solvent on the *endo/exo* selectivity.<sup>2,3</sup> This effect has been analysed by means of regression models using empirical solvent parameters and, depending on the reaction studied, has been attributed to the solvophobic,<sup>2</sup> polar and solvophobic,<sup>3a,b</sup> and polar and acidic<sup>3c,d</sup> properties of the solvent.

Given the lack of systematic work on the effect of the solvent on the *endo/exo* selectivity of Diels–Alder reactions, we decided to study this subject by using the reactions of cyclopentadiene with methyl vinyl ketone (henceforth MVK) and methyl acrylate as a benchmark (Scheme 1).

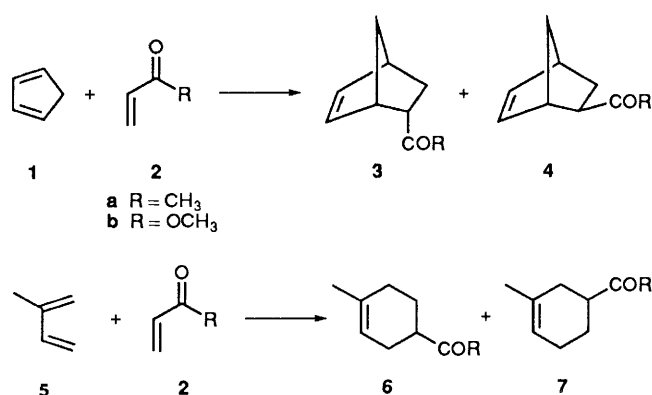
To the best of our knowledge, there is no systematic work on the effect of the solvent on the regioselectivity of Diels–Alder reactions, the only precedent being a paper of Nakagawa *et al.*,<sup>6</sup> so we have also studied this subject by using the reactions of 2-methyl-1,3-butadiene (isoprene) with MVK and methyl acrylate as a benchmark (Scheme 1).

### Results and Discussion

As we tried to cover a wide range of solvent characteristics, the solvents were selected according to their  $S_p$  values<sup>7</sup> and normalised  $E_T(30)$  ( $E_T^N$ ) values.<sup>8</sup> The reason for choosing these two solvent parameters is three-fold. In the first place, they have already proved to be of use in explaining results of *endo/exo* selectivity in Diels–Alder reactions.<sup>3b,c</sup> Secondly, there are to date few empirical solvent parameters that have been determined for a comprehensive set of organic solvents and binary aqueous mixtures. Finally, they account for most solvation mechanisms, namely solvophobic or cavity effects ( $S_p$ ), polar effects and hydrogen bonding donor (HBD) effects ( $E_T^N$ ).<sup>9</sup>

Table 1 gathers the 18 solvents and solvent mixtures studied, together with their corresponding empirical solvent parameters, and the results obtained in the Diels–Alder reactions of cyclopentadiene and isoprene with MVK and methyl acrylate.

These experimental results were treated by means of regression models, using empirical solvent parameters as independent variables. The results of the statistical analyses are gathered in Table 2.



Scheme 1

In order to interpret correctly these regression models, the high colinearities existing between the empirical parameter set used (Table 3) must be borne in mind. The origin of these colinearities may be mechanistic (as in the case of  $E_T^N$  and  $\alpha$ ), intrinsic (as in the case of  $S_p$  and  $\alpha$ ), or merely fortuitous (as in the case of  $\pi^*$  and  $S_p$ ). In any case, the linear dependence between independent variables can make the interpretation of the regression results considerably more difficult.

*endo/exo* Selectivity.—The results obtained using  $E_T^N$  and  $S_p$  as independent variables are very similar for both dienophiles. In both cases, there are good regression coefficients ( $r > 0.98$ ), and the coefficients of  $E_T^N$  and  $S_p$  are statistically significant (a cut-off of 95% of probability has been used throughout the work). These results are in good agreement with those previously described for the reactions of cyclopentadiene with methyl<sup>3b</sup> and (–)-menthyl<sup>3c</sup> acrylates, *i.e.* *endo/exo* selectivity depends on polarity and solvophobicity, both coefficients being of similar relative importance. The colinearity between  $E_T^N$  and  $S_p$  remains very high ( $r = 0.75$ ) despite the inclusion of highly polar solvents of medium solvophobicity,<sup>10</sup> such as the fluorinated alcohols 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP). This makes the discussion of the physico-chemical factors that influence the *endo/exo* selectivity difficult, as mentioned above.

In view of this, we tested a different empirical approach. The Abboud–Abraham–Kamlet–Taft (AAKT) model<sup>11</sup> avoids in principle this problem by using quasi-orthogonal parameters, namely  $\pi^*$ ,  $\alpha$  and  $\beta$ , which account for the dipolarity, and

**Table 1** Experimental results for the reactions of cyclopentadiene (**1**) and isoprene (**5**) with methyl vinyl ketone (**2a**) and methyl acrylate (**2b**) in several solvents and organic–aqueous mixtures

Solvent	$E_T^N$	$S_p$	$\pi^*$	$\alpha$	$\beta$	log (3a/4a)	log (3b/4b)	log (6a/7a)	log (6b/7b)
Hexane	0.009	0.009	-0.080	0.000	0.000	0.548	0.369	0.345	0.340
Dichloromethane	0.309	0.000	0.820	0.300	0.000	0.709	0.555	0.419	0.403
Methyl acetate	0.228	0.064	0.550	0.000	0.450	0.655	0.508	0.327	0.363
Acetonitrile	0.460	0.217	0.750	0.190	0.310	0.764	0.606	0.336	0.378
Nitrobenzene	0.324	0.065	1.010	0.000	0.390	0.650	0.506	0.340	0.326
Dioxane	0.164	0.079	0.550	0.000	0.370	0.636	0.489	0.344	0.362
Dioxane–Water 30%	0.818	0.755	1.088	0.740	0.494	1.185	0.965	0.411	0.517
Dioxane–Water 50%	0.707	0.521	0.989	0.610	0.575	1.109	0.827	0.418	0.461
Dioxane–Water 60%	0.667	0.390	0.919	0.570	0.596	1.050	0.788	0.364	0.443
Acetone	0.355	0.127	0.710	0.080	0.480	0.667	0.542	0.371	0.365
Acetone–Water 40%	0.799	0.608	—	—	—	1.153	0.918	0.409	0.488
Acetone–Water 80%	0.664	0.239	—	—	—	0.945	0.709	0.344	0.412
Methanol–Water 30%	0.904	0.808	1.110	0.920	0.320	1.229	1.020	0.439	0.524
Methanol–Water 60%	0.836	0.531	0.980	0.870	0.500	1.138	0.908	0.420	0.478
Methanol–Water 70%	0.818	0.446	0.910	0.910	0.530	1.097	0.858	0.429	0.461
Water	1.000	1.000	1.090	1.170	0.180	1.327	1.124	0.415	0.544
Trifluoroethanol	0.898	0.325	0.730	1.510	0.000	1.012	0.843	0.739	0.567
Hexafluoroisopropanol	1.068	0.280	0.650	1.960	0.000	0.997	0.884	0.877	0.699

**Table 2** Regression model results of *endo/exo* and *para/meta* selectivities with several empirical solvent parameters

	$n$	$r$	$s$	Intercept	$E_T^N$	$S_p$	$\pi^*$	$\alpha$	$\beta$
log (3a/4a)	18	0.982	0.049	0.546	$0.360 \pm 0.062$	$0.476 \pm 0.066$	—	—	—
	16	0.902	0.123	0.394	—	—	$0.318 \pm 0.144$	$0.293 \pm 0.068$	$0.294 \pm 0.194$
	16	0.987	0.049	0.521	—	$0.524 \pm 0.065$	$0.075 \pm 0.064$	$0.168 \pm 0.031$	$0.170 \pm 0.078$
log (3b/4b)	16	0.974	0.062	0.619	—	$0.648 \pm 0.063$	—	$0.125 \pm 0.033$	—
	18	0.996	0.021	0.382	$0.383 \pm 0.026$	$0.360 \pm 0.028$	—	—	—
	16	0.928	0.094	0.277	—	—	$0.311 \pm 0.110$	$0.265 \pm 0.052$	$0.151 \pm 0.148$
log (6a/7a)	16	0.997	0.019	0.380	—	$0.423 \pm 0.026$	$0.114 \pm 0.025$	$0.164 \pm 0.012$	$0.051 \pm 0.031$
	16	0.997	0.021	0.386	—	$0.432 \pm 0.027$	$0.133 \pm 0.024$	$0.153 \pm 0.011$	—
	18	0.828	0.086	0.220	$0.613 \pm 0.108$	$-0.459 \pm 0.115$	—	—	—
log (6b/7b)	16	0.924	0.065	0.420	—	—	$-0.109 \pm 0.076$	$0.228 \pm 0.036$	$-0.109 \pm 0.102$
	16	0.977	0.038	0.360	—	$-0.249 \pm 0.050$	$0.006 \pm 0.050$	$0.287 \pm 0.024$	$-0.050 \pm 0.061$
	16 <sup>a</sup>	0.735	0.029	0.335	$0.065 \pm 0.062$	$0.033 \pm 0.060$	—	—	—
	16	0.867	0.078	0.301	—	—	—	$0.222 \pm 0.034$	—
	14 <sup>a</sup>	0.844	0.023	0.347	—	—	—	$0.082 \pm 0.015$	—
log (6b/7b)	18	0.902	0.044	0.278	$0.334 \pm 0.055$	$-0.087 \pm 0.058$	—	—	—
	16	0.977	0.024	0.344	—	—	$0.007 \pm 0.028$	$0.166 \pm 0.013$	$0.002 \pm 0.038$
	16	0.979	0.024	0.352	—	$0.031 \pm 0.032$	$-0.007 \pm 0.032$	$0.158 \pm 0.015$	$-0.006 \pm 0.039$
	16 <sup>a</sup>	0.966	0.019	0.334	$0.071 \pm 0.041$	$0.150 \pm 0.040$	—	—	—
	16	0.977	0.022	0.350	—	—	—	$0.167 \pm 0.010$	—
14 <sup>a</sup>	0.961	0.021	0.350	—	—	—	$0.167 \pm 0.014$	—	

<sup>a</sup> Excluding fluorinated alcohols from the regression equation.**Table 3** Correlation coefficients between 16 solvents and organic–aqueous mixtures used in this work

	$E_T^N$	$S_p$	$\pi^*$	$\alpha$	$\beta$
$E_T^N$	1.00	—	—	—	—
$S_p$	0.79	1.00	—	—	—
$\pi^*$	0.65	0.68	1.00	—	—
$\alpha$	0.91	0.56	0.33	1.00	—
$\beta$	0.02	0.23	0.45	-0.32	1.00

hydrogen bond donating (HBD) and accepting (HBA) abilities of the solvent, respectively. Given that these parameters are not known for several aqueous mixtures, the set of solvents is reduced to 16 (Table 1). The results obtained using the AAKT model (Table 2) are slightly different for both dienophiles. Thus, in both cases, the coefficient of  $\alpha$  (HBD ability) is statistically significant. This result points to a role of the solvent as a mild Lewis acid catalyst, which agrees with the results previously described by Desimoni and co-workers.<sup>1a-c</sup> These authors have shown the correlation existing between Diels–

Alder reaction rate constants and Gutmann's acceptor number (AN).<sup>12</sup> However, in the case of methyl acrylate,  $\pi^*$  also shows a significant coefficient, in good agreement with previously described results for the reaction between cyclopentadiene and (–)-menthyl acrylate.<sup>3c</sup>

Some recent theoretical calculations carried out at high *ab initio* levels for the reaction of cyclopentadiene with methyl acrylate<sup>4d</sup> show that the energy differences between *endo* and *exo* transition structures (TSs) are greater for the *s-trans* than for the *s-cis* forms. This does not arise from a particularly greater stability of the *endo s-trans* TS, but because of the relative instability of the corresponding *exo s-trans* TS. This is probably due to the steric interactions between the methylene hydrogens of the cyclopentadiene and the methoxy group linked to the carbonyl group of the dienophile in the *exo* attack. These steric interactions must be greater in the case of the *s-trans* conformation of the dienophile. Theoretical calculations dealing with solvent effects on *endo/exo* selectivity in the same reaction<sup>4d</sup> show that solvent polarity increases the *endo/exo* ratio mainly by a relatively greater stabilisation of the *s-trans* TSs, and in particular of the *endo s-trans* one. This is also in

agreement with the experimental results about solvent effects on the direction of the asymmetric induction in the reactions between cyclopentadiene and chiral acrylates.<sup>3c,d</sup>

These theoretical calculations account for the influence of solvent polarity, as represented by  $\pi^*$ , observed for the reaction of cyclopentadiene with methyl acrylate. Unfortunately, the lack of similar theoretical calculations accounting for the solvation energies of the TSs for the reaction between cyclopentadiene and MVK makes it difficult to interpret solvent effects on this reaction.

As can be seen in Table 2, the AAKT model leads to poorer results with regard to the dual-parameter  $E_T^N$ - $S_p$  model. This may be due to the solvophobic effect, absent in our formulation of the AAKT model. The square of the Hildebrand's solubility parameter,  $\delta_H^2$ , has been used in the framework of the AAKT model to account for cavitation effects. However, its use is not possible in our case because the presence of aqueous mixtures, for which values of  $\delta_H$  cannot be determined. In order to overcome this problem, we tested the possibility of using  $S_p$  as a substitute for  $\delta_H^2$  in the AAKT model. The results obtained are gathered in Table 2.

As can be seen, not only do the regression coefficients improve ( $r > 0.98$ ), but  $S_p$  shows, in both cases, a significant coefficient. In the case of MVK, a model including only  $S_p$  and  $\alpha$  accounts for most of the variation observed in *endo/exo* selectivity, which seems to indicate that the acidity and solvophobicity of the reaction medium are mainly responsible for the variation in *endo/exo* selectivity. In the case of methyl acrylate,  $\pi^*$  has to be included together with  $S_p$  and  $\alpha$  in the regression model, indicating that the dipolarity also plays a significant role.

*para/meta* Selectivity.—The results obtained using  $E_T^N$  and  $S_p$  as independent variables in the case of the reaction between isoprene and MVK show that the coefficients of both parameters are significant, but the coefficient of  $S_p$  is negative. This seems to be contrary to any physico-chemical meaning of solvophobic effects on this reaction. In the case of the reactions of methyl acrylate, only the coefficient of  $E_T^N$  is significant (and smaller than that corresponding to the MVK reactions), but the sign of the coefficient of  $S_p$  is still negative. On the other hand, the use of the AAKT model leads to apparently similar results for both dienophiles. Only the coefficient of  $\alpha$  is significant in both regression models, which indicates that solvent acidity plays a fundamental role in the *para/meta* selectivity. The inclusion of  $S_p$  in the AAKT model leads again to a differentiation between both dienophiles. In the case of MVK,  $S_p$  displays a significant and negative coefficient, whereas it is insignificant in the case of methyl acrylate.

An examination of the residuals of the AAKT regression models reveals some interesting facts that help to interpret these striking results. In the case of the reactions of MVK, a plot of normalised residuals *vs.* the calculated *para/meta* selectivity (Fig. 1)<sup>13</sup> shows that both fluorinated alcohols deviate from the behaviour of the rest of solvents, *i.e.* the same regression model cannot account for all the observed changes in *para/meta* selectivity induced by the solvent. When these two solvents are excluded from the regression models, the results obtained are very different from the initial ones. Indeed, in the case of the dual-parameter  $E_T^N$ - $S_p$  model, the exclusion of fluorinated alcohols leads to an insignificant regression model, *i.e.* neither  $E_T^N$  nor  $S_p$  is able to explain the slight changes in *para/meta* selectivity. This is undoubtedly due to the fact that the most important changes in regioselectivity are observed for the fluorinated alcohols, which have high  $E_T^N$  and low  $S_p$  values. Therefore, the negative coefficient of the  $S_p$  parameter previously mentioned constitutes an artifact of the regression method, and has no physical meaning.

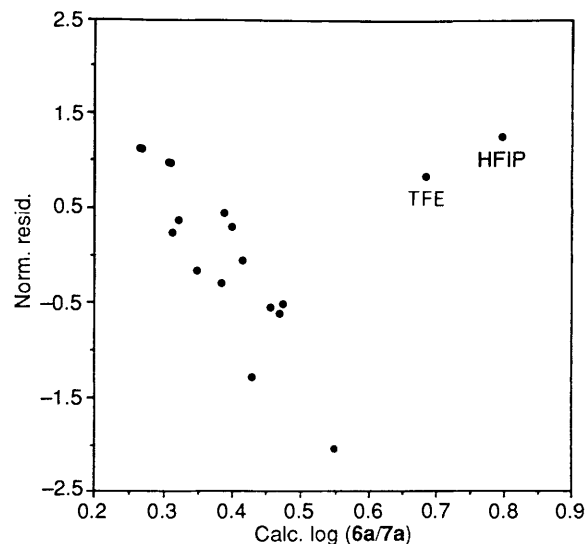


Fig. 1 Plot of normalised residuals *vs.* calculated (AAKT model) selectivity of the reactions between isoprene and MVK

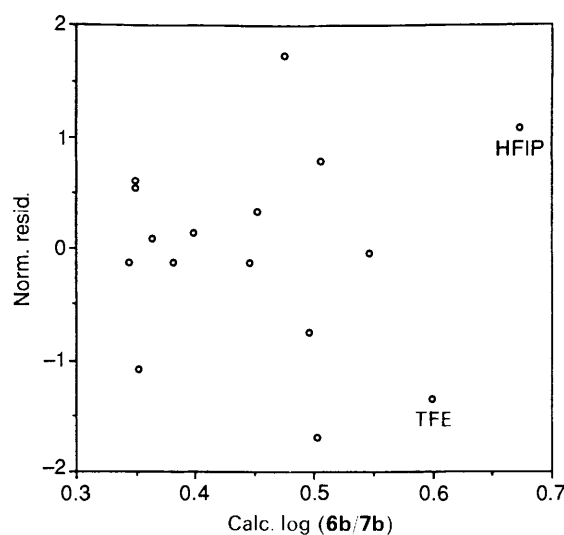


Fig. 2 Plot of normalised residuals *vs.* calculated (AAKT model) selectivity of the reactions between cyclopentadiene and methyl acrylate

In the case of the AAKT model, the exclusion of the fluorinated alcohols does not change the qualitative results, but does change the quantitative ones. So, only the coefficient of  $\alpha$  is significant, but its value is much lower. This can be interpreted as there being two mechanisms by means of which the acidity of the solvent can affect *para/meta* selectivity. We will return to this point later.

The examination of the residual plot for the same regression model in the case of the reactions between isoprene and methyl acrylate (Fig. 2) does not reveal any anomalous arrangement of points. This means that in all the solvents studied, including fluorinated alcohols, the same solvation mechanism influences *para/meta* selectivity. Indeed, if we consider the single regression model containing the only significant parameter in the previous AAKT model, namely  $\alpha$ , it can be seen that almost the same straight line is obtained irrespectively of the inclusion of fluorinated alcohols in the regression (Table 2).

The different behaviour of MVK and methyl acrylate towards the fluorinated alcohols deserves further comments. A possible explanation of this difference can be found if we consider the different basicity of the carbonyl group in both dienophiles. It has been speculated that fluorinated alcohols can act not only as mild Lewis acids, but as true Brønsted acids, giving rise to a proton transfer catalysis mechanism, in the case of the Diels-

**Table 4** Frequencies of the C=O stretching band<sup>a</sup> of methyl acrylate and methyl vinyl ketone in several solvents

Dienophile	Solvent	$\nu_{\text{C=O}}/\text{cm}^{-1}$				
Methyl acrylate	Hexane	1739.5	—	—	—	—
	Methanol	1733.5	1715.5	—	—	—
	TFE <sup>b</sup>	—	1712.5	—	—	—
	HFIP <sup>c</sup>	—	1705.0	—	—	—
MVK	Hexane	1710.0	1690.0	—	—	—
	Methanol	1706.0	1685.0	1687.0	1674.5	—
	TFE	—	—	1695.0	1674.5	1660.0
	HFIP	—	—	1693.0	1672.0	1654.0

<sup>a</sup> All the FTIR spectra were recorded from 0.5 mol dm<sup>-3</sup> solutions, and deconvoluted to obtain the exact frequencies. <sup>b</sup> 2,2,2-Trifluoroethanol. <sup>c</sup> 1,1,1,3,3,3-Hexafluoropropan-2-ol.

Alder reactions of acrolein, a dienophile of a similar basicity to that of MVK.<sup>14</sup> On the other hand, double coordination of solvent molecules to the carbonyl of the dienophile in the case of MVK can be also thought to account for the above-mentioned differential behaviour. In order to test this hypothesis, IR spectra of MVK and methyl acrylate were recorded in non-HBD (hexane), HBD (methanol) and highly HBD (TFE and HFIP) solvents. Table 4 gathers the frequencies of the C=O stretching bands of both dienophiles in each solvent.

As can be seen, methyl acrylate in hexane shows a single band at 1739.6 cm<sup>-1</sup>. In methanol, two bands appear, corresponding to dissociated (shifted to a lower frequency because of higher solvent polarity) and associated (shifted to an even lower frequency because of the hydrogen bonding) methyl acrylate. In both TFE and HFIP, the dissociated band completely disappears, indicating a total specific solvation of this dienophile.

The case of MVK is more complicated. In hexane, two bands, which have been previously assigned to the *s-cis* and *s-trans* conformers<sup>15</sup> appear at 1710.5 and 1690.2 cm<sup>-1</sup>. In methanol, these bands are again duplicated, showing both the dissociated (1705.9 and 1684.8 cm<sup>-1</sup>) and the associated (1696.8 cm<sup>-1</sup> and 1674.6 cm<sup>-1</sup>) forms of the dienophile. In TFE, the dissociated bands again disappear, but three bands are observed experimentally. The first two (1695.0 and 1674.0 cm<sup>-1</sup>) clearly correspond to the associated forms of the dienophile. The third one (1695.8 cm<sup>-1</sup>) appears at a low frequency, indicating a stronger association. Two molecules of TFE are possibly simultaneously coordinated to the carbonyl oxygen in this case. The same behaviour is observed in the case of HFIP, the three bands appearing at 1693.0, 1672.0 and 1654 cm<sup>-1</sup>.

This result is in agreement with the behaviour of the biphenylenediol catalyst<sup>16</sup> described by Kelly for these reactions. This catalyst presents two phenolic OH groups, whose coordination to the dienophile promotes the reaction. It has been described<sup>16</sup> that the reaction rate is increased by a factor of 30 in the case of MVK, but only by a factor of less than two in the case of methyl acrylate.

## Experimental

In a typical run, a thermostatted (30 ± 1 °C) solution of the corresponding amounts of diene and dienophile (Table 5) was stirred magnetically. Selectivities were determined at several reaction times by gas chromatography (FID form Hewlett-Packard 5890 II chromatograph, cross-linked methyl silicone column 25 m × 0.22 mm × 0.33 μm) in the following conditions.

*Cyclopentadiene (1) with methyl vinyl ketone (2a) reactions.* Helium as carrier gas (20 p.s.i.),† injector temperature 230 °C,

**Table 5** Amounts of reagents and solvent used in the reactions described in this work

Reaction medium	Diene/ mmol	Dienophile/ mmol	Volume/ cm <sup>3</sup>
Pure organic solvents	6.00	2.0	4
Methanol-Water	0.30	5.0	10
Acetone-Water	0.30	1.0	10
Dioxane-Water	0.30	1.0	10
Pure water	0.09	3.0	100

detector temperature 250 °C, oven temperature program (50 °C (3 min)–25 °C min<sup>-1</sup>–100 °C (9 min)); retention times: MVK (**2a**) 2.2 min, *exo*-cycloadduct (**4a**) 10.2 min, *endo*-cycloadduct (**3a**) 10.9 min.

*Cyclopentadiene (1) with methyl acrylate (2b) reactions.* Helium as carrier gas (17 p.s.i.), injector temperature 230 °C, detector temperature 250 °C, oven temperature program 50 °C (3 min)–25 °C min<sup>-1</sup>–100 °C (9 min); retention times: methyl acrylate (**2b**) 2.6 min, *exo*-cycloadduct (**4b**) 12.8 min, *endo*-cycloadduct (**3b**) 13.2 min.

*Isoprene (5) with methyl vinyl ketone (2a) reactions.* Helium as carrier gas (18 p.s.i.), injector temperature 230 °C, detector temperature 250 °C, oven temperature program 50 °C (3 min)–25 °C min<sup>-1</sup>–90 °C (13 min); retention times: MVK (**2a**) 2.4 min, *meta*-cycloadduct (**7a**) 16.5 min, *para*-cycloadduct (**6a**) 16.9 min.

*Isoprene (5) with methyl acrylate (2b) reactions.* Helium as carrier gas (18 p.s.i.), injector temperature 230 °C, detector temperature 250 °C, oven temperature program 50 °C (3 min)–25 °C min<sup>-1</sup>–100 °C (12 min), retention times: methyl acrylate (**2b**) 2.6 min, *meta*-cycloadduct (**7b**) 15.3 min, *para*-cycloadduct (**6b**) 15.6 min.

## Conclusions

To summarise, the use of empirical solvent parameters in multiple regression models indicates that the hydrogen bond-donating ability of the solvent plays an important role in explaining the selectivity (*endo/exo* stereoselectivity and *para/meta* regioselectivity) of the Diels–Alder reactions of carbonyl-containing dienophiles.

In the case of *endo/exo* selectivity, the solvophobicity, represented by Abraham's  $S_p$  parameter, also plays a determining role, whereas dipolarity, represented by the  $\pi^*$  parameter, is only important for the reactions of methyl acrylate.

In the case of the *para/meta* selectivity, there is a marked difference in the behaviour of both dienophiles towards the fluorinated alcohols. The *para/meta* selectivity increases smoothly with the Lewis acidity of the solvent in the case of methyl acrylate, but shows a breakdown for the fluorinated

† 1 p.s.i. = 6894.76 Pa.

alcohols in the case of MVK. This result can be attributed to the different basicity of the carbonyl of both dienophiles.

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