Influence of the Solvent Polarity on the Stereoselectivity of the Uncatalyzed [4+2] Cycloaddition of Cyclopentadiene to *N,N'*-Fumaroyldi[(2*R*)-borane-10,2-sultam]

by **Christian Chapuis**[a])[1])*, **Anna Kucharska**[b]), **Piotr Rzepecki**[b]), and **Janusz Jurczak**[a])[b])*

[a]) Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, PL-01-224 Warsaw
[b]) Department of Chemistry, University of Warsaw, Pasteura 1, PL-02-093 Warsaw

A correlation between the solvent polarity and the logarithm of the diastereoisomer ratio (dr) was found for the uncatalyzed [4+2] cycloaddition of cyclopentadiene to *N,N'*-fumaroyldi[(2*R*)-bornane-10,2-sultam]. Using the *Abboud-Abraham-Kamlet-Taft* parameters, predictive values for this method, allowed an optimum diastereoisomeric excess (de) of 96% (EtOH, −78°). A similar diastereoselectivity was achieved using 5M $LiClO_4/Et_2O$ or H_2O/β-cyclodextrin, and the influence of supercritical CO_2 is also reported. Selective cycloadditions of apolar diene in polar solvents are entropically favored by the greater dipole moment of the *N*-enoylcamphorsultam *syn*-s-*cis* conformers and of the C(α)-*re* transition states. Implications on the stereochemical course of the reaction are discussed.

Introduction. – We recently presented results of the catalyzed *Diels-Alder* cycloaddition of (−)-**1** to cyclopentadiene [1] and diverse dienes [2], which are related to a theoretical study of the transition states performed by PM3 calculations [3]. Pursuing our systematic study on the behavior of (−)-**1**, we now wish to report on solvent effects of its [4+2] cycloaddition to cyclopentadiene. Indeed, although the influence of the medium on the overall kinetic [4], the diastereo (*endo*/*exo*)- [5], and regioselectivity [6] of the *Diels-Alder* reaction is well-known, only a few reports describe the influence of the solvent on the π-facial selectivity for its diastereo- and enantiomorphic transition states [7]. In an early report, *Sauer et al.* concluded that the diastereoselectivity engendered during the uncatalyzed [4+2] cycloaddition of (−)-dimenthyl fumarate to cyclopentadiene could, surprisingly, result in the inversion of the poor diastereoselectivity observed, while that of the (−)-menthyl acrylate was almost independent of the solvent [7a]. *Helmchen* and coworkers then found a clear correlation between increasing solvent polarity and decreasing π-facial selectivity in the uncatalyzed ethyl *O*-acryloyl lactate cycloaddition to cyclopentadiene [7b]. In contrast, after a detailed study, *Cativiela et al.* concluded that the diastereoisomer-excess (de) values of the thermal cycloaddition of (−)-menthyl acrylate to cyclopentadiene seem to slightly increase with the polarity of the solvent [7c].

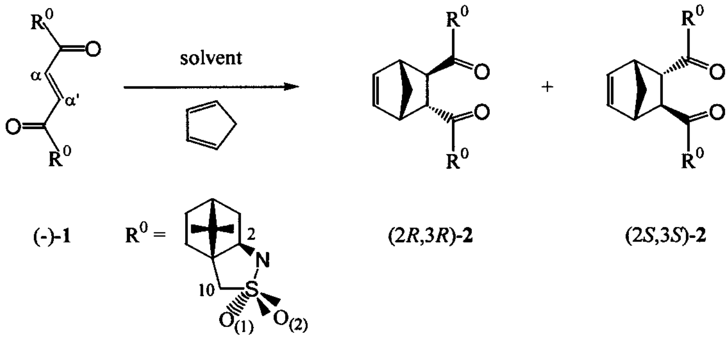
Results and Discussion. – The choice of the C_2-symmetrical dienophile (−)-**1** for the cycloaddition to cyclopentadiene (see *Scheme*) allowed to simplify the *endo*/*exo* analytical problem and to profit from the cooperative effect of two prosthetic groups

---

[1]) Present address: *Firmenich SA*, Corporate R&D Division, P.O. Box 239, CH-1211 Geneva.

[8]. The reaction was performed by addition of 4.0 mol-equiv. of cyclopentadiene to 0.02M (–)-**1** in the chosen solvent at 20°. The π-facial selectivity was measured after 18 h, as earlier reported [1], directly by ^{1}H-NMR analysis at 500 MHz of the olefinic signals of the diastereoisomeric cycloadducts **2** in the reaction mixture.

Scheme



(-)-1

(2*R*,3*R*)-2

(2*S*,3*S*)-2

After a rapid survey of common solvents such as toluene, THF, $CHCl_3$, AcOEt, acetone, and CH_2Cl_2, we empirically concluded that the diastereoselectivity improved from 64 to 84% de on increasing the polarity of the solvent (see *Table 1*). We then systematically studied the complete range of solvent polarity from CCl_4 (58% de) to MeCN (88% de), but could not find any direct correlation with either the dipole moment or the dielectric constant of the solvent. The best correlation was found with the solvent-polarity values $E_T(30)$ reported by *Reichardt* [9]. As illustrated in *Fig. 1*, the logarithm of the diastereoisomer ratio (dr) increased with increasing polarity. Thus, to reach the maximum selectivity, we performed the reaction in particularly polar solvents such as propane-1,3-diyl carbonate (88% de), sulfolane (90% de), or nitromethane (91% de); this latter solvent has an $E_T(30)$ value of 46.3 kcal/mol. We then turned our attention towards more polar and protic solvents such as MeOH, EtOH, and H_2O; in some cases, we found a depreciation of the diastereoselectivity, but the de nevertheless remained correlated with the polarity and parallelled the influence of the weak or non-H-bond donor (non-HBD) solvents. For example, in EtOH the de was 77% as compared to 82% in MeOH, 90% in 2,2,2-trifluoroethanol, and 92% in H_2O[2]). To optimize the de values, we then tested 1,1,1,3,3,3-hexafluoropropan-2-ol which possesses a higher solvent polarity ($E_T(30) = 65.3$ kcal/mol) than H_2O, but obtained a similar selectivity (90% de). Equally, the use of a liquid salt, such as ethyl ammonium nitrate ($E_T(30 = 61.6$ kcal/mol [10]), which is known to give better conversion and *endo*/*exo* selectivity than H_2O [5a], afforded 89% de. We then tried pentane-2,4-dione, whose polarity is higher than that of nitromethane, but found an intermediate selectivity of 86% de, which probably resulted from the H-bond donor (HBD) properties of the enol form. In 1986, *Sauer* and *Braun* studied the effects of solubilized

---

[2]) Double diastereoselection in H_2O showed poor differentiation between (–)-**1** or (+)-**1** in the presence of 1.0 mol-equiv. of (+)-α- or (+)-γ-cyclodextrin. The best matching conditions were found between (–)-**1** and (+)-β-cyclodextrin, which afforded 96% de (see *Table 2*).

$LiClO_4$ in Et_2O and various other ethers on the *endo*/*exo* selectivity of the *Diels-Alder* reaction, and determined the polarity of such ionic solutions [5c][11]. Later, *Grieco et al.* [12] and *Jouillié et al.* [13] exploited this aspect of enhanced rate and selectivity for the total syntheses of natural products. In our specific case, we were pleased to observe, under the conditions 5M $LiClO_4/Et_2O$, a de of 96%, in full agreement with our data concerning the non-HBD solvents.

Table 1. *Dependence of the Diastereoselectivity of the Cycloaddition* (–)-**1** → **2** *on the Polarity and Solvatochromic Indexes*[a])

Solvent	Conversion [%]	de [%]	$E_T(30)$ [kcal mol^{-1}]	log(dr)	π^*	α	β	δ	Calculated log(dr)	Residual log(dr)
H_2O	77	92	63.1	1.380	1.09	1.17	0.47	0.0	1.437	–0.057
$MeNO_2$	97	91	46.3	1.327	0.85	0.22	0.06	0.0	1.285	0.041
$(CF_3)_2CHOH$	100	90	65.3	1.279	0.65	1.96	0.00	0.0	1.264	0.015
CF_3CH_2OH	74	90	59.8	1.279	0.73	1.51	0.00	0.0	1.297	–0.019
Sulfolane	45	90	44.0	1.279	0.98	0.00	0.39	0.0	1.283	–0.004
$(-O(CH_2)_3O-)CO$	52	88	46.0	1.195	0.83	0.00	0.40	0.0	1.155	0.040
MeCN	100	88	45.6	1.195	0.76	0.00	0.29	0.0	1.129	0.066
DMSO	100	87	45.1	1.158	1.00	0.00	0.76	0.0	1.193	–0.035
Ac_2O	27	87	43.9	1.158	0.75	0.19	0.40	0.0	1.103	0.055
DMF	69	84	43.2	1.061	0.88	0.00	0.69	0.0	1.114	–0.053
Acetone	100	84	42.2	1.061	0.71	0.08	0.43	0.0	1.053	0.008
CH_2Cl_2	100	84	40.7	1.061	0.82	0.13	0.10	0.5	1.077	–0.016
Nitrobenzene	100	83	41.2	1.032	1.01	0.00	0.30	1.0	1.002	0.030
MeOH	100	82	55.4	1.005	0.60	0.98	0.66	0.0	0.961	0.043
AcOEt	100	78	38.1	0.908	0.55	0.00	0.45	0.0	0.908	0.000
EtOH	100	77	51.9	0.886	0.54	0.86	0.75	0.0	0.877	0.009
Dioxane	93	77	36.0	0.886	0.55	0.00	0.37	0.0	0.931	–0.045
$CHCl_3$	100	76	39.1	0.865	0.58	0.20	0.10	0.5	0.882	–0.017
THF	100	75	37.4	0.845	0.58	0.00	0.55	0.0	0.905	–0.059
Pyridine	100	74	40.5	0.826	0.87	0.00	0.64	1.0	0.788	0.037
Benzene	100	66	34.3	0.689	0.59	0.00	0.10	1.0	0.710	–0.022
Et_2O[b])	100	65	34.5	0.673	0.27	0.00	0.47	0.0	0.670	0.003
Toluene	100	64	33.9	0.659	0.54	0.00	0.11	1.0	0.666	–0.007
CCl_4	100	58	32.4	0.575	0.28	0.00	0.10	0.5	0.619	–0.043
Et_2NH	100	57	35.4	0.562	0.24	0.03	0.70	0.0	0.581	–0.019
Hexane[b])	100	56	31.0	0.550	–0.04	0.00	0.00	0.0	0.547	0.003
Et_3N	100	55	32.1	0.537	0.14	0.00	0.71	0.0	0.493	0.044

[a]) See text for definitions. [b]) 0.0005M.

Intrigued by the dichotomy between HBD and non-HBD solvents, we then turned our attention towards a more generalized definition of the polarity as expressed by the multi-parameter *Abboud-Abraham-Kamlet-Taft* model [14] where the log(dr) (dr = diastereoisomer ratio) may be expressed as a linear correlation of diverse solvatochromic parameters, such as defined in *Eqn. 1.* Therein,

$$\log(\mathrm{dr}) = a + b(\pi^* + c\delta) + d\alpha + \mathrm{e}\beta + f(\textit{Hildebrand}\ \text{index})^2 \tag{1}$$

the π^* parameter measures the exoergic effects of solute/solvent, dipole/dipole, and dipole/induced-dipole interactions. It measures the ability of a solvent to stabilize a

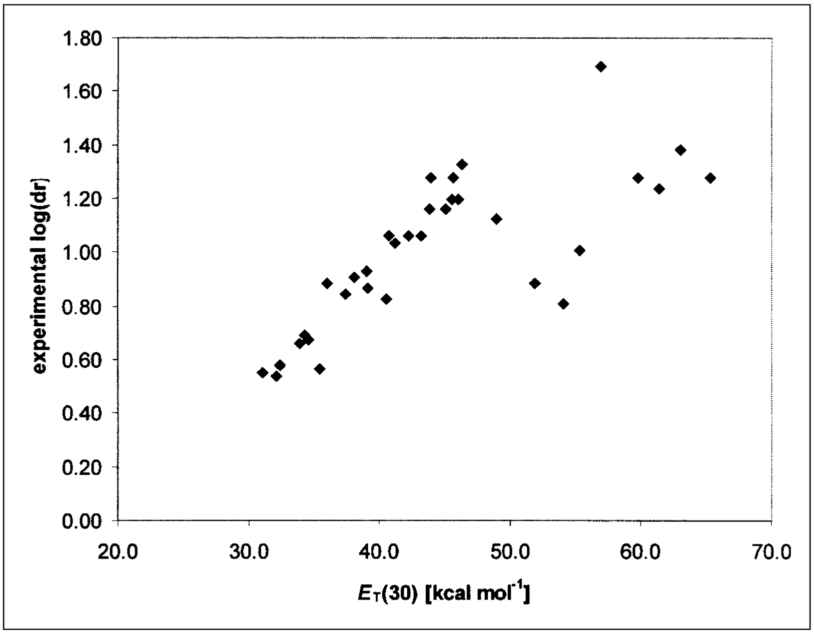


Fig. 1. *Diastereoselectivity of the cycloaddition of (–)-***1** *to cyclopentadiene as a function of the solvent polarity as defined by the* $E_T(30)$ *values of* Reichardt [9] (dr = diastereoisomer ratio)

neighboring charge or dipole by virtue of nonspecific dielectric interactions, and is thus nearly proportional to the dipole moment of the solvent. An empirically variable polarizability parameter δ must be added to correct the π^* term[3]). The solvatochromic parameter α is a quantitative empirical measure of the ability of a solvent to act as a HBD toward a solute, and is zero for non-HBD solvents such as aliphatic and aromatic hydrocarbons. The solvatochromic parameter β is a quantitative empirical measure of the ability of a bulk solvent to act as a H-bond acceptor or electron-pair donor toward a solute. The last term of *Eqn. 1*, the so-called cavity term, represents a physical solvent quantity, named cohesive pressure, which is related to *Hildebrand*'s solubility parameter. Its square corresponds to the endoergic process of separating the solvent molecules to provide a suitably sized enclosure for the solute and measures the work required to produce a cavity of unit volume in the solvent. This term is related to the tightness or structured nature of a solvent as caused by intramolecular solvent/solvent interactions. The π^*, α, β, δ, and *Hildebrand* indexes, as well as $E_T(30)$ values, are characteristic of the solvent and have been recently compiled by *Marcus et al.* [15] and *Chastrette et al.* [16]; in contrast, a, b, c, d, e, and f rely only on the solvent/solute property studied, since such a correlation may also be generalized to properties other than the diastereoselectivity. Based on 27 solvents, for which these parameters are available, we found that the square of *Hildebrand* index was statistically not relevant and could be omitted without further alteration of the linear correlation ($f = 0.0$). Thus,

---

[3]) For aromatic solvents, $\delta = 1.0$, for polychlorinated aliphatic solvents, $\delta = 0.5$, and for all other aliphatic solvents, $\delta = 0.0$.

a particularly good correlation was found between the experimental and calculated diastereoselectivity (log(dr)), for the cycloaddition of (–)-**1** to cyclopentadiene, as shown in *Fig. 2*. A correlation coefficient of 0.99 ($r^2 = 0.981$, $n = 27$) was found with a standard deviation of 0.039 when the equation was fitted with the parameters of *Eqn. 2*.

$$\log(\mathrm{dr}) = 0.580 + 0.831\pi^* - 0.331\delta + 0.073\alpha - 0.287\beta \quad (2)$$

At the two extremes of the solvent-polarity scale, we observe that the experimental values slightly diverge, and are either higher than that calculated according to *Eqn. 2* in Et_3N ($E_T(30) = 32.1$ kcal/mol, 55% de instead of calc. 51%) or lower in H_2O ($E_T(30) = 63.1$ kcal/mol, 92% de instead of calc. 93%)[4]. This may tentatively be explained by the influence of the excess of cyclopentadiene which slightly modifies the overall polarity of the solvent. When the reaction was performed in neat cyclopentadiene, a selectivity of 79% de was obtained. Similarly, when the amount of cyclopentadiene was increased relative to a constant amount of H_2O, the diastereoselectivity decreased from 92 to 78% de (see *Table 2*).

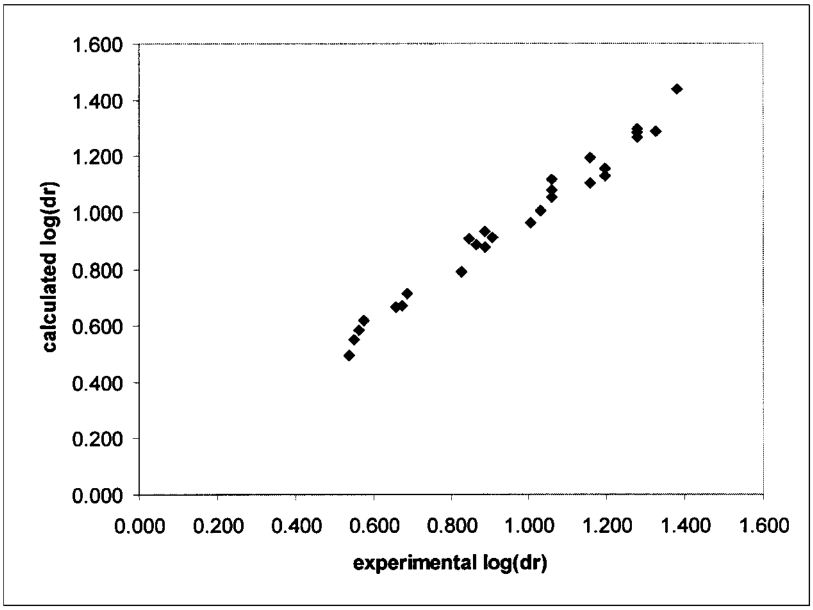


Fig. 2. *Experimental* vs. *predicted diastereoselectivity of (–)-***1** *based on the* Abboud-Abraham-Kamlet-Taft *model* [14–16] (dr = diastereoisomer ratio)

For several solvents such as hexane (70% de), cyclopentadiene (79% de)[5]), Et_2O (87% de), pentane-2,4-dione (86% de), and pentan-3-ol (90% de), the selectivity was superior to that expected according to *Eqn. 2* and, furthermore, the reaction mixture was not homogeneous. Indeed, both (–)-**1** and the cycloadducts (most probably the

---

[4]) Standard error of the analytical method, ±2%.

[5]) This suggests that $E_T(30) = 39.0$, which is too high for this diene. For comparison, cyclohexene has an $E_T(30)$ value of 32.2 [9][15].

Table 2. *Dependence of the Diastereoselectivity of the Cycloaddition* (−)-**1**→**2** *on the Polarity and Concentration of Additives*

Solvent	Conditions	Conversion [%]	de [%]	$E_T(30)$ [kcal/mol]	log(dr)
Pentan-3-ol		100	90	45.7	1.279
$(EtNH_3)NO_3$		100	89	61.4	1.235
Pentane-2,4-dione		100	86	49.0	1.123
Cyclopentadiene		100	79		0.931
CCl_3CH_2OH		100	73	54.1	0.807
H_2O	α-cyclodextrin	100	83		1.032
H_2O	(+)-**1**/α-cyclodextrin	100	81		0.979
H_2O	β-cyclodextrin	100	96		1.690
H_2O	(+)-**1**/β-cyclodextrin	100	87		1.158
H_2O	γ-cyclodextrin	100	82		1.005
H_2O	(+)-**1**/γ-cyclodextrin	100	89		1.235
H_2O	4.0 mol-equiv. of diene	61	92	63.1	1.380
H_2O	5.0 mol-equiv. of diene	77	91		1.327
H_2O	10.0 mol-equiv. of diene	100	84		1.061
H_2O	20.0 mol-equiv. of diene	100	79		0.908
H_2O	25.0 mol-equiv. of diene	100	78		0.826
Et_2O	5M $LiClO_4$	100	96	57.0	1.690
Et_2O	0.05M dienophile	100	88		1.195
Et_2O	0.02M dienophile	100	87		1.158
Et_2O	0.008M dienophile	100	69		0.737
Et_2O	0.0005M dienophile	100	65	34.5	0.673
Hexane	0.05M dienophile	43	83		1.032
Hexane	0.02M dienophile	60	70		0.753
Hexane	0.008M dienophile	83	68		0.720
Hexane	0.0005M dienophile	100	56	31.0	0.550

major (2*R*,3*R*)-cycloadduct **2**) crystallized out of the solvent. Since the reaction was irreversible at these temperatures[6]), this higher π-facial selectivity may hypothetically be attributed to the interaction of the diene with the dienophile at the solid/liquid interface, rather than to a consequence of a displacement of the reaction equilibrium by selective crystallization of the major cycloadduct. In these solvents, the diastereoselectivity depended on the dienophile concentration (see *Table 2*), and thus, under high-dilution conditions, lower de values, closer to the predicted ones, were obtained. Such an unexpected high diastereoselectivity was also observed in another apolar solvent, also leading to heterogeneous conditions, namely in supercritical CO_2, a well-known fluid used for the mild extraction of flavors and fragrances [17].

For CO_2, supercritical conditions are reached when the pressure and the temperature are superior to 72.8 bar and 31.8°, respectively. The polarity of the medium increases with larger pressure or, under isobar conditions, decreases with higher

---

[6]) The ground state energies of cyclopentadiene, (2*S*,3*S*)-**2**, and (2*R*,3*R*)-**2** are 31.75, −180.9, and −183.7 kcal/mol, respectively. Cycloadducts **2** were earlier shown to be thermodynamically stable in the presence of cyclohexadiene [3]. Nevertheless, since the bicyclo[2.2.2] adducts are sterically more crowded than their [2.2.1] analogues, and thus higher in energy, we preferred to test the stability of **2** in the presence of cyclopentadiene. Consequently, when the pure minor diastereoisomer (2*S*,3*S*)-**2** [1] was treated for 10 days in the presence of 10.0 mol-equiv. of cyclopentadiene in either refluxing CCl_4 or MeCN, no change occurred, thus confirming the thermodynamic stability of the minor diastereoisomer and the kinetic control of this [4+2] cycloaddition.

temperatures [18]. The influence of supercritical fluids has been studied on the kinetic [19], *endo/exo* [20], and regioselective [18b][21] outcome of the *Diels-Alder* reaction. We report here the first example, to the best of our knowledge, of a study related to its influence on the cycloaddition diastereoselectivity (*Table 3*). First of all, we note that, below the supercritical conditions, conversion was particularly poor (*Entry 1*). The best diastereoselectivity was obtained around the supercritical point (*Entry 2*), while a similar result was obtained at higher pressure and temperature (*Entry 4*). Comparison between *Entries 4–6* demonstrates that the polarity of the medium may even counterbalance the usual negative temperature effect[7]).

Table 3. *Cycloaddition of (–)-**1** to Cyclopentadiene after 4 h in Supercritical* CO_2

Entry	Pressure [bar]	Temperature [°]	Conversion [%]	de [%]	$E_T(30)$[a]) [kcal/mol]
1	65	33	1.4	56	29.9
2	74	33	65	93	31.5
3	76	43	100	88	31.3
4	78	43	100	92	31.5
5	78	53	100	79	31.0
6	90	63	100	82	31.4

[a]) Values from [18c].

This prompted us to turn briefly our attention to the influence of temperature on the relationship between π-facial selectivity and solvent polarity. We thus selected five solvents and performed the reaction as previously described (0.02M (–)-**1**, 4–18 h, complete conversion) between –78 and 110°. The results are summarized in *Table 4*, and the corresponding *Eyring* plots and parameters are shown in *Fig. 3* and *Table 5*.

Table 4. *Temperature and Solvent Polarity Dependence of the Cyclopentadiene Addition to (–)-**1***

Temperature	Diastereoselectivity (de [%])							
	110°	77°	36°	20°	0°	–23°	–42°	–78°
MeCN		86	87	88	89	90	91	
CH_2Cl_2			81	84	86	87	88	89
Toluene	44	46	60	64	66	68	69	76
CCl_4		44	56	58	65	68		
EtOH		66	75	77	83	87	91	96

First of all, the $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ are relatively small as compared to the usual $\Delta H^{\#}$ (15–18 kcal/mol) and $\Delta S^{\#}$ (14–34 cal/mol°) of the *Diels-Alder* reaction [22], and thus, in some instances, may be close to the error limit of our analytical method[4]). For this reason, we shall discuss qualitatively rather than quantitatively these specific aspects. Two trends emerge on inspection of this data. The enthalpic contribution $\Delta\Delta H^{\#}$, obtained from the slope, dominates in the less diastereoselective apolar or HBD reaction media, while the entropic contribution $\Delta\Delta S^{\#}$, obtained from the intercept, becomes more important with highly polar solvents. In apolar and HBD solvents, the

---

[7]) Although very small, the influence of the pressure may also enter in consideration with respect to the volumes of activation of the different transition states, the more compact volume of activation is represented by C(α)-*re* face attack of the diene on the *syn*-s-*cis*-s-*trans*-*syn* conformer (see below, *Table 6*).

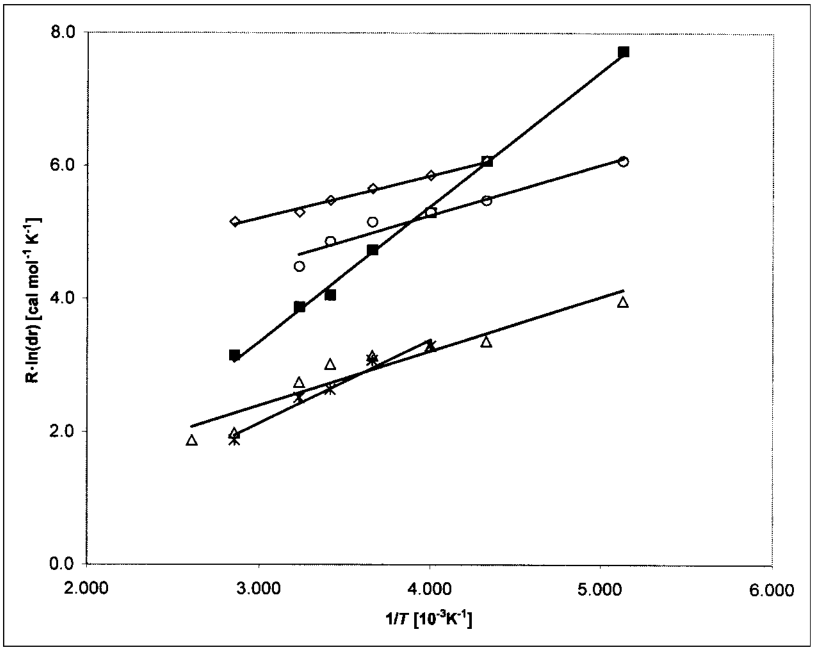


Fig. 3. Eyring *plot for temperature dependence in EtOH* (■), *MeCN* (◇), *CH_2Cl_2* (○), *toluene* (△), *and CCl_4* (*)

Table 5. *Enthalpic and Entropic Factors Derived from Solvent Polarity for the Cycloaddition of (–)-***1** *to Cyclopentadiene*

	$E_T(30)$ [kcal/mol]	$\Delta\Delta H^{\#}$ [kcal/mol]	$\Delta\Delta S^{\#}$ [cal/mol°]	r [%]
MeCN	45.6	0.65	3.24	99
CH_2Cl_2	40.7	0.73	2.33	96
Toluene	33.9	0.82	– 0.07	95
CCl_4	32.4	1.26	– 1.64	98
EtOH	51.9	2.03	– 2.76	99

entropic factor is even negative. The positive entropy difference may be attributed to a relatively higher degree of the solvent-matrix disruption[8]) or increased rotational/translational freedom in the transition state.

We suggested earlier that the generalized anomeric effect of the sultam moiety could be of prime importance on the N-atom pyramidalization, resulting in matching/mismatching steric/stereoelectronic influences, depending on the reactive conformations, and underlined the reactivity of the *syn*-s-*cis* species [3][23][9]). Thus, the

---

[8]) Displacement by the incoming diene of polar solvent molecules tightened and structured around the dienophile may partially account for the entropy increase.

[9]) Our hypothesis was initially based on the *anti*-periplanarity of the S=O(1) and N–H bonds observed in the X-ray analyses of the free toluene [24] and camphor sultams [25]. Very recently, Canadian authors, based on the X-ray analysis of a racemic six-membered-ring sultam, estimated the influence of the anomeric stabilization to 2.0 kcal/mol [26]. For the X-ray analysis of a *N*-fluorobornane-10,2-sultam, see [27].

rationalization of the observed enhanced diastereoselectivity in polar solvents may be based on two cooperative effects: the influence on the conformational stability of the dienophile[10] and the specific stabilization of certain transition states by the solvent. Since the cycloaddition involves two reactive centers, which at the origin of the reaction coordinate do not interact at all with the diene, one might expect a high degree of stereochemical communication in a later transition state. An early reactant-like transition state, with greater spatial separation between the diene and dienophile, should result in a poorer differentiation of the diastereoisomeric transition structures [30]. Solvents may affect changes in distances of the newly forming bonds in the transition state and thus alter the diene/chiral dienophile interactions. In the case of apolar solvents and a less ordered early transition state, a large entropic factor would be expected, in contrast to what is observed. We thus propose that the larger positive entropic factor observed in polar non-HBD solvents is better explained by the supplementary rotational freedom of *syn*-s-*cis* conformations.

The conformational stability of (−)-**1**, as well as the PM3 energy of the possible transition states, together with dipole moment and volume data, which govern the overall stereochemical course of the reaction, were earlier calculated in vacuum [3] and are summarized in *Table 6*.

First of all, if we consider that an energy difference of 2.5 kcal/mol in the transition state corresponds to the limit of detection of the ^{1}H-NMR analysis that we performed, we see that the minor diastereoisomer (2*S*,3*S*)-**2**, which results from C(α)-*si* attack, originates from the bis(*syn*-s-*cis*) conformation and possesses the smallest transition state intrinsic dipole moment. Leaving aside steric and stereoelectronic considerations related to the approach of the diene [3], this is thus the less disfavored transition state in apolar solvents[11]. Secondly, as a general feature, the transition states corresponding to the C(α)-*re* face attacks, leading to the major diastereoisomer (2*R*,3*R*)-**2**, always possess a higher dipole moment as compared to the respective C(α)-*si* face attacks. This may explain, at the level of the transition state, the favored C(α)-*re* approaches in polar solvents, which stabilize the higher resultant dipole moment.

We also extended our study to the influence of the solvent on the addition of cyclopentadiene (4.0 mol-equiv.) to *N*-acryloylbornane-10,2-sultam (0.02M, 20°) and found a similar correlation with the diastereoselectivity (in CCl_4 for 96 h: 34% de, 86% *endo*, 98% yield; in CH_2Cl_2 for 72 h: 66% de, 89% *endo*, 80% yield [32]; in MeCN for 96 h: 76% de, 90% *endo*, 99% yield; in EtOH for 96 h: 58% de, 90% *endo*, 98% yield). In the thermodynamically disfavored *syn*-s-*cis* conformation [3], this dienophile possesses a larger dipole moment (7.2 D) than the *anti*-s-*cis* conformer (3.3 D), a result

---

[10] Considering O=C−C=C coplanar restricted conformations of (−)-**1**, the batho/hyperchromic shifts observed for the C=C π-π^* band by UV analysis in polar or protic solvents (hexane ($\varepsilon = 1.89$ D): 227.8 nm (ε 5393): MeCN ($\varepsilon = 36.2$ D): 228.2 nm (ε 7541); propane-1,3-diyl-carbonate ($\varepsilon = 65.1$ D): 229.5 nm (ε 7988); CF_3CH_2OH ($\varepsilon = 26.5$ D): 229.0 nm ($\varepsilon = 8273$); MeOH ($\varepsilon = 32.6$ D): 230.3 nm (ε 5735)) are consistent with smaller energy differences between the HOMO and the LUMO of the reactive bis(*syn*-s-*cis*), *syn*-s-*cis*-s-*cis*-*anti* or H-bonded activated species as compared to the bis(*anti*-s-*cis*) conformer [3]. Nevertheless, this may not be considered as conclusive since such batho/hyperchromic shifts of the K band, in the case of α,β-enones, are also generally observed in UV, due to the influence of the dielectric constant ε of the solvent [28]. For comparison, dimethyl fumarate absorbs at 220 nm (ε 8709) in EtOH ($\varepsilon = 24.3$ D) [29].

[11] For examples of *endo*/*exo* selectivity governed by dipole-moment interactions, see [20][31].

Table 6. *PM3-Calculated Conformational and Transition-State Energies, Dipole Moments, and Volumes of (−)-***1**

	Dienophile		C(α)-*re* Face attack			C(α)-*si* Face attack		
	ground state energy [kcal/mol]	dipole moment [Debye]	$\Delta H^{\neq}$ [kcal/mol]	dipole moment$^{\neq}$ [Debye]	$V^{\neq}$ [Å^3]	$\Delta H^{\neq}$ [kcal/mol]	dipole moment$^{\neq}$ [Debye]	$V^{\neq}$ [Å^3]
syn-s-*cis*-s-*cis*-*anti*	– 196.6	8.3	*– 132.2*	9.1	523.3	– 129.6	7.3	523.5
syn-s-*cis*-s-*trans*-*syn*	– 196.9	11.7	– 126.5	12.3	*521.2*	– 130.0	10.3	521.3
bis(*syn*-s-*cis*)	– 196.9	1.2	*– 131.8*	3.1	522.6	*– 131.3*	*2.3*	522.2
bis(*anti*-s-*cis*)	– 197.1	1.9	*– 133.2*	4.8	524.2	– 129.6	3.9	524.2

of the additive vectorial composition of the two SO_2 and C=O groups, which point in the same direction. As a consequence, this conformation, which cooperatively cumulates both steric and stereoelectronic effects [3][23], is less destabilized in polar solvents. Furthermore, in the presence of a HBD solvent, coordinating either to the C=O and/or SO_2 moieties, the *anti*-s-*cis* conformation is more abundant, and thus the cooperation of the stereoelectronic effect is lost [3][12]. If the increased polarity of the solvent is positively influencing both the conformation and the transition states in terms of diastereoselectivity, the situation is more complicated for dienophile (−)-**1**. Indeed, due to its high symmetry, the bis(*anti*-s-*cis*) and bis(*syn*-s-*cis*) conformers possess only a small dipole moment, which is centered on the dienophile unsaturation and points in the S=O(1) pseudoaxial direction. The dipole moment of the latter conformer is slightly smaller due to a more concave structure. Thus, it is the nonsymmetrical *syn*-s-*cis*-s-*trans*-*syn* and *syn*-s-*cis*-s-*cis*-*anti* conformations, possessing larger dipole moments, which are better stabilized in polar solvents. Accordingly, it is the C(α)-*re* face transition state of the latter conformer which, in polar solvents, accentuates its participation as compared to the conformationally stable symmetric transition states.

Conclusion. – Almost complete diastereoselectivity (96% de) was obtained for the uncatalyzed [4+2] cycloaddition of (−)-**1** to cyclopentadiene. A perfect linear correlation between the diastereoselectivity and the solvatochromic properties of the solvent was found. *Eyring* analyses revealed that diastereoselectivity in the [4+2] cycloaddition of cyclopentadiene to (−)-**1** in polar non-HBD solvents relies mostly on entropic factors, while in less polar or HBD solvents, the π-facial selectivity is subject to greater enthalpic influence. Our initial hypothesis that the SO_2/C=O *syn* conformation of the dienophile in the transition state is a critical element for the [4+2] cycloadditions of sultam-derived dienophiles is thus reasonable and not in contradiction with our results. Polar solvents allow the stabilization of the thermodynamically

---

[12] It is noteworthy that also for this dienophile, the dipole moments of the transition state C(α)-*re* face attacks are larger (*syn*-s-*cis:* 7.54 D; *anti*-s-*cis:* 3.8 D) than the corresponding C(α)-*si* face approaches (*syn*-s-*cis:* 7.47 D; *anti*-s-*cis:* 2.6 D). An alternative rationalization for the lower diastereoselectivity observed with HBD solvents could be that the coordinated dienophile is activated by the H-bond, and thus the more reactive species would react in an earlier, less ordered transition state with larger spatial interactions. Restricted rotation would explain the large negative entropic factor. We privilege, nevertheless, the loss of the hypothetical cooperative steric/stereoelectronic effects of the *syn*-s-*cis* conformer for these examples. As regards the conditions using 5M $LiClO_4$ in Et_2O, the higher diastereoselectivity may be a result of chelation of the metal to the activated *syn*-s-*cis* dienophile [33].

less favored *syn*-s-*cis* conformers and thus a more effective cooperation between the steric and stereoelectronic effects for this class of dienophiles. This aspect is reinforced by the additional stabilization by polar solvents of the C(α)-*re* transition states exhibiting larger dipole moments in *syn* and *anti* conformations, as compared to the C(α)-*si* attacks. This work also shows the necessity to consider solvent effects when one transposes semi-empirical or *ab initio* calculations from qualitative to quantitative conclusions [34]. This has not always been the case [35].

We are indebted to Profs. *L. Jen-Jacobson*, *A. Collet*, and *F. P. Schmidtchen* for stimulating discussions, as well as to the University of Warsaw for financial support (BST 562/18/97).

Experimental Part

General. See [23b].

General Procedure for the Uncatalyzed Cycloaddition. To a soln. of (−)-**1** (51 mg, 0.1 mmol) in the appropriate solvent (5 ml), cyclopentadiene (33 µl, 0.4 mmol) was added dropwise (along the cold wall of the reaction flask when working at low temp.). After 4–18 h, the solvent and the excess of cyclopentadiene were evaporated under medium, then high vacuum. The crude cycloadduct **2** (99% yield) was submitted to ^{1}H-NMR analysis for conversion and de determination [1]. TLC (hexane/AcOEt 7:3): R_f ((−)-**1**). 0.38, R_f (major (2*R*,3*R*)-**2**) 0.34, R_f (minor (2*S*,3*S*)-**2**) 0.65.

General Procedure under CO$_2$ Supercritical Cycloaddition Conditions. A small test tube containing a magnetic stirring bar and cyclopentadiene (33 µl, 0.4 mmol) was placed vertically on the inside wall of an autoclave containing (−)-**1** (51 mg, 0.1 mmol) and equipped with a strong magnet on the external side wall. The autoclave was filled with solid CO_2 (15–25 g) and then sealed and heated. After obtaining the desired stabilized temperature and pressure, the magnet on the side was removed, and the mixture was stirred for 4 h. The cold autoclave was then cautiously depressurized and opened. The crude solid material (96–99% yield) was dried under high vacuum and then submitted to ^{1}H-NMR analysis.

REFERENCES

[1] C. Chapuis, P. Rzepecki, T. Bauer, J. Jurczak, *Helv. Chim. Acta* **1995**, *78*, 145.

[2] T. Bauer, C. Chapuis, A. Kucharska, P. Rzepecki, J. Jurczak, *Helv. Chim. Acta* **1998**, *81*, 324.

[3] C. Chapuis, J. Y. de Saint-Laumer, M. Marty, *Helv. Chim. Acta* **1997**, *80*, 146; G. Bernardinelli, C. Chapuis, A. J. Kingma, M. Wills, *ibid*. **1997**, *80*, 1607.

[4] M. E. Burrage, R. C. Cookson, S. S. Gupte, I. D. R. Stevens, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1325; A. I. Konovalov, J. P. Breus, I. A. Sharagin, V. D. Kiselev, *J. Org. Chem. USSR* **1979**, *15*, 315; M. Ahmad, J. Hamer, *J. Org. Chem.* **1966**, *31*, 2831; P. Haberfield, A. K. Ray, *ibid*. **1972**, *37*, 3093.

[5] a) D. J. Jaeger, C. E. Tucker, *Tetrahedron Lett*. **1989**, *30*, 1785; B) R. Breslow, T. Guo, *J. Am. Chem. Soc*. **1988**, *110*, 5613; c) R. Braun, J. Sauer, *Chem. Ber.* **1986**, *119*, 1269; d) R. Breslow, U. Maitra, D. Rideout, *Tetrahedron Lett*. **1983**, *24*, 1901; e) J. A. Berson, Z. Hamlet, W. A. Mueller, *J. Am. Chem. Soc.* **1962**, *84*, 297.

[6] S. Hiraoka, T. Yoshida, H. Kansui, T. Kunieda, *Tetrahedron Lett*. **1992**, *33*, 4341; H. Kansui, S. Hiraoka, T. Kunieda, *J. Am. Chem. Soc*. **1996**, *118*, 5346.

[7] a) J. Sauer, J. Kredel, *Tetrahedron Lett*. **1966**, 6359; b) T. Poll, G. Helmchen, B. Bauer, *ibid*. **1984**, *25*, 2191; c) C. Cativiela, J. I. Garcia, J. A. Mayoral, A. J. Royo, L. Salvatella, X. Assfeld, M. F. Ruiz-Lopez, *J. Phys. Org. Chem.* **1992**, *5*, 230; d) C. Cativiela, J. I. Garcia, J. A. Mayoral, A. J. Royo, L. Salvatella, *Tetrahedron: Asymmetry* **1993**, *4*, 1613; e) G. Naraku, K. Hori, Y. N. Ito, T. Katsuki, *Tetrahedron Lett*. **1997**, *38*, 8231; f) T. Saito, M. Kawamura, J. I. Nishimura, *ibid*. **1997**, *38*, 3231; g) C. Cativiela, J. I. Garcia, J. Gil, R. M. Martinez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar, M. H. Abraham, *J. Chem. Soc., Perkin Trans. 2* **1997**, 653; S. Otto, G. Boccaletti, J. B. F. N. Engberts, *J. Am. Chem. Soc*. **1998**, *120*, 4238.

[8] L. M. Tolber, M. B. Ali, *J. Am. Chem. Soc*. **1981**, *103*, 2104; *ibid*. **1982**, *104*, 1742; *ibid*. **1984**, *106*, 3806; *ibid*. **1985**, *107*, 4589.

[9] C. Reichardt, in 'Solvent Effects in Organic Chemistry', Verlag Chemie, Weinheim–New York, 1979; C. Reichardt, *Nachr. Chem. Tech. Lab*. **1997**, *45*, 759; C. Reichardt, *Chem. Rev*. **1994**, *94*, 2319; J. A. Paez, N. Campillo, J. Elguero, *Gazz. Chim. Ital*. **1996**, *126*, 307.

[10] S. Sugden, H. Wilkins, *J. Chem. Soc.* **1929**, 1291; I. M. Herfort, H. Schneider, *Liebigs Ann. Chem.* **1991**, 27.

[11] Y. Pocker, J. C. Ciula, *J. Am. Chem. Soc.* **1989**, *111*, 4728.

[12] P. A. Grieco, J. J. Nunes, M. D. Gaul, *J. Am. Chem. Soc.* **1990**, *112*, 4595; P. A. Grieco, *Aldrichim. Acta* **1991**, *24*, 59; P. A. Grieco, J. P. Beck, *Tetrahedron Lett.* **1993**, *34*, 7367.

[13] S. C. Mayer, Amy, J. Pfizenmayer, R. Cordova, W.-R. Li, M. M. Jouillié, *Tetrahedron: Asymmetry* **1994**, *5*, 519.

[14] M. J. Kamlet, J. L. Abboud, M. H. Abraham, R. W. Taft, *J. Org. Chem.* **1983**, *48*, 2877.

[15] Y. Marcus, *Chem. Soc. Rev.* **1993**, 409; Y. Marcus, *J. Soln. Chem.* **1991**, *20*, 929; Y. Migron, Y. Marcus, *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 1339.

[16] M. Chastrette, M. Rajzmann, M. Chanon, K. F. Purcell, *J. Am. Chem. Soc.* **1985**, *107*, 1.

[17] L. Wünsche, U. Keller, I. Flament, *J. Chromatogr.* **1991**, *552*, 539; I. Flament, U. Keller, L. Wünsche, in 'Supercritical Fluids Processing of Food and Biomaterials', Ed. S. S. H. Rizvi, Blackie Academic & Professional, Chapmann & Hall, London, 1994, p. 62.

[18] a) P. E. Savage, S. Gopolan, T. I. Mizan, C. J. Martino, E. E. Brock, *React. Kinet. Catal. Lett.* **1995**, *41*, 1723; b) Y. Ikushima, N. Saito, M. Arai, *J. Phys. Chem.* **1992**, *96*, 2293; c) *SF-Solver Program*™, Isco. Inc., 4700 Superior St., Lincoln, NE 68504, USA.

[19] M. E. Paulaitis, G. C. Alexander, *Pure Appl. Chem.* **1987**, *59*, 61.

[20] S. Kim, K. P. Johnston, *Chem. Eng. Commun.* **1988**, *63*, 49.

[21] Y. Ikushima, S. Ito, T. Asano, T. Yokoyama, N. Saito, K. Hatakeda, T. Goto, *J. Chem. Eng. Jpn.* **1990**, *23*, 96.

[22] A. A. Frost, R. G. Pearson, in 'Kinetics and Mechanism', 2nd edn., Wiley, New York, 1965, p. 376; J. B. Jaquith, C. J. Levy, G. V. Bondar, S. Wang, S. Collins, *Organometallics* **1998**, *17*, 914.

[23] a) T. Bauer, C. Chapuis, A. Jezewski, J. Kozak, J. Jurczak, *Tetrahedron: Asymmetry* **1996**, *7*, 1391; b) T. Bauer, C. Chapuis, J. Kiegiel, J. W. Krajewski, K. Piechota, Z. Urbanczyk-Lipkowska, J. Jurczak, *Helv. Chim. Acta* **1996**, *79*, 1059; c) J. Raczko, M. Achmatowicz, A. Jezewski, C. Chapuis, Z. Urbanczyk-Lipkowska, J. Jurczak, *ibid.* **1998**, *81*, 1264.

[24] W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117.

[25] J. Kiegiel, C. Chapuis, Z. Urbañczyk-Lipkowska, J. Jurczak, *Helv. Chim. Acta* **1998**, *81*, 1672.

[26] J. F. King, G. Yuyitung, M. S. Gill, J. C. Stewart, N. C. Payne, *Can. J. Chem.* **1998**, *76*, 164.

[27] F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Qi, W. Han, R. M. Preslawski, B. C. Chen, P. J. Carroll, *J. Org. Chem.* **1998**, *63*, 2273.

[28] C. N. R. Rao, in 'Ultra-Violet and Visible Spectroscopy, Chemical Application', Butterworths, London, 1961; G. Geiseler, in 'Ausgewählte Physikalische Methoden der Organischen Chemie', Akademie Verlag, Berlin, 1963, Band II.

[29] M. L. Stein, G. Giacomello, *Ricerca Sci.* **1952**, *22*, 1007; R. F. Rekker, P. J. Brombacher, H. Hamann, W. T. Nauta, *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 410.

[30] M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Güler, T. Ishida, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 948.

[31] K. Takeda, I. Imaoka, E. Yoshii, *Tetrahedron* **1994**, *50*, 10839.

[32] C. Chapuis, Ph.D. Thesis, Université de Genève, 1984, No. 2144, p. 46; W. Oppolzer, I. Rodriguez, J. Blagg, G. Bernardinelli, *Helv. Chim. Acta* **1989**, *72*, 123.

[33] T. Ooi, A. Saito, K. Maruoka, *Tetrahedron. Lett.* **1998**, *39*, 3745.

[34] J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 1064; C. Cativiela, J. I. Garcia, J. A. Mayoral, L. Salvatella, *Chem. Soc. Rev.* **1996**, 209.

[35] K. S. Kim, B. H. Kim, W. M. Park, S. J. Cho, B. J. Mhin, *J. Am. Chem. Soc.* **1993**, *115*, 7472.

Received September 7, 1998