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Dynamic solvation effects on the *endo*/*exo* selectivity of the Diels–Alder reaction

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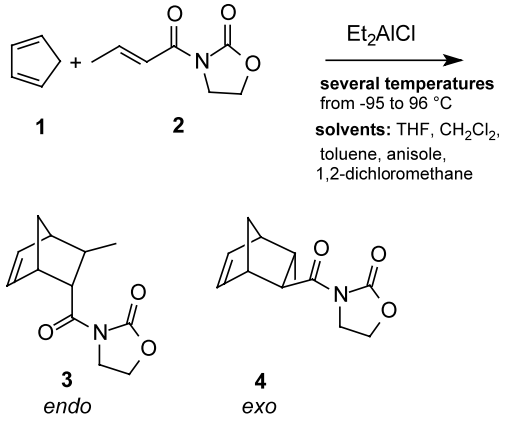
Abstract—The *endo*/*exo* stereoselectivity of the Diels–Alder cycloaddition between cyclopentadiene and 3-crotonoyl-2-oxazolidinone catalysed by Et_2AlCl is temperature- and solvent-dependent. Eyring plots of ln(*endo*/*exo*) versus $1/T$ show different inversion temperatures (T_{inv}) depending on the reaction solvent. Using toluene-d_8 we found a break temperature (T_{NMR}) in a variable temperature ^{13}C NMR experiment of the starting oxazolidinone, and this T_{NMR} corresponded to the T_{inv}. In several cases the differential activation entropy manages the observed stereoselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

The Diels–Alder reaction is one of the meanfully method for forming six-membered carbocycles as well as heterocycles.[1] The widespread importance of this reaction has been demonstrated in the synthesis of a variety of natural products and recently reviewed.[2,3] Although the influence of the solvent on the overall kinetic, on the diastereoselectivity (*endo*/*exo*), and on the regioselectivity of the Diels–Alder reaction is well-known, a deeper insight on solvent and temperature effects on the stereochemistry is sporadic.[4] The temperature dependence in the formation of two diastereoisomers can be analyzed according to the modified Eyring equation (1),[5] where S is the stereoselectivity and k and k' are the overall rate constants for the synthesis of the two stereoisomers.

$$\ln S = \ln(k/k') = -(\Delta\Delta H^{\neq}/RT) + (\Delta\Delta S^{\neq}/R) \qquad (1)$$

Eq. (1) shows that both the differential activation enthalpy and the differential activation entropy contribute to the stereoselectivity (S). In many cases it is observed the existence in Eyring plots of ln S versus $1/T$ of two linear trends intersecting at a point thus defining a temperature denoted as inversion temperature (T_{inv}).[6] We demonstrated that the presence of a T_{inv} accounts for dynamic solvation effects on the stereoselectivity.[7] In our interpretation, an Eyring plot featuring a T_{inv} is the result of two intersecting linear trends produced by two different solvation clusters. These two solute–solvent clusters behave like independent species with different thermodynamic properties, and hence different stereoselectivities. At temperatures lower than T_{inv}, one cluster is present in solution, while at temperatures higher than T_{inv} another, different cluster is present. The T_{inv} would represent the interconversion temperature between these two supramolecules. We have recently shown that in *n*BuLi addition to chiral aldehydes T_{inv} depends mainly on the aldehyde–solvent couple.[8] Its value may be determined by ^{13}C NMR analyses using variable temperature (VT) experiments by the presence in a plot of chemical shift versus temperature of a break temperature, denoted T_{NMR}, near to the corresponding T_{inv}. The presence of a T_{inv} is not limited to nucleophilic additions to chiral aldehydes[9] or imines[10] and we pointed out the presence



Scheme 1.

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and the correspondence of T_{inv} and T_{NMR} even in other different reactions, particularly in enzymatic resolutions of 3-amino-β-lactams and azirinols.[11]

As a part of our ongoing interest on solvent and temperature effects on stereoselectivity[12–15] we report here a preliminary study on the dependence of *endo*/*exo* selectivity in a Diels–Alder reaction on temperature and solvent, in particular we studied the cycloaddition between cyclopentadiene (**1**) and 3-crotonoyl-2-oxazolidinone (**2**) catalyzed by Et_2AlCl in THF, anisole, CH_2Cl_2, 1,2-dichloroethane (1,2-DCE) and toluene (Scheme 1). In all experiments, the reaction was performed at constant temperature by introducing Et_2AlCl (1 mmol, 1 M heptane solution) to a solution of oxazolidinone (**2**) (1 mmol) in 20 mL of the anhydrous solvent. After a 10 min stirring, 4 mmol of cyclopentadiene (freshly distilled) were added. The reaction was repeated at different temperatures over the range permitted by the boiling and the melting points of the solvent. The reaction proceeded smoothly in all solvents examined, thus producing the two racemic cycloadducts *endo* and *exo*.[16] The diastereomeric ratio *endo*/*exo* (**3**/**4**) was determined in each experiment by HPLC analysis (Daicel Chiracel OF *n*-hexane:*i*PrOH 87/13, 0.5 mL/min) on the crude.

Data were analysed by least-squares fitting to Eq. (1) to obtain linear correlations.[17] For each data set we applied a residual analysis to evaluate the number of linear trends and to ascertain the presence of the inversion temperature. $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ were obtained from slopes and intercepts of linear plots and correspond to $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{endo} - \Delta H^{\neq}_{exo}$, and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{endo} - \Delta S^{\neq}_{exo}$. The Eyring plots of ln(*endo*/*exo*) versus $1/T$ for all solvents are given in Figure 1. Data of differential activation parameters are reported in Table 1 and diastereomeric ratios *endo*/*exo* in Table 2.

The *endo* isomer is predominant in all solvents studied, with the best diastereoselectivity obtained in toluene (*endo*/*exo* 97.3:2.7) at −66°C. In THF in the high temperature region, the contribution of enthalpic differences is very small, thus, in this case, there is little temperature control on stereoselectivity, the *endo* predominance that still remain is entirely determined by the entropic term $\Delta\Delta S^{\neq}$. Flattened plots appears even in anisole, CH_2Cl_2, and 1,2-DCE in the low temperature region, showing that the entropy can drive the preferred formation of the *endo* isomer even at low T.

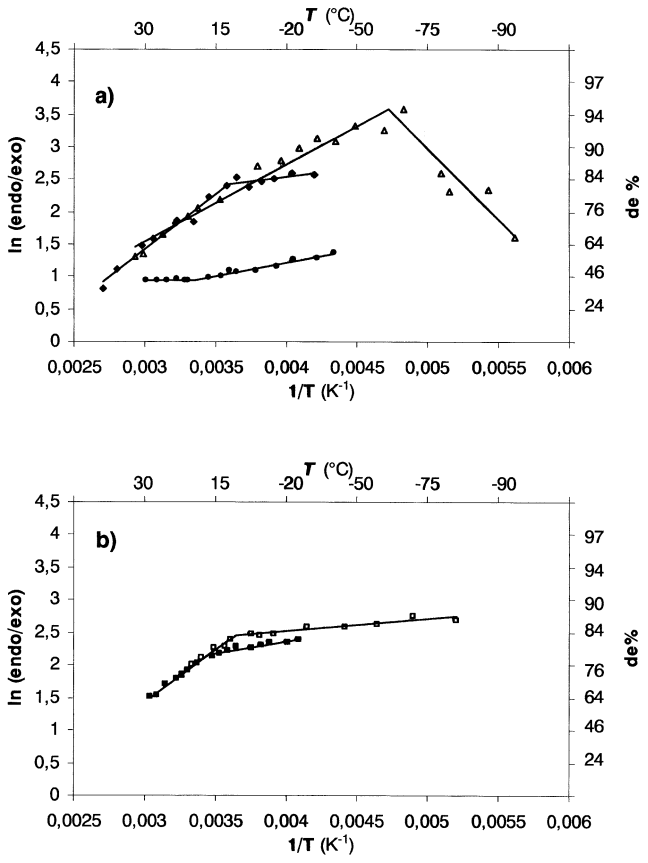

Figure 1. Eyring plots for the catalysed Diels–Alder reaction between cyclopentadiene and the oxazolidinone **2** in (a) THF (●), toluene (△), and anisole (◆), and (b) CH_2Cl_2 (□) 1,2-DCE (■).

CH_2Cl_2 and 1,2-DCE show superimposed plots at high temperature and little differences at low T due to a slight variation of the entropic term which contributes to their differentiation. Analyzing the differential activation parameters in Table 1 results that anisole toluene, dichloromethane and 1,2-DCE have similar $\Delta\Delta H^{\neq}$ values at $T > T_{inv}$: only through the presence of the inversion temperature and the consequent change in the activation parameters occurs a solvent-driven differentiation in stereoselectivity. In all cases but one, the differential activation enthalpy $\Delta\Delta H^{\neq}$ is negative thus favouring the predominance of the *endo* isomer. Tolu-

Table 1. Differential activation parameters and inversion temperatures for Et_2AlCl catalyzed Diels–Alder reaction between cyclopentadiene and oxazolidinone **2** in different solvents

Solvent	T_{inv} (°C)	$T > T_{inv}$		$T < T_{inv}$	
		$\Delta\Delta H^{\neq}$ (kcal/mol)	$\Delta\Delta S^{\neq}$ (cal/mol K)	$\Delta\Delta H^{\neq}$ (kcal/mol)	$\Delta\Delta S^{\neq}$ (cal/mol K)
THF	26	−0.06±0.03	1.71±0.1	−0.82±0.04	−0.8±0.2
Anisole	16	−3.4±0.2	−7.3±0.5	−0.5±0.3	3±1
Toluene	−61	−2.4±0.1	−4.0±0.5	4.3±1.0	28±5
CH_2Cl_2	1	−2.9±0.3	−5.8±1.0	−0.38±0.06	3.5±0.3
1,2-DCE	17	−3.2±0.1	−6.7±0.4	−0.75±0.09	1.7±0.3

Table 2. *Endo* (%) and *exo* (%) in the catalyzed Diels–Alder reaction between cyclopentadiene and **2** in different solvents

Solvent	T (°C)	*endo* (%)	*exo* (%)	Solvent	T (°C)	**3** *endo* (%)	**4** *exo* (%)
THF	59	71.9	28.1	Toluene	−43	95.6	4.4
THF	50	72.1	27.9	Toluene	−50	96.5	3.5
THF	43	72.1	27.9	Toluene	−60	96.3	3.7
THF	36.5	72.2	27.8	Toluene	−66	97.3	2.7
THF	30.5	72.1	27.9	Toluene	−77	93	7
THF	29	72.1	27.9	Toluene	−79	91	9
THF	16.5	72.8	27.2	Toluene	−89	91.1	8.9
THF	9.5	73.4	26.6	Toluene	−95	83.3	16.7
THF	5	74.8	25.2	CH_2Cl_2	33	86.3	13.7
THF	1	74.6	25.4	CH_2Cl_2	27	88.1	11.9
THF	−9	74.9	25.1	CH_2Cl_2	21	89.2	10.8
THF	−19	76.2	23.8	CH_2Cl_2	13	90.6	9.4
THF	−26	77.9	22.1	CH_2Cl_2	7	90.7	9.3
THF	−36	78.2	21.8	CH_2Cl_2	4	91.6	8.4
THF	−43	79.8	20.2	CH_2Cl_2	−7	92.2	7.8
Anisole	96	69.5	30.5	CH_2Cl_2	−11	92	8
Anisole	84	75.1	24.9	CH_2Cl_2	−18	92.3	7.7
Anisole	62	81.3	18.7	CH_2Cl_2	−32	92.9	7.1
Anisole	54	83	17	CH_2Cl_2	−47	93	7
Anisole	38	86	14	CH_2Cl_2	−58	93.3	6.7
Anisole	37	86.7	13.3	CH_2Cl_2	−69	94	6
Anisole	16	90.3	9.7	CH_2Cl_2	−81	93.6	6.4
Anisole	6	91.7	8.3	1,2-DCE	56	81.9	18.1
Anisole	−6	91.5	8.5	1,2-DCE	51	82.3	17.7
Anisole	−12	92.1	7.9	1,2-DCE	44	84.6	15.4
Anisole	−18	92.5	7.5	1,2-DCE	37	85.8	14.2
Anisole	−26	93.1	6.9	1,2-DCE	33	86.6	13.4
Anisole	−35	92.9	7.1	1,2-DCE	29	87.3	12.7
Toluene	68	78.7	21.3	1,2-DCE	23	88.4	11.6
Toluene	61	79.5	20.5	1,2-DCE	14	89.4	10.6
Toluene	46	83.8	16.2	1,2-DCE	10	89.8	10.2
Toluene	29	87.2	12.8	1,2-DCE	5	90.1	9.9
Toluene	23	88.6	11.4	1,2-DCE	1	90.7	9.3
Toluene	10	89.9	10.1	1,2-DCE	−7	90.6	9.4
Toluene	−10	93.7	6.3	1,2-DCE	−12	91	9
Toluene	−21	94.2	5.8	1,2-DCE	−16	91.2	8.8
Toluene	−29	95.2	4.8	1,2-DCE	−24	91.2	8.8
Toluene	−36	95.8	4.2	1,2-DCE	−29	91.6	8.4

ene at $T<T_{inv}$ is the exception: in this case the positive $\Delta\Delta H^{\neq}$ would favour the *exo* cycloadduct, but the positive $\Delta\Delta S^{\neq}$ drives the observed stereoselectivity toward the preferential formation of the *endo* one. This is another case in which the solvent determines the isomer preference through entropy.[18]

All plots feature different inversion temperatures indicating the presence in all solvents of two different solute–solvent clusters: one above and one below the T_{inv}. It is important to underline that the Eyring plot obtained in toluene derives from the particular behaviour of the two solute–solvent clusters. The one present at high T has the highest stereoselectivity lowering the T, on the contrary the cluster present at low T shows the highest *endo*/*exo* ratio raising the temperature. This opposite behaviour brings to the result that in toluene the highest stereoselectivity can be achieved at the inversion temperature, in other words, at the temperature of the interconversion of the two solute–solvent clusters. This behaviour cannot be certainly foreseen without an analyses of the temperature effect on the stereoselectivity.

Our proposed dependence of T_{inv} on solvation is reinforced by ^{13}C NMR experiment recording the evolution of chemical shifts with regard to the temperature. We

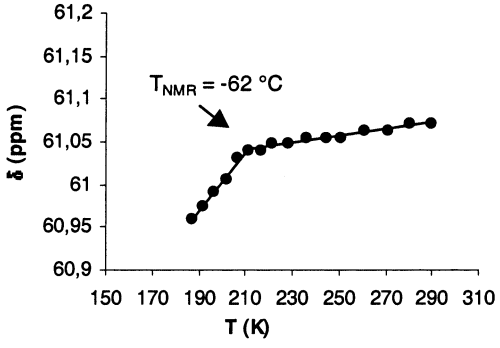

Figure 2. ^{13}C chemical shift versus temperature in the oxazolidinone **2** in toluene-d_8.

recorded ^{13}C NMR spectra of **2** in toluene-d_8 warming from −85 to 19.4°C. In Figure 2 we report the evolution of the peak at $\delta = 61$ ppm with the temperature. It could be easily recognized that the plot is composed of two linear segments, intersecting at a T_{NMR} of −62°C. This T_{NMR} corresponds well to the T_{inv} evident in the Eyring plots of the catalysed Diels–Alder reaction in toluene. In the VT NMR experiment the presence of Et_2AlCl and of cyclopentadiene is avoided, therefore the break temperature T_{NMR} is exclusively linked to the couple oxazolidinone–toluene. It appears clear that T_{NMR} and T_{inv}, even in this case, are linked as two independent experimental observations of the same reorganization cluster phenomenon. These results reinforce our hypothesis concerning the solvation-dependent natures of T_{inv} and T_{NMR}.

Although no microscopic interpretation of these solute–solvent clusters has yet been achieved, it is however important to study these dynamic solvation phenomena because they disclose how the stereoselectivity is mainly dictated by solvation. Work is in progress on temperature and solvent effects on diastereofacial Diels–Alder reaction on chiral oxazolidinones.

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References

1. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, p. 315.
2. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.
3. Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
4. For a review, see: Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, 209.
5. Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941; Chapter 4.
6. Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.
7. Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567.
8. Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Angew. Chem.* **2000**, *112*, 533; *Angew. Chem., Int. Ed.* **2000**, *39*, 523.
9. Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P.; Paradisi, F. *Eur. J. Org. Chem.* **1999**, 61.
10. Cainelli, G.; Giacomini, D.; Galletti, P. *Eur. J. Org. Chem.* **1999**, 61.
11. Cainelli, G.; De Matteis, V.; Galletti, P.; Giacomini, D.; Orioli, P. *Chem. Commun.* **2000**, 2351.
12. Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2849.
13. Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* **2001**, *42*, 7383.
14. Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Eur. J. Org. Chem.* **2001**, 4509.
15. Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P.; Polidoro, M. A.; Righetti, M. C. *Helv. Chim. Acta* **2000**, *83*, 1951.
16. Compounds **3** and **4** are known products, see: Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11632.
17. The average standard deviation for the *endo*/*exo* ratio was less than 1%. Error bars are omitted in Fig. 1 for clarity.
18. For entropy-driven stereoselectivity see Ref. 14 and references cited therein.