

# Temperature and solvent effects in facial diastereoselectivity of nucleophilic addition: entropic and enthalpic contribution

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Received (in Cambridge, UK) 27th October 1998, Accepted 23rd December 1998

Solvent and temperature effects on facial diastereoselectivity of nucleophilic addition have been long observed but often neglected. Temperature dependent measurements according to the modified Eyring equation allow the evaluation of stereoselectivity in terms of differential enthalpy and entropy of activation, and demonstrate the paramount importance of entropic contribution in directing the facial diastereoselectivity. Even the reaction solvent proved to be important in determining the isomer ratio. In many cases Eyring plots show a non-linear behavior consisting of two linear regions intersecting at a point called the inversion temperature ( $T_{inv}$ ) which, for the same reaction, depends on the nature of the solvent and correlates with their melting points. We propose that  $T_{inv}$  is the temperature value for the interconversion between two different solvation clusters which should behave like two different molecules.

## Introduction

Selectivity is the keyword for organic synthesis in recent years. Among the various categories, stereoselectivity represents the main goal for researchers involved either in total synthesis or in new methodologies. Moreover, the synthetic process for a new drug or for a biologically active compound cannot avoid a correct and accurate control on the final target stereochemistry.

Nowadays, many methods are available for stereocontrolled synthesis.<sup>1</sup> However, in spite of excellent experimental results obtained in asymmetric induction and asymmetric catalysis,

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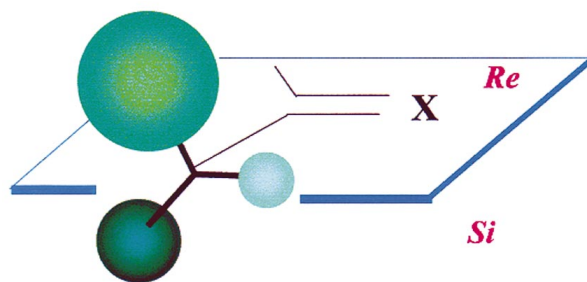


Fig. 1

comprehension of mechanisms and identification of the molecular species involved in transferring the chiral information is still at the beginning.

The stereochemical aspect of addition reactions to carbonyls is discussed in terms of face-selectivity (Fig. 1).<sup>2</sup> The process will be stereotopically divergent<sup>3</sup> whenever, between the two competing attacks to either the *re* or *si* face, one is preferred. Such stereoselection is commonly observed in asymmetric induction on  $\alpha$ -chiral  $\pi$ -compounds. In this case an addition reaction can afford two diastereoisomers (*anti* and *syn*<sup>4</sup>), whose kinetics are the same as those of parallel independent reactions with two different products. In a kinetically controlled process, the selectivity ( $S$ ) is expressed as in eqn. (1), where  $k$  and  $k'$  are

$$S = \ln(k/k') \quad (1)$$

the overall rate constants leading to the two isomers.

A lot of experimental and theoretical work deals with steric and stereoelectronic effects over face-selectivity,<sup>4</sup> while temperature and solvent effects have been less investigated.

## Temperature-controlled diastereoselectivity

The temperature effect on diastereoselection has long been observed but often neglected. Its influence on diastereoselection is not uniform. Depending on the circumstances, upon increasing the reaction temperature the diastereoselection may decrease, but it may also be constant or even increase. In the latter case we could observe the best diastereomeric excess (de) at high temperature, a behavior that is generally not expected.

The temperature dependence in diastereofacial selectivity can be analyzed according to the Arrhenius equation for the two reaction paths [eqn. (2)], which in the framework of the Eyring

$$\ln(k/k') = -(E_a - E'_a)/RT + \ln A - \ln A' \quad (2)$$

transition state theory becomes eqn. (5) via eqn. (3) and (4),

$$\ln k/k' = -(\Delta G^\ddagger - \Delta G'^\ddagger)/RT = -\Delta\Delta G^\ddagger/RT \quad (3)$$

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (4)$$

$$\ln k/k' = -(\Delta\Delta H^\ddagger/RT) + (\Delta\Delta S^\ddagger/R) \quad (5)$$

where  $k$  and  $k'$  are the observed overall rate constants, and  $\Delta\Delta G^\ddagger$  is the difference in free activation energies for *re* and *si* face attack. In diastereoselective reactions,  $k/k'$  can be expressed as the final concentration ratio of the two isomers *anti* and *syn*. Temperature dependent measurements on the basis of eqn. (5) allow the evaluation of stereoselectivity in terms of differential enthalpy and entropy of activation. It is important to underline that in diastereoselective processes, where little differential enthalpic contribution exists, temperature values in the experimentally accessible range often render the differential entropy of activation a determining contribution, especially at high temperature.<sup>5</sup> Under these conditions, any prediction of stereoselectivity based on classical models, such as Cram's chelated model or the Felkin-Ahn model based only on enthalpic differences, are not effective because of entropy underestimation.

Entropy and enthalpy can play in favor of opposite isomers, leading to an inversion of selectivity by temperature.<sup>6</sup> In this case, we get a predominance of one diastereoisomer at low temperature and the other one at high temperature. In the linear Eyring plot of  $\ln k/k'$  versus  $1/T$  (Fig. 2), reversal of de by

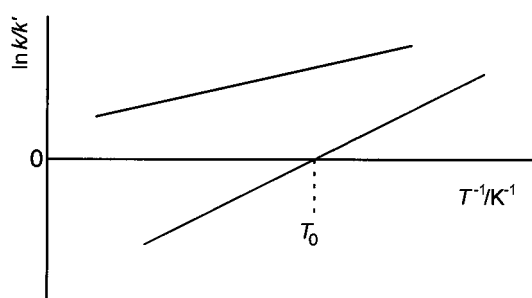


Fig. 2

reaction temperature<sup>7</sup> gives rise to an  $x$ -axis crossing ( $\ln k/k' = 0$ ,  $de = 0\%$ ) thus identifying an equiselective temperature  $T_0 = \Delta\Delta H^\ddagger/\Delta\Delta S^\ddagger$ . Because of the positive value of absolute temperature, reversal of de occurs when the differential enthalpic and entropic terms have the same sign.

In this case, there exists a temperature range where  $T\Delta\Delta S^\ddagger < \Delta\Delta H^\ddagger$  and another where  $T\Delta\Delta S^\ddagger > \Delta\Delta H^\ddagger$ . For example, in the formation of *anti* and *syn* isomers, whenever the former prevails, a negative value of the differential activation enthalpy ( $\Delta\Delta H^\ddagger_{anti} - \Delta\Delta H^\ddagger_{syn} = \Delta\Delta H^\ddagger < 0$ ) results. Assuming that an addition reaction is accompanied by a loss of activation entropy,  $\Delta S^\ddagger_{anti}$  and  $\Delta S^\ddagger_{syn}$  are both negative and the condition for the de inversion,  $\Delta\Delta S^\ddagger < 0$ , requires  $|\Delta S^\ddagger_{anti}| > |\Delta S^\ddagger_{syn}|$ : this means that the entropic loss in the formation of *anti* is larger than those of *syn*. As a consequence, the *anti* isomer is enthalpically driven whereas the *syn* is entropically driven: at low temperature the former prevails, while at high temperature the latter. It is important to emphasize that if both enthalpy and entropy cooperatively work in favor of the same isomer [this condition results when  $\Delta\Delta S^\ddagger$  and  $\Delta\Delta H^\ddagger$  have opposite signs in eqn. (5)], an inversion in the diastereomeric excess can never be obtained by solely controlling the temperature.

Eqn. (5) shows a linear correlation between  $1/T$  and selectivity. However, there are experimental data that show a non-linear behavior (Fig. 3). In these cases, the corresponding Eyring plots generally consist of two linear regions intersecting at a point defining a temperature called the inversion temperature ( $T_{inv}$ ).<sup>8</sup> This break point leads to two sets of activation parameters; one for  $T < T_{inv}$  and the other for  $T > T_{inv}$ .

This phenomenon has been nicely reviewed by Scharf,<sup>9</sup> who considers the conditions for the existence of a  $T_{inv}$  in an Eyring plot showing the occurrence of two levels of selectivity in a two step reaction mechanism. He describes the  $T_{inv}$  as the temperature where a change occurs in the dominance of enthalpy and entropy in the partially selective step.

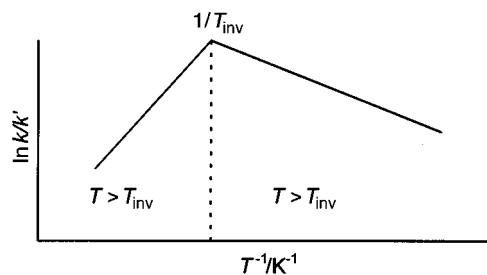


Fig. 3

More recently, Ridd<sup>10</sup> has interpreted non-linear Eyring plots as evidence of two potential rate determining steps in the reaction process, with only one of the two linear regions providing valid evidence on the enthalpic and entropic discrimination involved, the other coming from the transitional region in which no single stage of the reaction can be considered as rate determining.

Anyway, the debate on the very nature of inversion temperature is still open and we want to show experimental results that suggest a different interpretation.

### Solvent-controlled diastereoselectivity

The solvent in which chemical processes take place is really a non-inert medium and it plays a prominent role in solution chemistry.<sup>11</sup> The complex interaction between solvent and solute molecules results in a gross modification of their free energies, and consequently, reactivities and stereoselectivities.

There are many examples of solvent effects on face-selectivity. In many cases a variation in the diastereomeric excess is observed<sup>12</sup> and other examples are known where a complete reversal of diastereoselectivity occurs because of a change in the reaction solvent. For example, some years ago, we reported a de reversal in MeMgBr addition to an *O*-triisopropylsilyloxy lactal.<sup>13</sup> The reaction leads to an *anti/syn* ratio of 64:36 in THF and 16:84 in Bu<sup>t</sup>OMe. Very recently, Luh reported a reversal in diastereoselectivity of MeLi and Bu<sup>n</sup>Li addition to hydrazones of 1,4-di-*O*-*tert*-alkoxy-*L*-threitol on going from THF to Et<sub>2</sub>O.<sup>14</sup> These results show how the solvent plays a role in determining the prevailing isomer.

The solvent effect on face-selectivity reflects its different influence on the two diastereomeric reaction paths through a differential contribution to  $k$  and  $k'$  [eqn. (1)]. A change in the reaction medium corresponds to a change in the microscopic solute-solvent interactions. These interactions could differ in number or strength in different solvents, and they contribute to free activation energies  $\Delta G^\ddagger$  and  $\Delta G'^\ddagger$  in such a way that they can cause a face-selectivity reversal.

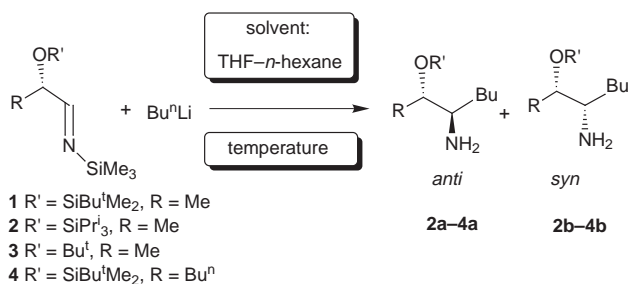
In the case of reaction in solution, it is hard to describe the system formed by reagents with their solvation shell or the solvated transition state, but some hypothesis can be considered. Two cases can be analyzed: (i) the solvent enthalpically favors and entropically disfavors an isomer whenever the solute-solvent interactions are high in strength or in number, thus stabilizing conformers with the lowest intramolecular steric interactions; (ii) the solvent entropically favors and enthalpically disfavors an isomer whenever the solute-solvent interactions are mild or low in number which results in the solvation being less ordered, thus making the system conformationally less rigid.<sup>15</sup>

By this brief discussion it appears to be clear that any theoretical model<sup>4</sup> for the analysis of stereochemical problems completely loses its predictive value by ignoring solvent effects. A detailed modelling of solvation<sup>16</sup> and information about its effects on the dynamics of stereoselective processes are necessary to get a deeper insight into the diastereofacial selectivity, but at the moment, research in this field is still at the beginning.

## Diastereofacial selectivity in Bu<sup>n</sup>Li addition to lactal imines<sup>17</sup>

During our studies on the stereocontrolled synthesis of 1,2-amino ethers by means of nucleophilic addition to *N*-trimethylsilyl imines of (2*S*)-lactal, we observed an impressive influence of solvent and temperature over the diastereofacial selectivity.

Bu<sup>n</sup>Li cleanly reacted with *O*-protected *N*-trimethylsilyl imines of (2*S*)-lactal either in an ether (THF) or hydrocarbon (*n*-hexane) affording optically active *anti* and *syn* 1,2-amino ethers (Scheme 1). The stereochemical results are strongly dependent



Scheme 1

on solvent and temperature. We observed a complete reversal in the diastereomeric excess due to the solvent. For example, in the case of (2*S*)-*N*-trimethylsilyl-*O*-*tert*-butyldimethylsilyloxy lactal imine **1** at  $-90\text{ }^{\circ}\text{C}$  in THF, we obtained an *anti*/*syn* ratio of 2:98, while in *n*-hexane the *anti*/*syn* ratio = 72:28. Moreover, a screening over a range of  $150\text{ }^{\circ}\text{C}$  showed a reversal of diastereoselection due to the reaction temperature (e.g. in *n*-hexane at  $T = -90\text{ }^{\circ}\text{C}$ , *anti*/*syn* = 72:28, at  $T = 54\text{ }^{\circ}\text{C}$  *anti*/*syn* = 22:78). In Fig. 4 the Eyring plots for all the imines **1–4** in THF and *n*-hexane are reported. The diastereomeric excess is defined as the difference % *anti* – % *syn*. Each imine–solvent pair showed a non-linear temperature dependence, and a characteristic inversion temperature ( $T_{\text{inv}}$ ) was observed in all cases.

Diastereomeric excesses for imines **2** and **3** in THF cross the *x*-axis (de = 0%) at the equiselective temperatures  $T_o = -71.2$  and  $-8.6\text{ }^{\circ}\text{C}$ , respectively, so that a neat inversion in stereoselectivity occurred. In *n*-hexane, the imines **1**, **2** and **4** showed equiselective temperatures at  $T_o = -54.9$ ,  $15.4$ , and  $-36.5\text{ }^{\circ}\text{C}$ .

In THF for  $T > T_{\text{inv}}$ , all the imines show a flattened trend of the de, meaning that in this range there is no temperature control of the stereoselectivity. According to eqn. (5), this result requires that the face-selection that still exists is entirely determined by  $\Delta\Delta S^{\ddagger}$ .

In this entropy driven region, the differentiating parameter between the four substrates is the protecting group. The *O*-TIPS and the *O*-TBDMS-*N*-TMS imines show opposite diastereofacial selectivity; for **2** the differential entropy  $\Delta\Delta S^{\ddagger}$  is positive, for **1** it is negative. As a matter of fact, in one case the *anti* isomer is favored, in the other the *syn* is preferred. It is remarkable to note that for imine **1** the negative value of  $\Delta\Delta S^{\ddagger}$  implies that the transition state leading to the *anti* isomer is more ordered than that which leads to the *syn* one. This result excludes the hypothesis that the prevailing *syn* isomer derives from a chelated transition state. At low temperature, all substrates give *syn* isomers. However, slopes are not markedly different and all four plots can be reproduced by translation of each other. Once again, in the face of small differential enthalpic contributions, an entropic factor determines the face-selectivity.

In *n*-hexane, imines **1**, **2** and **4** have a positive slope and exhibit a reversal of de on going from a predominance of *syn* isomers at high temperature to a predominance of *anti* isomers at lower  $T$ . Even the *O*-*tert*-butyl-*N*-TMS imine has a positive

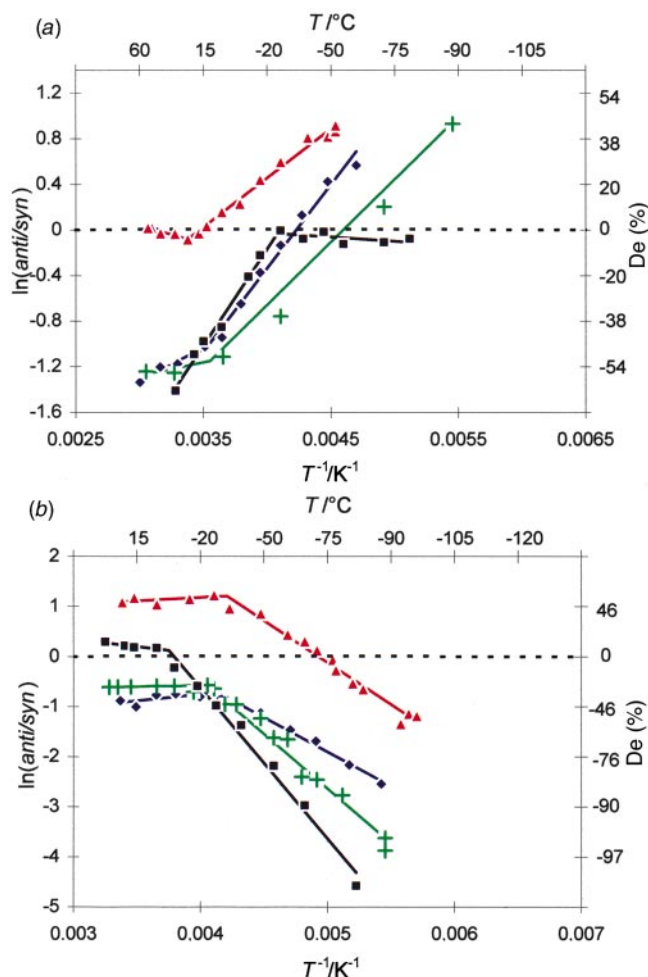


Fig. 4 Eyring plots for imines **1–4** in (a) *n*-hexane and (b) THF: (+) **1**, (▲) **2**, (■) **3** and (◆) **4**.

slope, and should behave in the same way as the others, but, in this case, the  $T_{\text{inv}}$  exerts a breakdown and starts up a new linear trend with a different intercept and slope, so that the de inversion is prevented.

Temperature and solvent effects on de might be attributed to different organometallic species involved. In fact, it is known that the aggregation state of Bu<sup>n</sup>Li changes with these parameters.<sup>18</sup> However, the dynamic process that involves the aggregation state of Bu<sup>n</sup>Li acts before the reacting event, so that their rate constants are identical for both diastereomers and vanish in eqn. (5). Thus a mere ground state effect would be irrelevant, but the Bu<sup>n</sup>Li tendency to aggregate may to some extent influence the structure of the transition states. However, the de reversal with temperature and the existence of  $T_{\text{inv}}$  are observed in several different reactions<sup>9,12</sup> where no organometallic species are involved.<sup>19</sup>

All the activation parameters for  $T > T_{\text{inv}}$  and for  $T < T_{\text{inv}}$  are listed in Table 1.

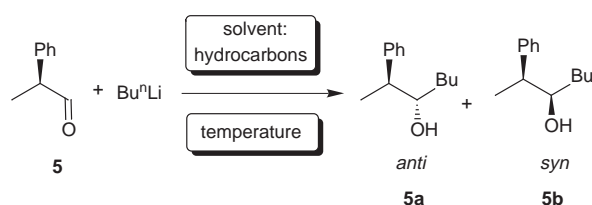
It is significant to note that in all cases differential entropies and enthalpies have equal sign leading to an inversion of diastereoselectivity due to temperature, as discussed in the previous section. However, for imines **1**, **2** and **4**, but not **3**, the activation parameters for  $T < T_{\text{inv}}$  showed a further switch in sign from THF to *n*-hexane, thus showing the overwhelming role of the solvent in determining the thermodynamic parameters.

## Diastereofacial selectivity in Bu<sup>n</sup>Li addition to 2-phenylpropanal<sup>20</sup>

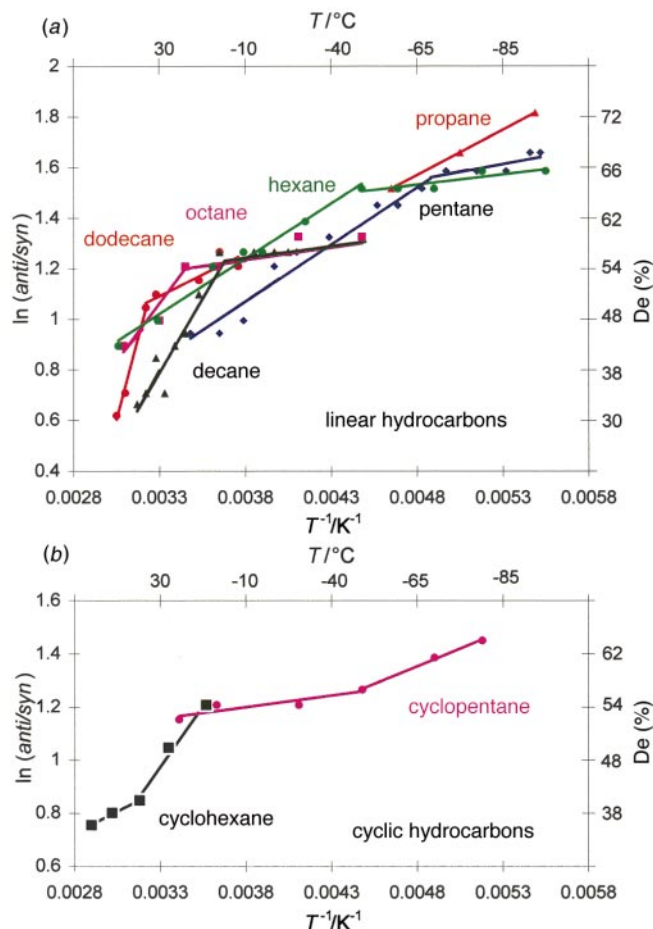
The solvent effect obtained in the stereoselective addition of Bu<sup>n</sup>Li to 2-phenylpropanal is quite peculiar (Scheme 2). We

**Table 1** Differential activation parameters and inversion temperatures for Bu<sup>n</sup>Li addition to imines **1–4**

Imine	Solvent	$T_{inv}/^{\circ}\text{C}$	$T > T_{inv}$		$T < T_{inv}$		$\Delta\Delta G^{\ddagger}$ (298 K)/kcal mol <sup>-1</sup>
			$\Delta\Delta H^{\ddagger}/\text{kcal mol}^{-1}$	$\Delta\Delta S^{\ddagger}/\text{cal mol}^{-1}$	$\Delta\Delta H^{\ddagger}/\text{kcal mol}^{-1}$	$\Delta\Delta S^{\ddagger}/\text{kcal mol}^{-1}$	
<b>1</b>	THF <sup>a</sup>	-26.8	-0.10 ± 0.01	-1.59 ± 0.02	4.3 ± 0.3	16.4 ± 1.4	0.37
<b>1</b>	<i>n</i> -Hexane <sup>a</sup>	7.9	-0.58 ± 0.22	-4.3 ± 0.7	-2.2 ± 0.4	-10.4 ± 1.7	0.71
<b>2</b>	THF	-35.8	-0.28 ± 0.22	1.2 ± 0.8	3.3 ± 0.2	16.4 ± 0.9	-0.63
<b>2</b>	<i>n</i> -Hexane	22.4	0.65 ± 0.11	2.0 ± 0.4	-1.7 ± 0.1	-5.9 ± 0.3	0.05
<b>3</b>	THF	-7	0.59 ± 0.18	2.4 ± 0.6	5.9 ± 0.3	22.7 ± 1.5	-0.14
<b>3</b>	<i>n</i> -Hexane	-28.4	-3.36 ± 0.13	-13.8 ± 0.5	0.14 ± 0.1	0.52 ± 0.5	0.75
<b>4</b>	THF	-31.8	-0.52 ± 0.37	-3.6 ± 1.4	2.7 ± 1.5	9.8 ± 0.7	0.05
<b>4</b>	<i>n</i> -Hexane	8.6	-1.17 ± 0.07	-6.2 ± 0.3	-2.9 ± 0.2	-12.3 ± 0.7	0.67



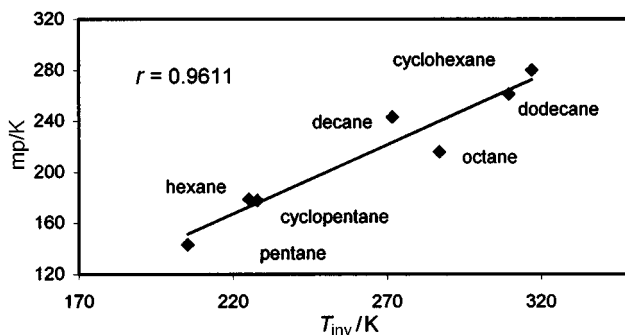
established inversion temperatures in aliphatic hydrocarbons and Eyring plots for a series of linear and cyclic hydrocarbons are shown in Fig. 5.

**Fig. 5** Eyring plots for (a) linear and (b) cyclic hydrocarbons.

Interestingly, for cyclic and linear solvents the plot concavities are opposite. For linear hydrocarbons the pattern is consistent with the chain length of the solvent: the longer the chain, the lower the de; for example, the diastereofacial selectivity obtained with propane is doubled with respect to that of *n*-dodecane (*n*-propane de = 70%, *n*-dodecane de = 30%).

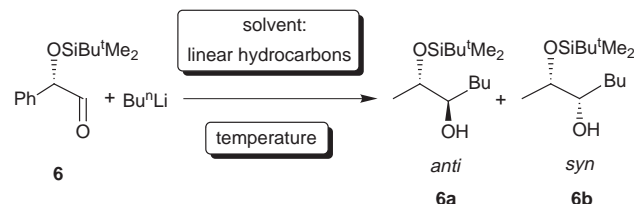
This result reveals the deep influence of solvation forces, although weak and non-specific, on the face-diastereoselectivity. The slopes of regression lines, which reflect the enthalpic contribution, flatten at low temperatures. Once more, differential entropy modulates the selectivity because only differences in the intercepts still remain when differential enthalpies vanish, and therefore the effect of solvent chain length on face-selectivity might be ascribed to entropic control. On the other hand, at high temperature, lengthening the solvent chain increases the slope, thus increasing the enthalpic contribution to de. The inversion temperatures for all linear and cyclic hydrocarbon solvents examined ranged between 205 and 317 K, increasing upon going from *n*-pentane to *n*-dodecane.

Assuming that the inversion temperature is unique to each substrate–solvent pair, all efforts to correlate inversion temperatures with classical solvent parameters, such as relative permittivity and viscosity, have failed. Interestingly, analyzing  $T_{inv}$  and the melting points of linear and cyclic hydrocarbons results in a straight line with a correlation coefficient  $r = 0.96$  (Fig. 6).

**Fig. 6**

### Diastereofacial selectivity in the Bu<sup>n</sup>Li addition to mandelic aldehyde<sup>21</sup>

The dependence of facial selectivity upon hydrocarbon solvents becomes more strict in the case of Bu<sup>n</sup>Li addition to *O*-*tert*-butyldimethylsilyloxymandelic aldehyde **6** (Scheme 3). On this



substrate the reaction with Bu<sup>n</sup>Li was performed in a series of linear hydrocarbons with odd and even numbers of carbon atoms.

Although this aldehyde produced diastereomeric excesses in a low range (from 20 to -10% de), in all plots an inversion



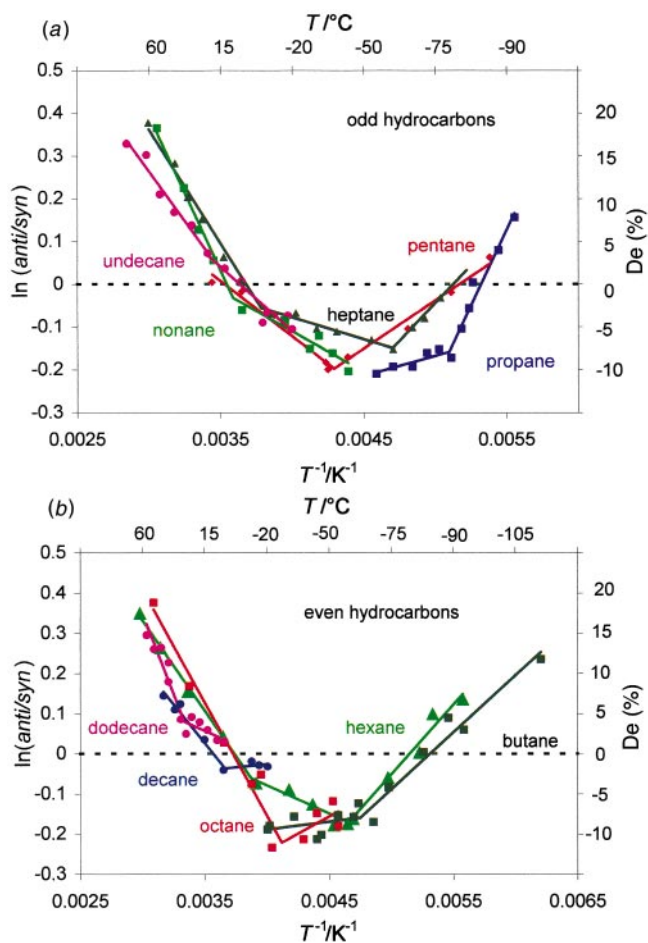


Fig. 7 Eyring plots for (a) odd and (b) even numbered hydrocarbons.

temperature was recognized (Fig. 7). Notably, this substrate exhibited the best diastereoselectivity at high temperature ( $T = 60.5\text{ }^{\circ}\text{C}$ ,  $de = 19\%$ ).

The majority of these plots cross the  $x$ -axis because of an opposition between the enthalpic and entropic contribution to the two isomers, as discussed above. Some plots cross the  $x$ -axis twice, once in the high and the other in the low temperature region. It is interesting to note that in the cases of  $n$ -hexane and  $n$ -heptane two inversion temperatures were obtained. It is hard to explain this experimental result as a consequence of a double change in the reaction mechanism in the light of the above mentioned interpretation of the  $T_{inv}$ .<sup>22</sup> As in the case of phenylpropanal **5**, the  $T_{inv}$  increases with the longer solvent alkyl chain. For mandelic aldehyde **6** each series shows a concavity opposite to that of **5**.

A plot of the inversion temperatures *versus* the number of solvent carbon atoms exhibits the same swinging feature as that for the melting points (Fig. 8). Even in this case the correlation of  $T_{inv}$  and the melting points exists, and it correlates better if we consider the odd and even series of hydrocarbons separately.

It is really surprising how the simplicity of a linear relationship between its two parameters overcomes the complexity of the physical events involved.

It is known that even and odd linear hydrocarbons differ in the crystalline form,<sup>23</sup> and this fact causes the melting point alternation. The same behavior has been observed for the inversion temperatures and this, along with the strict linear correlations found for both aldehydes **5** and **6**, suggests a relationship with the phase modification that occurs upon melting. An attractive possible explanation can be formulated: the inversion temperature could constitute a sort of transition between two 'phases' which, in the case of solutions, could be represented by two different solute-solvent clusters with a different order.<sup>24</sup> This 'phase transition' could be interpreted as the interconversion of two solute-solvent clusters having a

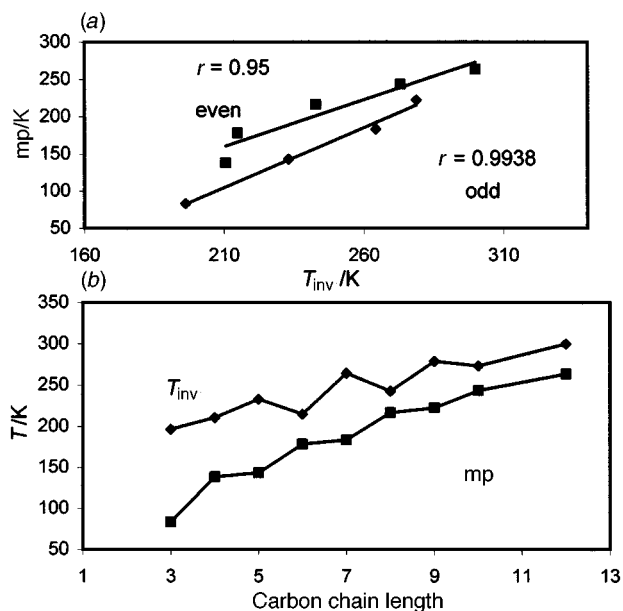


Fig. 8 (a) Plot of  $T_{inv}$  vs. mp of solvent. (b) Plots of  $T_{inv}$  and solvent mp vs. carbon chain length of solvent.

more defined tridimensional structure than generally supposed. These supramolecular structures behave like different molecules, producing a measurable change in their thermodynamic properties and therefore in the diastereoselectivity. In this hypothesis, the  $T_{inv}$  represents the interconversion temperature between two supramolecules and it does not imply any change either in the rate determining step or in the reaction mechanism.

Because of the complexity of the solvation process, it is difficult to formulate a detailed microscopic model of these supramolecules. However their interconversion could involve a solvent reorganization phenomenon due to transfer of solvent molecules between the bulk and the supramolecules or an internal rearrangement of the solvation cluster.

## Conclusion

Our results confirm that not only do enthalpic contributions act in determining diastereocontrol, but even entropic factors can acquire importance with increasing reaction temperature. Indeed, whenever enthalpy and entropy favor different isomers, a *de* reversal can be obtained.

Solvent effects are determinant on face selectivity because solute-solvent interactions modulate the free activation energies acting on both enthalpic and entropic terms. In this way different solvents can lead to an opposite diastereoselectivity.

The correlation with melting points suggests an alternative interpretation of the very nature of inversion temperatures. We propose that  $T_{inv}$  is the temperature value for the interconversion between two different solvation clusters represented by two different supramolecules.

All these arguments support the hypothesis that the main factor in diastereofacial control is a stereospecific solvation of the  $\pi$ -system.<sup>25</sup>

Our interpretation simply constitutes an attractive proposal and an intriguing challenge for forthcoming research on stereoselectivity.

## Acknowledgements

This work was supported by Ministero dell'Università e della Ricerca scientifica e Tecnologica (MURST), the University of Bologna (fund for selected topics) and CNR. We thank all students involved in this project: Argnani Miriam, Marini Andrea, Nerozzi Fabrizio, Paradisi Francesca, Scardova Lucia and Martin Walzl.

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Paper 8/08307J