Dynamic Solvation Effects in Ethylmagnesium Bromide Addition to (2*S*)-*O*-(*tert*-Butyldimethylsilyl)lactal

Gianfranco Cainelli,*[a] Daria Giacomini,*[a] Paola Galletti,[a] and Paolo Orioli[a]

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The diastereofacial selectivity of (2*S*)-*O*-(*tert*-butyldimethylsilyl)lactal towards nucleophilic addition of ethylmagnesium bromide is strongly solvent-dependent. We have shown that solute–solvent interactions occurring in a series of ethers, such as tetrahydrofuran, tetrahydropyran, diethyl ether, dipentyl ether, *tert*-butyl methyl ether, diisopropyl ether, diisopentyl ether, and anisole, can govern a diastereomeric switch from the *anti* to the *syn* isomer. Determination of the temperature-dependence of the *anti*/*syn* ratio has enabled the selectivity to be analysed in terms of the differential enthalpies and entropies of activation of the two diastereomeric reaction paths. We have demonstrated that the predominance of one isomer over the other is often due to an entropy effect on the diastereofacial selectivity. The phenomenon of the inversion temperature was evident in the corresponding Eyring plots.

Introduction

The solvent plays a key role in condensed-phase chemistry, because interaction of solvent molecules with reactants, products, and transition states can greatly affect a chemical reaction. It is indeed well known that both equilibrium constants and reaction rates may be different in different solvents.[1] Solvent effects are closely related to the nature and extent of solute−solvent interactions locally developed in the microenvironment of the solute molecules. The description of solvation processes and their effects on the energetics and dynamics of chemical reactions from a microscopic point of view constitutes a general and relevant topic of investigation, but research in this field is still at its beginning.[2]

Solvent effects on stereoselectivity (either enantio- or diastereoselectivity) have already been recognized. In particular, several examples of solvent-dependent face selectivity have been reported, but investigation of solvent effects in many studies has been limited to sporadic data showing a change in the diastereomeric ratio on changing the solvent.[3] Those results have generally been obtained at low temperatures, in accordance with the widespread opinion that the best stereochemical result could be obtained by chilling the reaction. However, stereoselectivity is a kinetic phenomenon governed by the ratio of the overall kinetic constants, which are the result of all the steps necessary to convert the reagents into one stereoisomer, with respect to those producing the other. A better insight into solvent effects on stereoselectivity can be obtained from studies in which the reaction temperature is varied. In fact, temperature-dependent measurements shed light on the interplay of differential activation enthalpies and entropies by means of the modified Eyring equation:[4]

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

where S is the stereoselectivity and k and k' are the overall rate constants for the synthesis of the two stereoisomers. Equation (1) shows a linear correlation of selectivity vs. $1/T$ but there are many experimental results that feature nonlinear behaviour. In these cases, the corresponding Eyring plot of $\ln(k/k')$ vs. $1/T$ generally consists of two linear regions intersecting at a point defining a temperature called the inversion temperature (T_{inv}).[5]

This T_{inv} constitutes a break point, leading to two sets of activation parameters: one for $T > T_{inv}$ and one for $T < T_{inv}$. In previous papers we have demonstrated that the presence of a T_{inv} discloses a dynamic solvation effect on stereoselectivity.[6]

Very recently, in addition reactions of organolithium and Grignard reagents to (2*S*)-*O*-(*tert*-butyldimethylsilyl)lactal and (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandelic aldehyde, we observed that T_{inv} is only slightly dependent on the nucleophiles, but mainly on the aldehyde−solvent couple.[7]

These results show that temperature-dependent changes in solvation bring about the presence of the inversion temperature and tune its value. We have therefore formulated a new interpretation of the inversion temperature.

An Eyring plot featuring a T_{inv} is the product 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} represents the interconversion temperature between these two supramolecules (Figure 1).

[a] Department of Chemistry "G. Ciamician", University of Bologna
Via Selmi 2, 40126, Bologna, Italy
Fax: (internat.) + 39-051/2099456
E-mail: cainelli@ciam.unibo.it, giacomin@ciam.unibo.it

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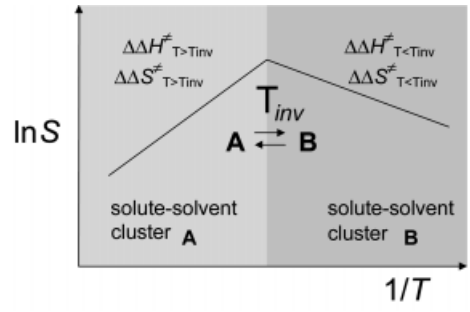


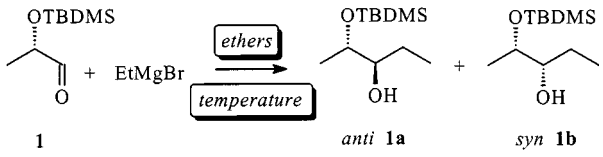
Figure 1. The T_{inv} in an Eyring plot, as the interconversion temperature between two supramolecules

This interpretation has a general significance, because it does not depend on the particular reaction investigated and does not imply any change either in the rate-determining step or in the reaction mechanism.[8] Inversion temperatures have indeed been found in a large number of completely different reactions, such as asymmetric Sharpless dihydroxylation, the Paternò–Buchi reaction and catalytic hydrogenation.[5,9]

A change in solute–solvent clusters can affect the stereoselectivity to different extents until, in some cases, it can reverse the selectivity altogether, resulting in preferential formation of the opposite isomer. Some years ago we reported a reversal of diastereoselectivity caused by solvent in the addition of MeMgBr to (2*S*)-*O*-(triisopropylsilyl)lactal.[10] At −78 °C the reaction in THF produced an *anti*/*syn* ratio of 64:36, and in *t*BuOMe it had a ratio of 16:84. This prompted us to turn our attention on the temperature-dependence of addition reactions of Grignard reagents to α-hydroxy aldehydes, in order better to evaluate the effect of solvents on diastereofacial selectivity. In this paper we investigate in particular the influence of ethereal solvents on the addition of ethylmagnesium bromide to (2*S*)-*O*-TBDMS-lactal (**1**).

Results

We selected a series of ethereal solvents (tetrahydrofuran, tetrahydropyran, diethyl ether, dipentyl ether, *tert*-butyl methyl ether, diisopropyl ether, diisopentyl ether, anisole), in which EtMgBr was prepared. We then performed reactions at constant temperature by dropwise addition of the freshly prepared Grignard to a solution of aldehyde **1** in the same solvent. The reaction was repeated at different temperatures over the range permitted by the boiling and melting points of the solvent. The reactions proceeded smoothly in all solvents examined, to give *anti* (**1a**) and *syn* (**1b**) 1,2-monoprotected diols (Scheme 1). The diastereomeric *anti*/*syn* ratio was determined in each experiment by GC analysis (see Table 1).



Scheme 1

Data were analysed according to the modified Eyring equation [Equation (1)], where $k/k' = anti/syn$ are expressed as the ratio of the corresponding chromatographic areas-%, $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$, and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$. The data were subjected to least-squares analysis to fit Equation (1). For each data set we applied a residual analysis to evaluate the number of linear trends and to ascertain the presence of the T_{inv}. $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ were obtained from slopes and intercepts of linear plots (Table 2).

It is useful to remember that a negative $\Delta\Delta H^{\neq}$ derives from a $\Delta H^{\neq}_{syn} > \Delta H^{\neq}_{anti}$, and there is then a lower activation barrier in the formation of the *anti* isomer, that is to say, the *anti* isomer is preferred by enthalpy. The opposite applies for $\Delta\Delta H^{\neq} > 0$: the enthalpy favours the *syn* isomer. Regarding the entropy, if it is assumed that an addition reaction is accompanied by a loss of activation entropy, a $\Delta\Delta S^{\neq} < 0$ derives from $|\Delta S^{\neq}_{anti}| > |\Delta S^{\neq}_{syn}|$: this means that the entropic loss in the formation of the *anti* isomer is larger than that of the *syn* one, so the entropy favours the formation of the *syn* stereoisomer. The opposite holds for $\Delta\Delta S^{\neq} > 0$: the entropy now favours the *anti* isomer.

Cyclic Ethers

Tetrahydrofuran (THF) and tetrahydropyran (THP) are suitable solvents for preparation of EtMgBr and for the nucleophilic reaction with *O*-(*tert*-butyldimethylsilyl)lactal (**1**). The plots in Figure 2 refer to EtMgBr addition to **1** in THF and THP. Both plots feature inversion temperatures (T_{inv}) indicating the presence in each solvent of two different solute–solvent clusters: one above and one below the T_{inv}. In THF, the temperature scarcely affects diastereofacial selectivity[11] over a wide T range from −94.5 °C to T_{inv}, whereas at $T > T_{inv}$ the *de* rapidly decreases. It is noteworthy that the flattened part of the plot, and consequently the steady diastereomeric excess, derives from a small $\Delta\Delta H^{\neq}$ (see Table 2, entry 1); the good diastereoselectivity is thus entirely attributable to an entropy effect.

THP shows a smaller variation of *de* with T than THF does. The two plots show opposite concavity (THF down and THP up). This is the consequence of a change in sign of the differential enthalpy of activation at $T > T_{inv}$. This fact implies that the enthalpy favours the *anti* isomer in THF, while in THP it favours the *syn* one. In THP, however, we still obtain a predominance of the *anti* isomer, due to entropy control.

Linear Ethers

Plots in Figure 2 refer to EtMgBr addition to **1**, in diethyl ether and in dipentyl ether. These two solvents show parallel and flattened trends at $T > T_{inv}$, in which both show very low differential enthalpies (Table 2, entries 3 and 4). In the same T region, dipentyl ether shows zero diastereoselectivity, due to a small $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, while Et_2O shows

Table 1. *anti*/*syn* ratio in EtMgBr addition to **1** at selected temperature in different ethers

Solvent	*T* [°C]	*anti* % (**1a**)	*syn* % (**1b**)	Solvent	*T* [°C]	*anti* % (**1a**)	*syn* % (**1b**)
THF	−94.5	77.6	22.4	dipentyl ether	−62	70.1	29.9
THF	−79.5	78.2	21.8	dipentyl ether	−53.4	66.8	33.2
THF	−68	76.5	23.5	dipentyl ether	−41.5	62.2	37.8
THF	−61.5	77.2	22.8	dipentyl ether	−31.7	56.1	43.9
THF	−45	77.3	22.7	dipentyl ether	−24	54	46
THF	−39	77.1	22.9	dipentyl ether	−14	51.8	48.2
THF	−23	76.9	23.1	dipentyl ether	−11	52.7	47.3
THF	−9.5	76.9	23.1	dipentyl ether	11	51.3	48.7
THF	1	76.5	23.5	dipentyl ether	18	49.3	50.7
THF	15	76.6	23.4	dipentyl ether	30.3	50.9	49.1
THF	20.5	75.5	24.5	dipentyl ether	39	50.1	49.9
THF	28	75	25	dipentyl ether	48.8	50.5	49.5
THF	33	73.1	26.9	diisopentyl ether	−78.1	72.7	27.3
THF	38	72.6	27.4	diisopentyl ether	−69	68.5	31.5
THF	43.5	72.3	27.7	diisopentyl ether	−57.6	65	35
THF	46.5	72.4	27.6	diisopentyl ether	−49	60.8	39.2
EtOEt	−94.5	81.3	18.7	diisopentyl ether	−36.8	56.6	43.4
EtOEt	−86.3	77.4	22.6	diisopentyl ether	−24.2	53.7	46.3
EtOEt	−77.6	76.7	23.3	diisopentyl ether	−15.6	52.7	47.3
EtOEt	−71.2	74.1	25.9	diisopentyl ether	−7	50.2	49.8
EtOEt	−63.3	71.3	28.7	diisopentyl ether	1.8	47.9	52.1
EtOEt	−59.7	68.3	31.7	diisopentyl ether	8.3	47.5	52.5
EtOEt	−53.7	68.8	31.2	diisopentyl ether	19.9	48.8	51.2
EtOEt	−42.4	65.2	34.8	diisopentyl ether	28.7	49.9	50.1
EtOEt	−34.9	64.3	35.7	diisopentyl ether	39	48	52
EtOEt	−22.7	63	37	diisopentyl ether	49	48.5	51.5
EtOEt	−15.2	61.2	38.8	anisole	−30.4	39.4	60.6
EtOEt	−9.2	60.4	39.6	anisole	−25.8	38.2	61.8
EtOEt	−4.1	61	39	anisole	−22.6	38.5	61.5
EtOEt	0.5	59.8	40.2	anisole	−18.9	37.7	62.3
EtOEt	4.9	58.7	41.3	anisole	−13.8	37.6	62.4
EtOEt	8.6	59.9	40.1	anisole	−8.4	38.2	61.8
EtOEt	15	60.5	39.5	anisole	1.6	40.2	59.8
EtOEt	16.7	60.7	39.3	anisole	5.8	41.3	58.7
EtOEt	18.9	60.3	39.7	anisole	13.9	40.8	59.2
*t*BuOMe	−78	60.3	39.7	anisole	21	41.8	58.2
*t*BuOMe	−65.5	58.2	41.8	anisole	27.8	42.3	57.7
*t*BuOMe	−54.7	55.9	44.1	anisole	33.2	44.9	55.1
*t*BuOMe	−42.5	53.3	46.7	anisole	47	46.2	53.8
*t*BuOMe	−33.6	53.2	46.8	PhOMe/THF, 1:1	−59.1	78.3	21.7
*t*BuOMe	−28.0	50.4	49.6	PhOMe/THF, 1:1	−48.	77.6	22.4
*t*BuOMe	−21.7	48.4	51.6	PhOMe/THF, 1:1	−37.8	76.4	23.6
*t*BuOMe	−20.1	48.7	51.3	PhOMe/THF, 1:1	−31.0	76.7	23.3
*t*BuOMe	−3.9	49.6	50.4	PhOMe/THF, 1:1	−25.6	76.6	23.4
*t*BuOMe	17.6	51.4	48.6	PhOMe/THF, 1:1	−9.5	76.2	23.8
*t*BuOMe	34.7	52.1	47.9	PhOMe/THF, 1:1	−4.6	75.9	24.1
*t*BuOMe	43.5	52.9	47.1	PhOMe/THF, 1:1	0.7	76.0	24.0
diisopropyl ether	−64.4	53.9	46.1	PhOMe/THF, 1:1	4.6	75.2	24.8
diisopropyl ether	−53.2	52.9	47.1	PhOMe/THF, 1:1	10.8	74.0	26.0
diisopropyl ether	−51.2	53.0	47.0	PhOMe/THF, 1:1	20.1	73.5	26.5
diisopropyl ether	−47	49.6	50.4	PhOMe/THF, 1:1	32.7	72.7	27.3
diisopropyl ether	−39.8	49.2	50.8	PhOMe/THF, 1:1	50	71.8	28.2
diisopropyl ether	−28.9	46.1	53.9	PhOMe/4 equiv. THF	−27.4	7.07	29.3
diisopropyl ether	−21.3	46.6	53.4	PhOMe/4 equiv. THF	−21.7	69.8	30.2
diisopropyl ether	−11.1	45.6	54.4	PhOMe/4 equiv. THF	−11.0	70.5	29.5
diisopropyl ether	−9.3	45	55	PhOMe/4 equiv. THF	−9.4	70.9	29.1
diisopropyl ether	0.5	43.4	56.6	PhOMe/4 equiv. THF	−5.0	69.2	30.8
diisopropyl ether	6.5	45.7	54.3	PhOMe/4 equiv. THF	1	68.5	31.5
diisopropyl ether	15.4	46.7	53.3	PhOMe/4 equiv. THF	10.5	68.4	31.6
diisopropyl ether	25.2	45.7	54.3	PhOMe/4 equiv. THF	17.1	68.9	31.1
diisopropyl ether	31.7	47	53	PhOMe/4 equiv. THF	21.4	70.1	29.9
diisopropyl ether	39.2	48	52	PhOMe/4 equiv. THF	30.2	68.3	31.7
diisopropyl ether	54	49.6	50.4	PhOMe/4 equiv. THF	32.5	68.3	31.7
THP	−39	75	25	PhOMe/4 equiv. THF	37.9	69.4	30.6
THP	−30	74.9	25.1	PhOMe/4 equiv. THF	45.0	70.0	30.0
THP	−15.6	74	26	PhOMe/4 equiv. THF	49.6	69.5	30.5
THP	−6.4	74	26				
THP	1	73.8	26.2				
THP	7	73.5	26.5				
THP	14.1	73.3	26.7				
THP	25.3	72.8	27.2				
THP	29.7	73.2	26.8				
THP	36	73.3	26.7				
THP	46.6	73.6	26.4				

Table 2. Differential activation parameters and inversion temperatures for EtMgBr addition to aldehyde **1**

Entry	Solvent	T_{inv} [°C]	$T>T_{inv}$ $\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol·K]	$T<T_{inv}$ $\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol·K]
1	THF	13.9	−1.4±0.2	−2.5±0.5	−0.06±0.02	2.2±0.1
2	THP	25.9	0.3±0.1	3.1±0.2	−0.24±0.02	1.1±0.1
3	Et_2O	−18.1	−0.1±0.1	0.4±0.5	−1.16±0.06	−3.7±0.3
4	Pen_2O	−10.4	−0.04±0.2	−0.1±0.7	−1.7±0.1	−6.6±0.5
5	$i Pen_2O$	0.1	0.1±0.1	0.3±0.5	−1.39±0.05	−5.2±0.2
6	*t*BuOMe	−17.3	0.42±0.02	1.5±0.1	−0.81±0.06	−3.3±0.3
7	$i Pr_2O$	−2.5	0.7±0.1	2.0±0.4	−0.8±0.1	−3.3±0.3
8	PhOMe	−14.1	0.9±0.1	2.5±0.3	−0.6±0.1	−3.1±0.6
9	PhOMe:THF, 1:1	−4.0	−0.7±0.1	−0.4±0.3	−0.24±0.04	1.4±0.2
10	PhOMe·4equiv. THF	–	−0.12±0.07	1.2±0.2		

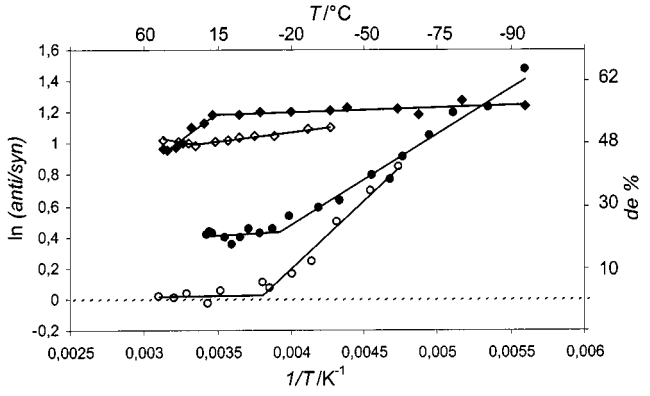


Figure 2. Eyring plots for addition of EtMgBr to **1** in tetrahydrofuran (solid diamonds), tetrahydropyran (open diamonds), diethyl ether (solid circles), and dipentyl ether (open circles)

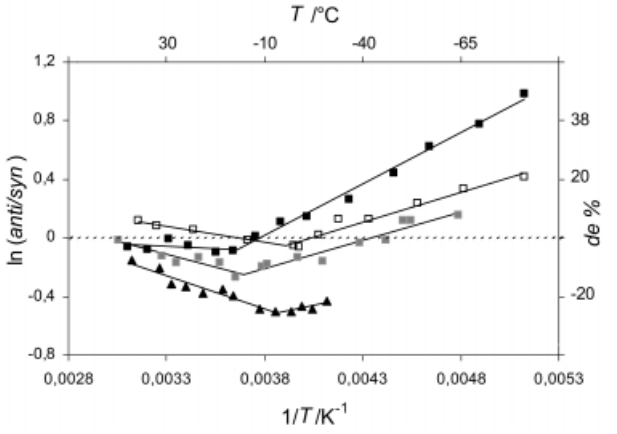


Figure 3. Eyring plots for addition of EtMgBr to **1** in *tert*-butyl methyl ether (open squares), diisopropyl ether (grey solid squares), diisopentyl ether (black solid squares), and anisole (solid triangles)

a 60:40 *anti*/*syn* ratio due entirely to entropy control. This is a case in which the solvent determines the isomer preference through entropy.

At low *T*, while $\Delta\Delta S^{\neq}$ favours the *syn* isomer, the $\Delta\Delta H^{\neq}$ with its significantly high value favours and dictates the formation of the *anti* isomer.

Interestingly, diethyl ether and dipentyl ether have quite similar inversion temperatures.

Branched and Aromatic Ethers

Diastereoselection in the addition of EtMgBr to **1** was also studied in branched ethers such as diisopropyl ether, *tert*-butyl methyl ether and diisopentyl ether, and in the aromatic ether anisole (Figure 3). All three branched ethers predominantly afforded the *anti* isomer at low *T*, while on warming there was a slight preference for the *syn* one in diisopropyl and diisopentyl ether. Interestingly, anisole is *syn*-stereoselective at all temperatures.

$\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ have the same sign in all these four solvents whether at low or at high temperature (Table 2 entries 5, 6, 7, 8); this means that while enthalpy favours the formation of one isomer the entropy favours the other: the two terms are opposite with respect to stereoselectivity.

At $T > T_{inv}$ the positive $\Delta\Delta S^{\neq}$ would favour the *anti* isomer, but the positive $\Delta\Delta H^{\neq}$ controls the selectivity, favouring the *syn* one. At $T < T_{inv}$ the signs of $\Delta\Delta S^{\neq}$ and $\Delta\Delta H^{\neq}$ reverse, thus dictating a reversal in the preferred isomer by enthalpy and entropy; again the $\Delta\Delta H^{\neq}$ controls the selectivity, favouring the *anti* isomer in this case. In anisole, which has the lowest $\Delta\Delta H^{\neq}$ value, in contrast, the $\Delta\Delta S^{\neq}$ controls the selectivity at low *T*, favouring the formation of the *syn* isomer.

Once again, it is interesting to note that diisopropyl and diisopentyl ether have very similar inversion temperatures.

Mixtures of Two Solvents

As the above results show, solute−solvent interactions modulate the free activation energies of the two reaction paths so as to favour the formation of two different diastereoisomers, demonstrating a stereospecific solvation control over diastereoselectivity.

In this context, it was interesting to evaluate the effect of solvent mixtures on stereoselectivity, keeping in mind that solute−solvent interactions should be much more complex in mixtures than in pure solvents.[12] In a pure solvent, in

fact, the composition of the microsphere of solvation of a solute molecule is the same as in the bulk solvent, whereas in binary mixtures the composition in this microsphere can be different. The solute can interact with the different components of the mixture to different extents, and this difference in interactions is reflected in the composition of the microsphere of solvation.

We first explored a 1:1 mixture of THF/PhOMe. As pure solvents, these showed opposite selectivities (the former favoured the *anti* isomer, the latter the *syn* one at all temperatures; Figure 4). EtMgBr was prepared in a THF/PhOMe mixture (1:1) and added to aldehyde **1** dissolved in the same mixture. The reaction proceeded smoothly, affording a predominance of the *anti* isomer over the entire T range, and the corresponding Eyring plot was quite similar to that in pure THF. In pure solvents, T_{inv}'s are clearly recognisable, whereas in the mixture the presence of a T_{inv} is less evident. It is noteworthy that, when only 4 equivalents of THF in anisole were used, the *anti*/*syn* ratio was lower than that in pure THF, the $\Delta\Delta H^{\neq}$ was smaller and the T_{inv} disappeared completely. In this case only one solvent cluster is present over all the T range: the mixture prevents a temperature-dependent rearrangement of the solute−solvent cluster into a different one.

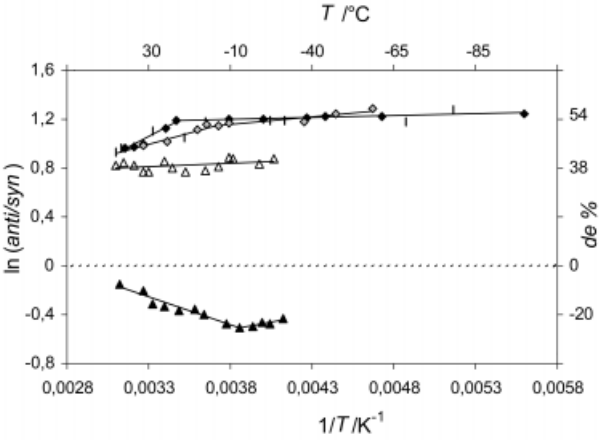


Figure 4. Eyring plots for addition of EtMgBr to **1** in PhOMe/THF mixtures: 1:1 (grey solid diamonds), mixture of 4 mol % THF in PhOMe (open triangles), the pure THF (black solid diamonds) and PhOMe (solid triangles)

Discussion

Usually, solvent effects observed in the chemistry of Grignard reagents have been attributed to the polarity of the solvents, basicities, steric hindrance, and shifts in the Schlenk equilibrium. Grignard reagents are complex mixtures of the Schlenk components dialkylmagnesium, alkylmagnesium halide, and magnesium halide, which are solvated with ethers and exist in a fluxional state in which the magnesium ligands, alkyl groups, halide ions, and solvent molecules are exchanged in very fast equilibria.[13] Moreover, the constitution of the Grignard reagent changes when it is added to an excess of the aldehyde (as in our experimental procedure) because of fast coordination equilibria with the carbonyl compound. Molecular weight measurements have shown that a number of Grignard reagents such as EtMgBr are essentially monomeric at low concentrations (up to at least 0.1 M).[14] The reaction with carbonyl compounds produces alkoxides that could influence the stereochemical outcome, because they have a marked tendency to dimerize with the starting RMgX bearing the active alkyl, thus generating new organometallic species. However, it had been shown that these mixed alkoxides, in the presence of MgX_2, immediately underwent redistribution to form monomeric alkoxide and the RMgX.[15] The two Schlenk components R_2Mg and RMgX can both react with carbonyl groups; it is thus important to discuss the solvent influence on the Schlenk equilibrium in order to ascertain whether a change in diastereoselectivity is due to a change in the quantities of these two different organometallic species. Although the symmetric organomagnesium compound R_2Mg is much more reactive than the Grignard reagent, the predominant species in diluted Et_2O solutions (0.1−0.3 M) is RMgBr, with equilibrium constant values of magnitude 10^2-10^3; while in THF values of 1−10 are most common.[15,16] Thus, in THF, all species of the Schlenk equilibrium are present in appreciable concentration. In a previous paper, however, we demonstrated that the diastereoselectivity in the addition of MeMgBr to aldehyde **1** was deeply affected by the reaction solvent, while addition of Me_2Mg to **1** did not show solvent effects.[10] All these considerations relating to the composition of Grignard reagents, along with the fact that T_{inv} phenomena are evident in very different reactions in which no organometallic reagents are involved,[5,9] confirm that the T_{inv} cannot be attributed to a temperature-dependent change in the predominant organomagnesium species.

In a previous paper on the addition of *n*BuLi to 2-phenylpropanal and (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandelic aldehyde in a series of linear hydrocarbons, we observed that the T_{inv}'s increased with the carbon chain length of the reaction solvent.[6] In the case of addition of EtMgBr to **1,** the value of T_{inv} is less dependent on the carbon chain length of the solvent. This fact could be attributable to specific solvation exerted by ethers through their oxygen atoms, in contrast to weak and unspecific solvation exerted by hydrocarbons.

As to the stereochemistry, the reversal in diastereoselectivity observed on going from THF to anisole might be explained by a change in solvent coordinating ability. It has been observed that the use of solvent with low coordinating ability would maximise *syn* isomer formation, which could derive from chelated transition states.[17] From this perspective, the *anti* selectivity that we obtained in THF might be explained by the assumption that the magnesium atom would remain strongly coordinated by solvent molecules, thus disfavouring the formation of chelated cyclic structures. However, an analysis based only upon enthalpic contributions due to steric and stereoelectronic interactions in the transition state, as in the case of classical chelated or nonchelated models, appears quite limited and unable to explain our results, especially those in THF, in which the diastereoselectivity is governed, over a large temperature

range, solely by differential entropies of activation. Other research groups have recognised the importance of entropy in controlling stereoselective processes.[18] Entropy differences are really a determinant factor, especially in enantio- or diastereoselective reaction in which there are small differences in activation enthalpies between the two diastereoisomeric reaction paths. Entropies of activation ($\Delta S^{\neq}$) can be closely related to differences in number and character of the degrees of freedom between starting materials and transition states, which may be differently solvated in solution. The differential entropy of activation ($\Delta\Delta S^{\neq}$) for our diastereoselective reactions reflects the entropy difference between the two diastereomeric transition states. In THF at $T < T_{inv,}$ $\Delta\Delta S^{\neq}$ acts in favour of the *anti* isomer ($\Delta\Delta S^{\neq}$ is positive see Table 2, entry 1): the pathway resulting in the *anti* isomer loses less entropy than the *syn* one because of a solvent effect. Assuming aldehyde **1** as nonchelating because of the presence of the *tert*-butyldimethylsilyl group,[19] the loss in entropy for the *syn* isomer could be caused by a small number of microstates, due to the solvating THF. The same argument can explain the entropy-driven *anti* diastereoselectivity ($\Delta\Delta S^{\neq} > 0$) evident in THP and *t*BuOMe at $T > T_{inv}$. In anisole, the *syn* isomer is always predominant, but at $T > T_{inv}$ the positive $\Delta\Delta H^{\neq}$ dictates *syn* selectivity, while at $T < T_{inv}$ it is once again the negative differential entropy that drives stereoselectivity toward the *syn* isomer. In spite of a difficulties in modelling the entropy, our results clearly demonstrate how deep its influence on diastereofacial selectivity can be.

Conclusion

We have shown that solute−solvent interactions, such as those occurring in ethers, can control a diastereoisomeric switch from *anti* to *syn* in the addition of EtMgBr to *O*-TBDMS-lactal. We demonstrated that the predominance of one isomer with respect to the other is often due to an entropy effect on the selectivity. This solvent-controlled diastereofacial selectivity is not only of academic interest but also has synthetic and industrial potential, since predominances of opposite stereoisomers may be achievable solely through changes in reaction solvent. Although no microscopic interpretation of these dynamic solvation phenomena has yet been achieved, we believe that solute−solvent clusters are always the real reacting species in solution chemistry. Study of temperature-dependent stereoselectivity can help to identify which aspects of solute−solvent molecular interactions can be tuned to produce changes in differential free energies. It is likely that the combined use of solvent and temperature will open up new channels in the multidimensional control of stereoselectivity.

Experimental Section

General Remarks: All reactions were performed in flame-dried glassware under an atmosphere of argon. − ^{1}H and ^{13}C NMR were recorded with a Varian Gemini 300 instrument operating at 75.5 MHz, using a 5 mm probe. All chemical shifts are quoted relative to deuterated solvent signals, δ in ppm, *J* in Hz. − GC-MS: HP5980, capillary column HP-1 or HP-5 connected to HP5970 (70 eV). − GC: Fisons G8000, column: HP-5 M.S. crosslinked 5% PhMeSilicone, 30 m × 0.25 mm × 0.25 μm, chiral column OV 1701 H. During reactions, in order to set and maintain temperatures in ranges of ±1 °C, liquid-N_2/acetone baths in Dewar containers or oil baths with water cooling were used. Temperature refer to the interior of the reaction apparatus.

Starting Materials: THF, THP, diethyl ether, dipentyl ether, diipropyl ether, diipentyl ether, *t*BuOMe, and anisole were distilled from sodium/benzophenone under inert atmosphere and stored over 4 Å molecular sieves. Aldehyde **1** was prepared from the corresponding ethyl *O*-(*tert*-butyldimethylsilyl)lactate by DIBAl-H reduction.[20]

Preparation of EtMgBr: A solution of ethyl bromide (1.5 mmol, 0.11 mL) in 2 mL of the appropriate ethereal solvent was added dropwise to magnesium turnings (1.5 mmol, 0.036 g). At the very beginning the reaction required activation by heating. The resultant light grey, clear solution was added as such to aldehyde **1**.

In a typical experiment, aldehyde **1** (1 mmol) was dissolved in anhydrous solvent (20 mL) under an inert atmosphere, and the solution was cooled or warmed to the desired temperature. Ethylmagnesium bromide solution (freshly prepared in the same solvent by the procedure reported above) was then added. After the starting aldehyde had disappeared (GC monitoring), the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3 × 50 mL), and dried with Na_2SO_4. Chromatography of the residue on a silica gel column gave a mixture of alcohols **1a** and **1b**, so that the chemical yields could be calculated; these ranged from 80 to 90%. From GC analysis of the corresponding *O*-trimethylsilyl derivatives, the *anti*/*syn* ratio and the de % value were obtained. The average standard deviation for the de % measurements was less than 1%. After removal of the *O*-protecting group, the 1,2-diol configurations were determined by comparison with reported data.[21]

(2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxy-3-pentanol, *anti* Isomer (1a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.90 (s, 9 H), 0.97 (t, *J* = 7.5 Hz, 3 H), 1.07 (d, *J* = 6.2 Hz, 3 H), 1.41 (m, 2 H), 1.76 (br. s, 1 H), 3.45 (m, 1 H), 3.78 (dq, *J* = 6.2 Hz, *J* = 3.4 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): −4.9, −4.5, 10.4, 16.6, 18.0, 24.8, 25.8, 70.9, 76.6.

(2*S*,3*S*)-2-*tert*-Butyldimethylsilyloxy-3-pentanol, *syn* Isomer (1b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.90 (s, 9 H), 0.98 (t, *J* = 7.2 Hz, 3 H), 1.16 (d, *J* = 6.1 Hz, 3 H), 1.47 (m, 2 H), 1.76 (br. s, 1 H), 3.20 (m, 1 H), 3.65 (dq, *J* = 6.1 Hz, *J* = 5.0 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): −4.9, −4.1, 10.2, 18.5, 20.3, 25.7, 26.4, 71.3, 77.2.

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