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Solvent and temperature effect in aldol condensation between the lithium enolate of *tert*-butyl acetate and 2-phenyl propanal: enthalpy and entropy contribution

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Abstract—An analysis of nucleophilic addition of the lithium enolate of *tert*-butyl acetate and 2-phenyl propanal in two different solvents, such as THF and *n*-hexane, revealed the great importance of solvent effect in determining the stereoselectivity. In particular, temperature-dependent measurements of diastereomeric ratio allow the evaluation of diastereoselectivity in terms of differential enthalpy and entropy of activation for this reaction. Either in THF or *n*-hexane we obtained a predominance of the *anti* isomer in all temperature ranges, but in THF the diastereoselection is controlled by the differential activation enthalpy, whereas in *n*-hexane it is the sole differential activation entropy that accounts for the *anti* predominance. © 2001 Published by Elsevier Science Ltd.

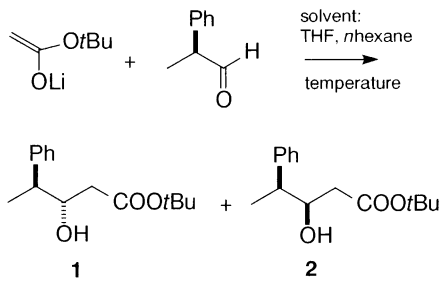
In recent years, we have been involved in studying the effect of solvent and temperature on diastereofacial selectivity in nucleophilic addition to α-chiral aldehydes and imines.[1] We found that solute–solvent interactions are able to affect the stereochemical outcome of a reaction even in the case of hydrocarbon solvents in which only weak and non-specific interactions are involved.[2] We observed that a change in the reaction solvent can affect the stereoselectivity at different extents until, in some cases, it can reverse the selectivity leading to the preferential formation of the opposite isomer.[3]

A better insight into solvent effect on stereoselectivity can arise from studies where the reaction temperature is varied. In fact, temperature-dependent measurements shed light on the interplay of differential activation enthalpy and entropy by means of the modified Eyring Eq. (1), where S is the stereoselectivity and k and k' are the overall rate constants in the formation of the two stereoisomers.[4]

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

The solvent effect on selectivity reflects its different influence on the two diastereomeric paths through differential contributions to the overall rate constants k and k'. A change in the reaction medium corresponds to a change in the microscopic solute–solvent interactions. These interactions can differ in number or strength modifying the differential free activation energy $\Delta\Delta G^{\ddagger}$ and thus generating a solvation effect on the stereoselectivity.

Here we report the effects of temperature and solvent in the course of the aldol condensation between the lithium enolate of *t*-butyl acetate and the racemic 2-phenyl propanal[5] in THF and *n*-hexane (Scheme 1). The enolate was prepared in THF or in *n*-hexane as follows: *t*-butyl acetate (1 mmol, 0.134 mL) was added to a solution of LDA (1 mmol, prepared from diiso-



Scheme 1.

Keywords: aldol reactions; solvents and solvent effects; enolates; diastereoselection; aldehydes.

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Table 1. Influence of solvent and temperature on the diastereomeric ratio *anti*/*syn* in THF and *n*-hexane

Solvent	*T* (°C)	*anti*/*syn*	Solvent	*T* (°C)	*anti*/*syn*
n-Hexane	−90	75/25	*n*-Hexane	26.0	73.6/26.4
n-Hexane	−84	74.7/25.3	*n*-Hexane	42.0	73.4/26.6
n-Hexane	−70.0	74.6/25.4	THF	−68.5	85.2/14.8
n-Hexane	−64.0	74.4/25.6	THF	−52.5	83.7/16.3
n-Hexane	−53.5	75/25	THF	−38.0	81.9/18.1
n-Hexane	−41.0	74.7/25.3	THF	−20.0	80.2/19.8
n-Hexane	−32.0	73.7/26.3	THF	8.0	78.9/21.1
n-Hexane	−7.0	73.2/26.8	THF	23.0	76.5/23.5
n-Hexane	1.0	72.4/27.6	THF	37.0	75.3/24.7
n-Hexane	7.0	74.2/25.8			

propylamine and *n*-BuLi in 10 mL of anhydrous THF or *n*-hexane) at 0°C. After 15 min the enolate solution was brought to the desired constant temperature and then the 2-phenylpropanal (1 mmol, 0.134 mL) was added via a gas-tight syringe. In order to avoid re-equilibration phenomena and crotonization, the reaction was immediately quenched in 20 mL of 5% $NaHCO_3$ solution and extracted with dichloromethane (3×25 mL). The reaction was repeated at different temperatures over the range −90 to 42°C for *n*-hexane, −68.5 to 37°C for THF. The reaction proceeded to give the racemic *anti* (**1**) and *syn* (**2**) aldols.[6]

The diastereomeric *anti*/*syn* ratio within the crude reaction mixture was determined by HPLC analysis (Chiracel OF, eluent hexane:*i*-propanol = 99:1). The results are reported in Table 1.

In both solvents we obtained a predominance of the *anti* isomer **1** at all temperature values. Data were analyzed according to Eq. (1), where $k/k' = anti/syn$ are expressed as the ratio of the corresponding chromatographic area %, and treated by least square analysis to fit Eq. (1) (Fig. 1). The value of $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, obtained from slopes and intercepts of linear plots ($\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$, and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$), are reported in Table 2 together with the value for the $\Delta\Delta G^{\neq}$ at 298 and 200 K. These results show that changing the reaction solvent from THF to *n*-hexane resulted in a change in the differential enthalpy and differential entropy of activation. In THF the differential entropy is very small so that only the $\Delta\Delta H^{\neq}$ determines the prevalence of the *anti* isomer. In contrast, in *n*-hexane beside an almost null enthalpy contribution, it is the $\Delta\Delta S^{\neq}$ that manages the diastereomeric ratio. This switch from an enthalpy control over the diastereofacial selectivity observed in THF to an entropy control in *n*-hexane could be due to different factors. First of all, it may depend on the structure of the ester enolate that can exist as different homo- and mixed aggregates in the two solvents.[7] Even the conformation of the starting aldehyde can be affected by the solvent.[8] However, solvents are always neglected in the formulation of the classical models of asymmetric induction as Cram's, Cram-chelated and Felkin–Ahn models[9] and in almost all quantomechanical calculations. Only enthalpic factors, such as steric- and stereoelectronic effects are commonly take into account, whereas, as shown by our result in *n*-hexane, *the entropy can be the unique cause of the observed diastereoselectivity*.[10]

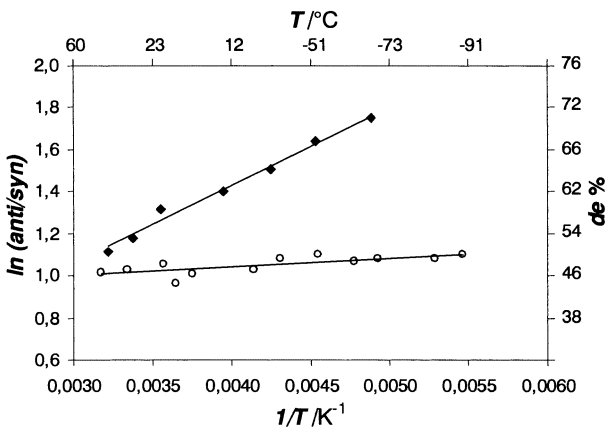

Figure 1. Eyring plots for the diastereomeric excess obtained in the aldol reaction between lithium enolate of *t*-butyl acetate and 2-phenylpropanal in THF (◆) and *n*-hexane (○).

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Table 2. Differential activation parameters

	$\Delta\Delta H^{\ddagger}$ (kcal/mol)	$\Delta\Delta S^{\ddagger}$ (cal/mol K)	$\Delta\Delta G^{\ddagger}$ (298 K) (kcal/mol)	$\Delta\Delta G^{\ddagger}$ (200 K) (kcal/mol)
THF	−0.74 ± 0.04	−0.1 ± 0.1	−0.70 ± 0.08	−0.71 ± 0.07
n-Hexane	−0.08 ± 0.02	1.7 ± 0.1	−0.59 ± 0.05	−0.43 ± 0.04

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