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Rationalising diastereoselection in the dynamic kinetic resolution of α-haloacyl imidazolidinones: a theoretical approach

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Abstract—A new model for the rationalisation of previously reported DKR results is presented. The proposed model is based both on experimental and molecular modelling results which indicate that selectivity arises from the interaction between the leaving group and the stereodifferentiating substituent of the chiral auxiliary. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The results obtained in the previously reported DKR reactions clearly showed two trends (Fig. 1): with metalated nucleophiles (the dimethylmalonate and azide anions) the most reactive diastereomer of starting material was the 2′*R* and, with amine nucleophiles, the most reactive was the 2′*S* diastereomer.[1,2] The results of DKR reactions using sulphur nucleophiles are also in agreement with this dichotomy: methylthioglycolate (MTG) and benzylmercaptan behaved similarly to amines whereas thiophenol (which should be in the form of the thiophenolate anion under the reaction conditions used) showed the same preferential reactivity as the metalated nucleophiles.[2] The sensitivity of the amine nucleophiles to the ionic strength of the medium is also noteworthy.

Considering that the R group adopts a *cis* conformation relatively to the carbonyl group, as evident in X-ray structures[3] and molecular modelling studies (see Discussion), an anti-parallel carbonyls conformation of the substrates would render the 2′*R* diastereomer the most reactive (Fig. 2), thus explaining the selectivity observed with metalated nucleophiles. However, the DKR reactions with amine nucleophiles as well as with MTG and benzylmercaptan required further rationalisation.

Nunami and co-workers had previously reported similar trends of selectivity in related DKR reactions. They used molecular mechanics calculations, which showed that compound **2** should exist mostly in the anti-parallel carbonyls conformation (energy difference of approx. 23 kJ mol^{-1}), with the lowest energy rotamer having the R group *cis* relative to the carbonyl bond. They proposed that

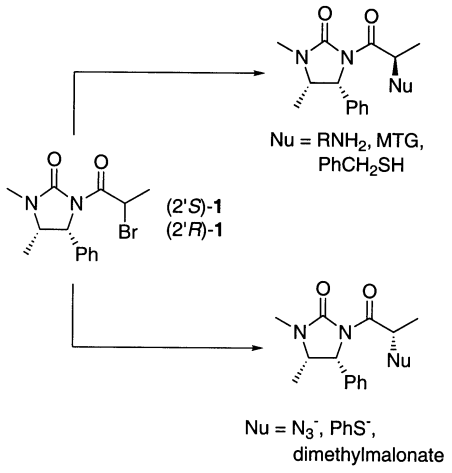

Figure 1. Dichotomy found in DKR reactions using compound **1**.

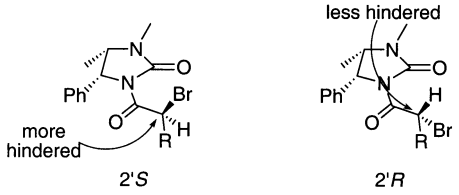

Figure 2. Nucleophilic attack to the 2′ carbon atom of diastereomers 2′*S* and 2′*R* in the antiparallel carbonyl groups conformation.

Keywords: molecular modelling; ab initio; transition states; dynamic kinetic resolutions (DKR).

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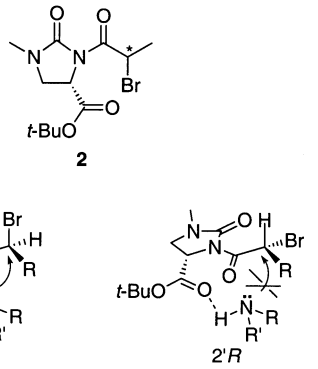


Figure 3. Assembly proposed by Nunami and co-workers: hydrogen bonding between the amine nucleophile and the carbonyl group of the chiral auxiliary's substituent.[4]

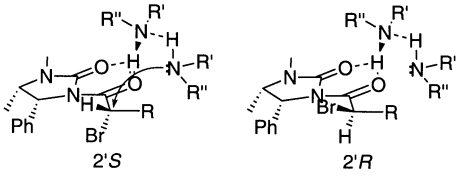


Figure 4. Previously proposed model for the rationalisation of the selectivities observed with amine nucleophiles.[1]

the unexpected result of reactions involving amine nucleophiles could arise from hydrogen bonding between the amine and the carbonyl group of the chiral auxiliary's substituent (Fig. 3).[4,5] The formation of such a bond would deliver the molecule of attacking amine from the more hindered side of the substrate and lead to an enhancement of the rate of nucleophilic displacement of diastereomer 2′*S*, resulting in a reversal in the selectivity (compared to that obtained with metalated nucleophiles).

Nunami and co-workers also showed that DKR of the corresponding ether (derived by reduction of the *tert*-butoxylcarbonyl group) led to a pronounced decrease rather than to a reversal in selectivity comparatively to the ester, as might be expected. Moreover, in our related work using substrates **1**, the establishment of such a hydrogen bond was not possible and yet the same dichotomous selectivity was observed. These results prompted us to propose a new model which also relied on hydrogen bonding between the amine nucleophile and the substrates, involving the formation of a bifurcated hydrogen bond and two molecules of amine (Fig. 4).[1]

In this model, the molecule of amine that displaces the bromide would be assisted by another molecule of amine, that acts as a general base, in an assembly that would lead to the

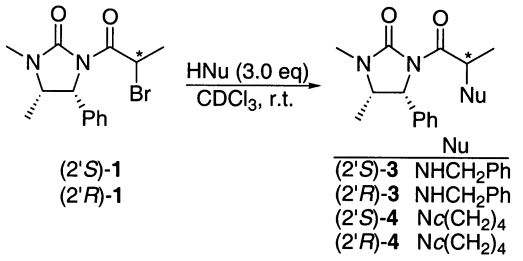


Figure 6. Reaction conditions used for the study of the nucleophilic displacement of the individual diastereomers of **1** by ^{1}H NMR; HNu=benzylamine, pyrrolidine.

preferential attack of the 2′*S* diastereomer and, thus, could explain the selectivities observed. Furthermore, the proposed model also explained the sense of selectivity of the thiol nucleophiles MTG and benzylmercaptan. As regards these, the poor selectivities might, in part, be a reflection of the relatively poor hydrogen bond donor properties of thiols.

2. Results and discussion

The overall process leading to the formation of the assemblies proposed in our previous model is actually composed of two sequential steps, as depicted in Fig. 5 for the 2′*S* diastereomer, which can be described as follows:

- formation of a bifurcated hydrogen bond between a molecule of amine and the two carbonyl groups of the substrate, in an assembly that might favour the required parallel carbonyl groups conformation of the substrates (assembly **I**);
- establishment of another hydrogen bond with a second molecule of amine (assembly **II**).

The proposed model thus depend on the formation of an initial assembly (assembly **I**) which would probably have different NMR spectra. As the formation of assembly **II** and, consequently, the formation of product, depends on the prior formation of assembly **I**, it was reasonable to expect that the latter would be present in detectable amounts; if it were otherwise, the formation of product via assembly **II** would be a highly unlikely event. Therefore, the nucleophilic substitutions of the isolated diastereomers of compound **1**, both with benzylamine and pyrrolidine, were followed by ^{1}H NMR. These reactions were carried out in deuterated chloroform, at room temperature, in the presence of 3.0 equiv. of the nucleophilic amine (Fig. 6).

Despite the remarkable difference in the rate of substitution

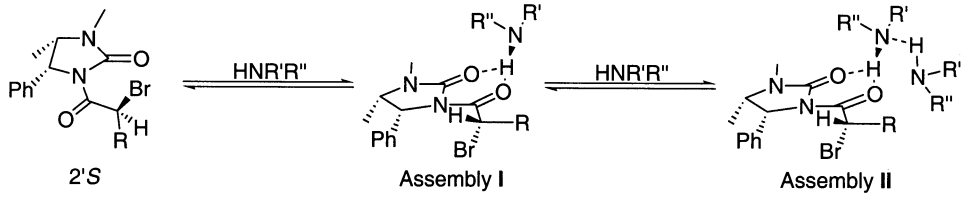


Figure 5. Consecutive steps involved in the formation of the proposed assemblies, illustrated for the case of diastereomer 2′*S*.

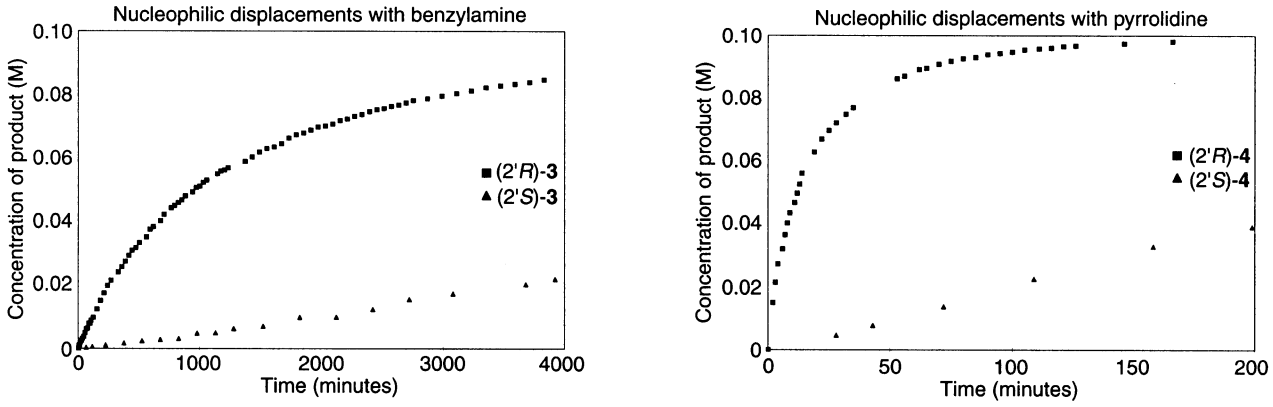


Figure 7. Concentration of the product of nucleophilic displacement of the individual diastereomers of **1** with benzylamine and pyrrolidine versus time, as detected by ^{1}H NMR.

of the individual diastereomers (Fig. 7), no other signals were visible in the spectra besides those of the starting material, product and amine (in the case of pyrrolidine the soluble ammonium hydrobromide salt was also detected).

Nevertheless, it could still be argued that the amount of the hydrogen bonded aggregate (assembly **I**) that exists in solution at a given moment, is neither enough nor sufficiently long lived to be detected by NMR spectroscopy. Increasing the stability of the aggregate might enable its detection by NMR and we attempted to do so resorting to the use of the strong complexing agent lithium cation, added in the form of lithium perchlorate. However the ^{1}H and ^{13}C NMR spectra of diastereomer (2′*S*)–**1** in deuterated toluene, at r.t., 50, 70 and 90°C, before and after the addition of lithium perchlorate showed no differences.

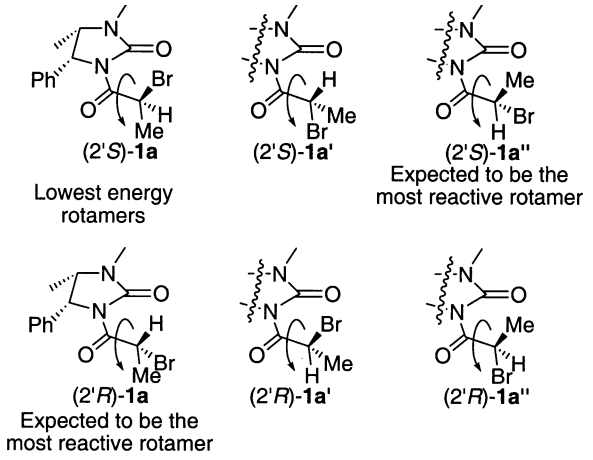


Figure 8. Different conformations of the side chain of compounds (2′*S*)–**1** and (2′*R*)–**1**.

Table 1. Enthalpy of the different conformations of the side chain of diastereomers (2′*S*)**1** and (2′*R*)–**1**, brought about by rotation of the C1′–C2′ bond, relative to the lowest energy conformers

Diastereomer	Conformer	ΔH (kJ mol^{-1})
(2′*S*)–**1**	**a**	–
	a′	6.8
	a″	24.7
(2′*R*)–**1**	**a**	–
	a′	23.6
	a″	8.2

These NMR studies revealed an apparent difficulty in effecting the conformational change required for the formation of an assembly of type **I**, even in the presence of a strong complexing agent such as lithium, clearly indicating that this is an unfavourable process. From a statistical standpoint it would be, thus, unreasonable to expect that a reaction that can proceed at a relatively high rate (as seen, for instance, in the reaction between the isolated diastereomer (2′*S*)–**1** and pyrrolidine, Fig. 7) would require the formation of such an assembly.

The lack of experimental data to support the previously proposed model and the apparent difficulty in effecting the conformational change required by it, prompted us to turn to the molecular modelling of the substrates used in the DKR reactions.[†]

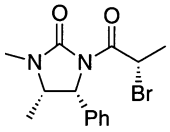
Nunami and co-workers had previously carried out a molecular mechanics modelling study[4] which was, as previously noted, the basis for his proposed mechanism. However, molecular mechanics does not perform well when applied to amidic systems and for this reason, along with the recognition that our case involves complex conjugated systems, we decided to study them using HF theory at 3-21G*. In this paper, we will present only the results concerning compound **1**, but identical results have been obtained for the other systems.

We started out by studying the conformation of the side chain since, at least in theory, the rotation of the C1′–C2′ bond can lead to a conformation of the 2′*S* diastereomer whose reactivity might be identical to that of epimer 2′*R*, with both diastereomers in the antiparallel carbonyls conformation (rotamers (2′*S*)–**1a**″ and (2′*R*)–**1a**, Fig. 8, Table 1).

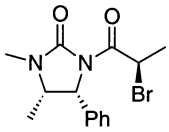
From Fig. 8 and Table 1, it is possible to conclude that the

[†] All the calculations presented, with exception of the ts calculations using semi-empirical methods, were performed at ab initio level, in gas phase, using the Hartree–Fock approximation and the 3-21G* basis set, with thermal energy correction for 298.15 K and 1.00 atm. The software used was Spartan 5.1 and MacSpartan Pro, Wavefunction, Inc.

Table 2. Enthalpy of the parallel carbonyl groups conformation of diastereomers (2′*S*)**1b** and (2′*R*)–**1b**, relative to the corresponding anti-parallel carbonyls conformers (2′*S*)–**1a** and (2′*R*)–**1a**



(2′*S*)-**1b**

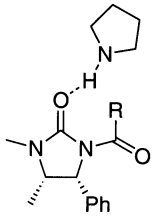


(2′*R*)-**1b**

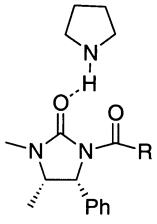
Diastereomer	Conformer	ΔH (kJ mol^{-1})
(2′*S*)–**1**	**b**	50.2
(2′*R*)–**1**	**b**	29.3

(2′*S*)–**1a**′′ rotamer in which the bromine atom is adequately oriented for a nucleophilic attack from the less hindered side of the chiral auxiliary, has an energy difference of about 25 kJ mol^{-1}, relative to rotamer (2′*S*)–**1a**; the equivalent rotamer in compound (2′*R*)–**1** is the lowest energy conformer (2′*R*)–**1a**. Thus, if the reaction were to take place through a direct attack of the nucleophile, the most reactive epimer would be the 2′*R* and the product distribution should reflect that preference. Since the stereoselectivity could not be explained by a simple rotation of the C1′– C2′ carbon bond, we moved on to the minimisation of the parallel carbonyl groups conformers, with the aim of verifying the previously proposed mechanism (Table 2).[1] Only the lowest energy rotamer of the C1′–C2′ bond rotation for each diastereomer was considered, since the energy pattern was identical to that discussed above for the side chain conformation with the antiparallel carbonyls (see Fig. 8, Table 1).

The considerable energy differences shown in Table 2 clearly indicate that the vast majority of molecules will be in the anti-parallel carbonyls conformation. Nevertheless, the energy differences shown are not by themselves sufficient to exclude the proposed model, if the stabilisation



(2′*S*)-**1a.1**
(2′*R*)-**1a.1**



(2′*S*)-**1b.1**
(2′*R*)-**1b.1**

Figure 9. Assemblies resulting from hydrogen bonding between one molecule of pyrrolidine and one molecule of substrate, both in the anti-parallel and parallel carbonyl groups conformation, respectively; R=CHBrCH$_3$.

Table 3. Enthalpy of the assemblies resulting from hydrogen bonding between the conformers **a** and **b** of both diastereomers and a molecule of pyrrolidine

Diastereomer	Assembly	ΔH (kJ mol^{-1})[a]
(2′*S*)–**1**	**a.1**	21.3
	b.1	28.9
(2′*R*)–**1**	**a.1**	20.5
	b.1	23.4

[a] $\Delta H=(H_{\text{conformer}}+H_{\text{pyrrolidine}})-H_{\text{assembly}}$.

Table 4. Comparison of the enthalpy values required for the conformational change from anti-parallel to parallel carbonyl groups and released by the formation of hydrogen bonded assemblies with a molecule of pyrrolidine, for diastereomers (2′*S*)–**1** and (2′*R*)–**1**

	Enthalpy values (kJ mol^{-1})			
	I	II	III	IV
Diast.	**a** to **b**[a]	**a.1**	I+II	**b.1**
(2′*S*)–**1**	50.2	21.3	71.5	28.9
(2′*R*)–**1**	29.3	20.5	49.8	23.4

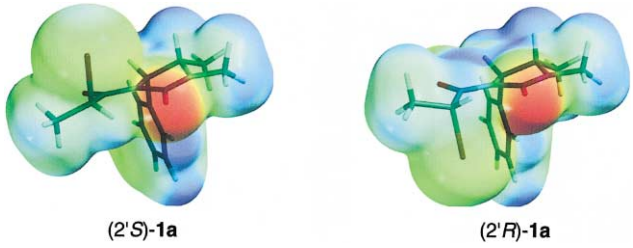
[a] Conformational change from **a** to **b**.

caused by hydrogen bonding with the amine can surpass them. Therefore, we proceeded to the determination of the decrease in energy resulting from hydrogen bonding of an amine (pyrrolidine was chosen for this study) with both the anti-parallel and parallel carbonyl groups conformations of epimers (2′*S*)–**1** and (2′*R*)–**1** (Fig. 9, Table 3). For both epimers, we considered only the assemblies in which the amine lies closest to the side chain, which are those most likely to lead to the formation of a bifurcated hydrogen bond with both carbonyls. In the case of the anti-parallel carbonyls conformers, only hydrogen bonding with the carbonyl group of the chiral auxiliary was studied, because this is the most accessible of the two carbonyl groups of the molecule.

As can be seen from the results summarised in Table 3, hydrogen bonding with the amine results, in all cases, in assemblies that are stabilised relatively to the isolated substrate and amine. The energy values determined for the stabilisation are overestimated, since the molecular modelling calculations that were carried out assume that molecules are in the gas phase and do not take into account solvation. However, it is reasonable to assume that this will affect in a similar way the energy values obtained for each complex, enabling us to proceed with a comparative analysis of the results.

For the formation of assemblies **b.1** to be a favourable and likely process, the stabilisation generated by their formation (Table 4, column IV) has to be greater than the energy required for the anti-parallel to parallel carbonyl groups conformational change (Table 4, column I), plus the stabilisation introduced by the formation of assemblies of type **a.1** (Table 4, column II).

The comparison of columns III and IV of Table 4 enables us



(2′*S*)-**1a** (2′*R*)-**1a**

Figure 10. Molecular electrostatic potentials of diastereomers (2′*S*)**1** and (2′*R*)–**1** in the anti-parallel carbonyls conformation (conformers **a**) mapped on electronic isodensity surfaces (0.002 e$^-$ au^{-3}), at ab initio HF 3-21G*. Red zones indicate negative potential and blue zones indicate positive potential.

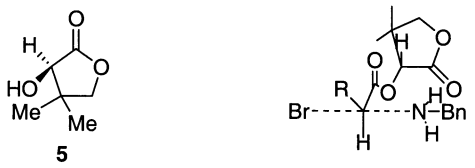


Figure 11. Model proposed by Ben and Durst to rationalise the stereochemistry obtained when using chiral auxiliaries of type **5**.[6]

conformation) preferentially in the direction of the carbonyl group of the chiral auxiliary, leading to the energetically favoured formation of assemblies of type **a.1** (see Fig. 9). It is, therefore, reasonable to assume that the substitution reaction will proceed via the formation of these aggregates.

At this stage, it becomes clear that the attacking amine approaches the auxiliary from a direction that is unaffected by the presence of the substituent group of the chiral auxili-

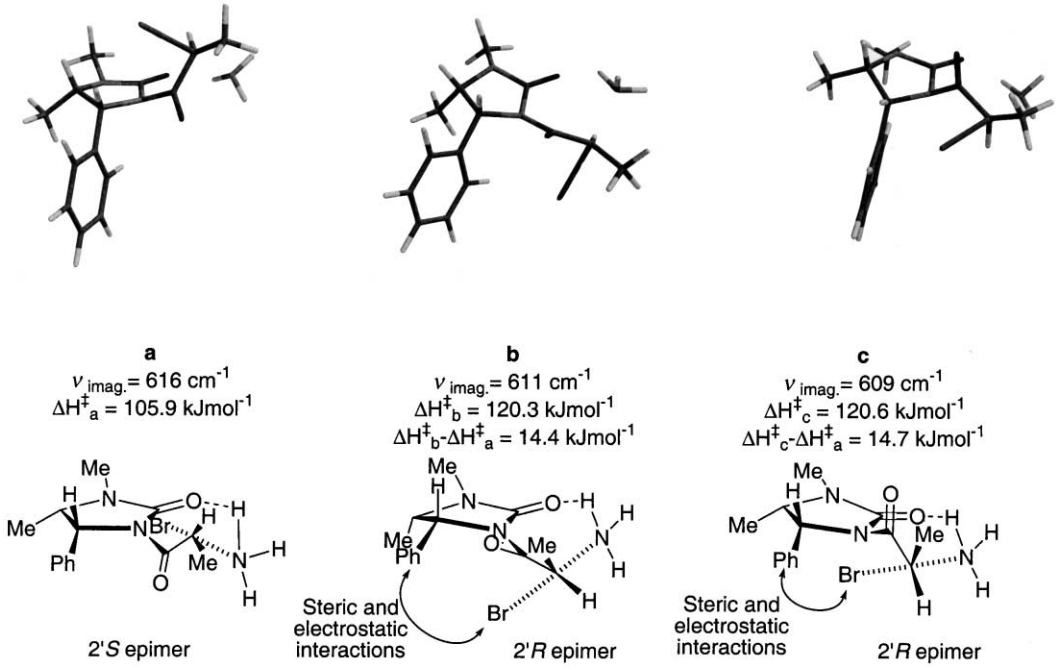


Figure 12. Transition states of both diastereomers of compound **1**, using semi-empirical PM3 approximation.

to say that the formation of assemblies of type **b.1** is highly unlikely compared to assemblies **a.1** that does not require the energetically demanding conformational change. It is also noteworthy that the energy difference between columns III and IV for epimer (2′*S*)–**1**, the one which has to undergo the conformational change in order to explain the observed stereochemistry, is larger than the energy difference for epimer (2′*R*)–**1**, clearly indicating that the mechanism of the reaction has to be somewhat different from that we had previously proposed.[1]

We then determined the electrostatic potentials of both diastereomers in the anti-parallel carbonyls conformation and mapped them on an electronic isodensity surface (0.002 e^- au^{-3}) (Fig. 10). The analysis of these representations reveals that the most accessible highest negative value lies on the carbonyl group of the chiral auxiliary. This means that a molecule of amine approaching a molecule of substrate will do so preferentially in the direction of the carbonyl group of the chiral auxiliary, with the subsequent establishment of a hydrogen bond, rather than attack directly the C2′ atom.

In summary, the calculations presented thus far indicate that a molecule of amine should approach the molecule of substrate (that exists mainly in the anti-parallel carbonyls ary, i.e. the attacking amine and the stereodifferentiating element of the chiral auxiliary do not directly interact. Therefore, the selectivity of the reaction must be a result not of interactions with the attacking amine, but of other factors that have not yet been considered. These considerations find support in a recent paper from Ben and Durst,[6] where a similar dependence from a hydrogen bond between the attacking group and the carbonyl of a chiral auxiliary of type **5**, Fig. 11, is reported.

For the actual nucleophilic attack to take place it is necessary to re-orient the C2′ carbon atom relative to the amine which, in theory, can be achieved by rotation either of the C1′–C2′ bond or of the amide bond. The former is energetically less demanding, but can be ruled out on the basis that the transition state is stabilised when the departing bromine atom and the attacking amine are in a perpendicular orientation relatively to the carbonyl bond,[7] and that this optimal arrangement would be destroyed by any rotation of the C1′–C2′ bond.[‡]

[‡] Bach et al.[7] have shown that for substitutions of the chlorine atom in α-chloroacetaldehyde, the energy of a transition state in which the halogen atom and the nucleophile are parallel to the carbonyl group exceeds that of an orthogonal transition state by more than 40 kJ mol^{-1}.

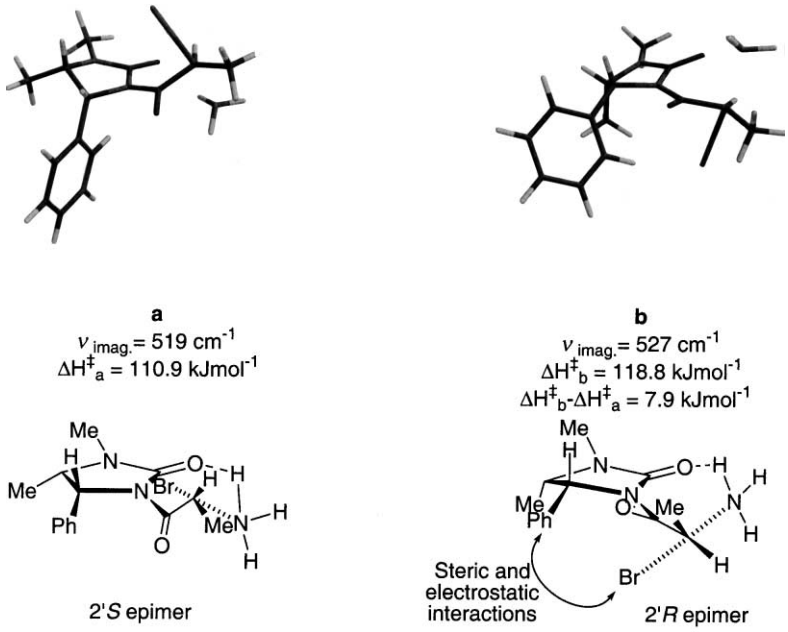


Figure 13. Transition states of both diastereomers of compound **1**, at ab initio HF 3-21G*.

We then proceeded to calculate the transition states of both epimers of compound **1**. Initially, we carried out the calculations using semi-empirical methods,[§] due to the size of the molecules. For the same reason, the attacking species used was NH_3. We obtained two different transition states for epimer (2′*R*)–**1** (structures **b** and **c**, Fig. 12), with nearly the same enthalpy, and displaying a shift in the position of the aromatic ring from axial (**c**) to equatorial (**b**) (Fig. 12). For the *S* epimer, only a transition state was reached (Fig. 12, structure **a**). From the analysis of the structures in Fig. 12, it is possible to conclude, as expected, that, in spite of having kept the reaction coordinate orthogonal to the carbonyl group, PM3 is not a good theory to model this type of compounds. In fact, the amide bonds became too distorted, far from the ideal planar structures that we can observe when full optimisations are carried out with ab initio methods. Moreover, the amidic dihedral angles are too large in the transition states (approximately 30° in structure **a**, 57° in structure **b** and 90° in structure **c**), indicating that the strength of the hydrogen bond is being overrated, comparative to the energy stabilisation due to the conjugated system. In fact, in model **c**, this conjugation has been completely destroyed, which indicates that this is an unreasonable structure. Nevertheless, the energy difference of about 14.4 kJ mol^{-1} between structures **a** and **b**, is in acceptable agreement with the experimental values obtained for the diastereoisomeric excess (up to 95%).

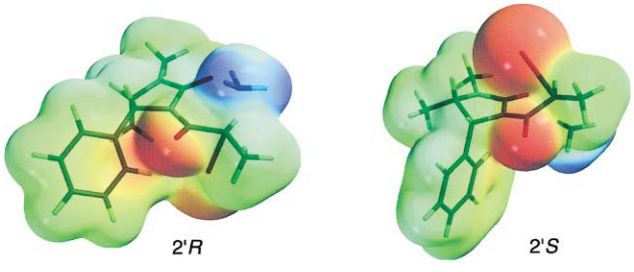


Figure 14. Electronic isodensity surfaces (0.002 e$^-$ au^{-3}) mapped with the electrostatic potential, for both transition states, at ab initio HF 3-21G*. Red zones indicate negative potential and blue zones indicate positive potential.

In order to obtain a more accurate description of the transition states, we then decided to calculate them at ab initio HF 3-21G*. At this level of theory, only one transition state was found for each epimer, with the one of diastereoisomer (2′*R*)–**1** showing a strong change in the molecular conformation (see Fig. 13), being the aromatic ring in equatorial position. This conformational change reduces the repulsion between the halogen atom and the aromatic ring and also minimises the effect on the ring of the amide bond rotation (necessary to keep the planarity of the amide bonds). It is possible to see that the amide groups keep their planar conformation and that the rotation of the amide bond required to reach the transition state is less than 20°, with the reaction coordinate being kept orthogonal to the carbonyl bond, in accordance with the literature.[7] Moreover, the energy difference of about 7.9 kJ mol^{-1} between the transition states of the two epimers is in good agreement with the experimental data.

Based on the results here presented, we can suggest that the stereoselectivity of DKR reactions in which these types of auxiliaries are used is controlled by the interaction of the leaving group with the group which confers chirality to the auxiliary, that arises when the amide bond is rotated in the transition state, and not because of any interaction with the nucleophile. In Fig. 14, which shows electronic isodensity surfaces (0.002 e$^-$ au^{-3}) mapped with the

[§] Calculations performed with a semi-empirical approximation, using PM3 parameterisation, in gas phase, with thermal energy correction for 298.15 K and 1.00 atm. The software used was Spartan 5.1 and MacSpartan Pro, Wavefunction, Inc.

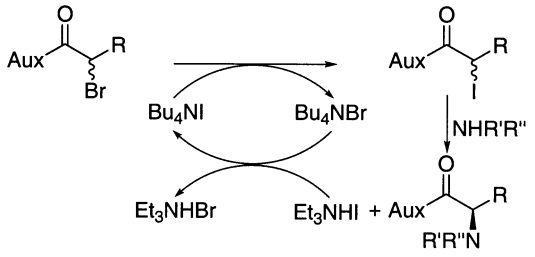


Figure 15. Cycle of reactions that take place when tetrabutylammonium iodide is used as epimerising agent.

electrostatic potential, for both transition states, it is easy to visualise this effect.

Since the establishment of a hydrogen bond with the carbonyl group can be a difficult process for hindered amines, we have to conclude that, in such a case, direct reaction without hydrogen bonding can take place, thus, possibly leading to lower selectivities.

The model proposed here, by relying initially on hydrogen bonding, is consistent with the lower selectivities obtained both in the DKR reactions with amines carried out in experimental conditions that decrease the probability of hydrogen bonding taking place (media of high ionic strength), as well as in the DKR reactions with the thiol nucleophiles MTG and benzylmercaptan, given the relatively poor hydrogen bond donor properties of thiols.

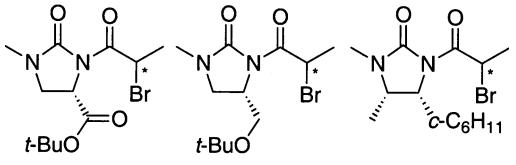
A convenient explanation for the d.e. dependence with the temperature can also be obtained from our theoretical results using the ab initio method. If we consider also the entropic contribution to the energy of the transition states, we find that at 25°C (298.15 K) the difference in entropy between the two transition states is about 4.3 kJ mol^{-1}. At 100°C (373.15 K) this contribution rises to about 5.9 kJ mol^{-1}, indicating that there is an increasing difference in the transition state energy with increasing temperature. Thus, as observed experimentally, we would expect to see an increase in diastereoselectivity as the temperature rises.

For the dynamic kinetic resolutions with metalated nucleophiles, sodium 1,3-dimethoxy-2-malonyl and sodium azide,[1] a different result can be expected. In fact, considering that the counter-ion of these nucleophiles can only be weakly complexed to the carbonyl group of the chiral auxiliary, direct attack of the anion should be more relevant and should take place preferentially from the less hindered side of the substrates in the anti-parallel carbonyls conformation. Therefore, the most reactive diastereomer will be the 2′*R* (as was obtained experimentally) and the selectivity will depend mainly on the ability of the chiral auxiliary's substituent to generate steric/electrostatic repulsions with the nucleophile.

These observations are also in accordance with the results from Ben and Durst ,[6] for chiral auxiliaries of type **5** (Fig. 11). In this case, since there is no possible interaction between the leaving group and the ring's methyl substituents, the stereocontrol is entirely dependent on the attacking group, namely its size and ability to hydrogen bond with the carboxyl oxygen. Because of that, for this type of auxiliary, there is no difference between using metalated or non-metalated nucleophiles and both classes follow the same stereochemical pathway.

Our proposed model also allows the rationalisation of the influence of the epimerising agent. When tetrabutylammonium iodide is used in dynamic kinetic resolutions with amines, the reaction can be generally described by the scheme shown in Fig. 15. Consequently, the leaving group in the nucleophilic substitution will be iodide, rather than bromide. The former, being larger in size, should give rise to a more pronounced steric/electrostatic repulsion with the substituent group of the chiral auxiliary, therefore, increasing the difference between the transition state energies of the two diastereomers and resulting in higher selectivities, as was, in fact, obtained.

Although metalated nucleophiles should react preferentially via direct attack to the carbon atom, the nature of the leaving group also affects the final outcome. In this case, the smaller leaving group that leads to a weaker interaction with the substituent of the chiral auxiliary will lower the transition state energy of the already more reactive 2′*R* diastereomer, thus, increasing its difference with respect to diastereomer 2′*S* and enhancing selectivity. Consistent with this explanation, it was found that the use of tetrabutylammonium bromide as epimerising agent led to higher selectivities in the DKR reactions with metalated nucleophiles than those obtained when using the iodide salt, i.e. the opposite of what was observed with amine nucleophiles. Also, if the final outcome of the DKR reactions with metalated nucleophiles is a result of a competition between direct attack and complexed attack (through the sodium ion), the use of iodide instead of bromide would increase the d.e. of the complexed pathway, thus lowering the resulting final d.e (direct plus complexed attacks).



2 **6** **7**

Our model can also explain the results obtained in the DKR reactions carried out with the chiral auxiliaries **2**, **6**[4,5] and **7**.[2] In the case of the auxiliary **2** used by Nunami and co-workers, in spite of the low steric effect of the carbonyl group, the electrostatic repulsion it generates is very strong and the latter is translated into high stereoselectivities in the DKR reactions. For compound **6**, both the steric and the electrostatic effects are small, leading to the consequent reduction in the stereoselectivity. For compound **7**, we observed a slight increase in the stereoselectivity of the DKR reaction,[2] relative to compound **1**, since the cyclohexyl group has a higher steric effect over the bromine atom than the aromatic ring.

Finally, the proposed model can also be used to explain the mild methanolysis method.[2] Hydrogen bonding between

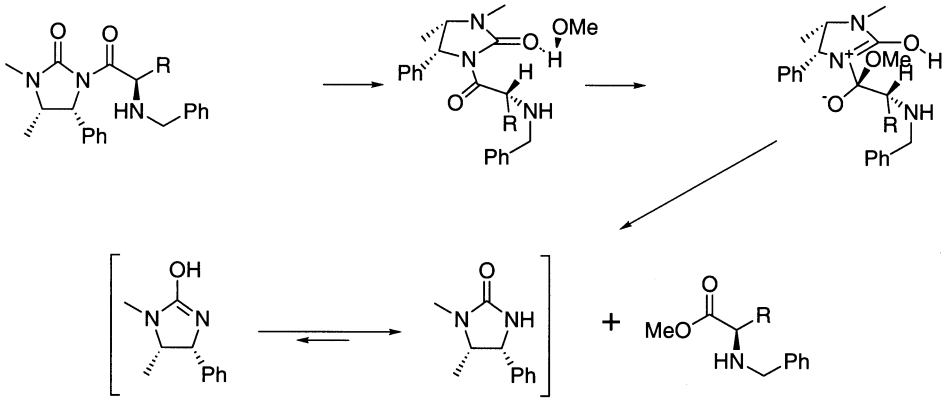


Figure 16. Mechanism proposed for the methanolysis reaction. Reaction conditions used for R=Me, Et, *n*-Bu: NEt_3 (1.2–6.0 equiv.), 0.11–0.12 M of substrate in MeOH, at reflux for 1–7 days; results in the range of 62–84% of methyl ester and 73–79% of chiral auxiliary.

methanol and the carbonyl group of the chiral auxiliary should take place (with the substrate molecule in the anti-parallel carbonyl groups conformation), with the concomitant increase in the nucleophilicity of the oxygen atom of the molecule of methanol, followed by nucleophilic attack to the carbonyl group of the side chain (Fig. 16).

A similar explanation can be given for the mild hydrolysis conditions found in the literature[8,9] for the same type of compounds, where simple refluxing in water for 12 h liberates the free chiral auxiliary and the products in high yield and with a very low degree of racemisation.

3. Conclusion

As a result of experimental data and molecular modelling studies of compound **1**, it is possible to propose a new model for the rationalisation of the selectivity seen in DKR reactions, in particular those involving amine nucleophiles. The proposed model explains not only the dichotomous behaviour of these systems but also the influence of temperature, media's ionic strength and epimerising agent on the selectivities obtained. With this model, it is possible to rationalise not only our own experimental results, but also those described by others. The model is now being used as the basis for the design of new synthetic methods based on substitution reactions employing DKR conditions.

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