Tetrahedron 66 (2010) 8021–8028

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Proline-catalyzed aldol reactions of cyclic diketones: fluorine modifies pathways as well as transition states

Jesús Díaz [†], Jonathan M. Goodman [*]

Unilever Centre for Molecular Science Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

ARTICLE INFO

Article history:
Received 26 May 2010
Received in revised form 22 July 2010
Accepted 3 August 2010
Available online 7 August 2010

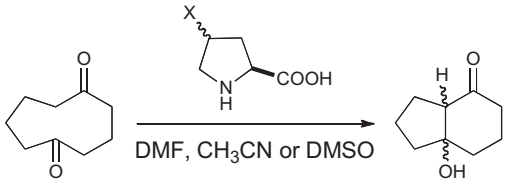
Keywords:
Aldol reactions
Epimerization
Proline
Asymmetric catalysis
DFT

ABSTRACT

Proline-catalysed aldol reactions are central to the development of organocatalysis, and have been the subjects of many studies. List's results on the effect of fluorine substitution on proline catalysts for an intramolecular aldol condensation provide a perfect test set for computational analysis, as subtle changes in the catalyst structure lead to clear changes in the product ratios. The results show that the carbon–carbon bond forming transition states for the Hajos–Parrish–Wiechart reaction do not account for the observed selectivity in all cases. However, if an analysis of post transition-state epimerization pathways is also included, together with the effect of water, it is possible to account for all of the experimental data.

1. Introduction

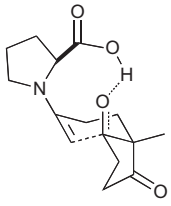
The aldol reaction is a well-known process for carbon–carbon bond formation and the aldolase enzymes carry out these reactions in a catalytic way through an enamine based mechanism.[1,2] Amino acids can be good catalysts and (*S*)-proline is one of the most widely used. Intramolecular aldol reactions have been widely studied both computationally and experimentally. List and Chandler have recently published a total synthesis of (+)-hirsutene[3] in which the key step was an intramolecular aldol reaction catalyzed by *trans*-4-fluoro-(*S*)-proline. They screened the reactions of cyclononane-1,5-dione with variously substituted (*S*)-proline catalysts, Scheme 1. The results showed that the use of *trans*-4-fluoro-(*S*)-proline lead to enhancement of the enantioselectivity of the reaction, but the reasons for this are not completely clear. We have undertaken a computational analysis of this reaction in order to discover how the substituents influence the stereochemical course of the reaction. The conformational constraint of forming a bicyclic product, coupled with the differences in experimentally observed enantioselectivity from small changes in the organocatalyst structure, make this a particularly good system for computational analyses.



X = H, F (*R* or *S*), OH (*R*), OTBS (*R*) or O^{t}Bu (*R*)

Scheme 1. a key step in List's synthesis of hirsutene.

The first proline-catalyzed intramolecular aldol reactions were described in 1971 by Hajos and Parrish[4] and by Eder et al.[5] The mechanism has been investigated in detail by List,[6] and Houk has reported computational studies on the uncatalysed process and on four possible catalysed mechanisms.[7,8] These studies led to the identification of the key transition structure for the process: the



Scheme 2. Hajos–Parrish–Wiechart reaction stereochemistry-controlling transition structure.

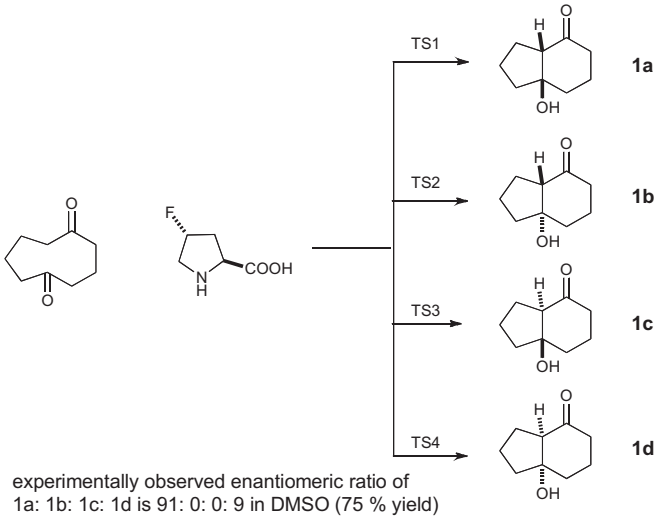
* Corresponding author. Fax: +44 1223 763076; e-mail address: J.M.Goodman@ch.cam.ac.uk (J.M. Goodman).
† Present address: Department of Organic and Inorganic Chemistry, University of Extremadura, Avda. Universidad s/n, Cáceres E-10071, Spain.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.08.003

carbon–carbon bond forming reaction of an enamine with a ketone, Scheme 2. The acid group of the proline activates one of the ketones for the attack by the enamine formed from the same proline molecule.

Analyses of the intramolecular aldol reactions have been reported by Santos et al.[9] in a computational study of dialdehydes catalyzed by (*S*)-proline, and by List et al.[10] The results are in agreement with the Houk's transition structure for the stereochemistry forming step of the intramolecular aldol reaction, but they suggest the inclusion of water is necessary in some cases. The inclusion of a water molecule leads to a decrease in enantioselectivity and diastereoselectivity and this may be the explanation for some experimental results with surprisingly low selectivity. When the calculations were carried out using a continuum model for the solvent (DCM) there was a large increase in the energy of the transition states leading towards the intramolecular proton catalysis by the acidic moiety of (*S*)-proline.

List's synthesis of hirsutene provides an ideal platform for the study of this reaction, because of the geometric constraints introduced by the ring systems. Small changes to a conformationally restrained and well-characterized system led to clear changes in enantioselectivity. Therefore, we undertook a computational study of the intramolecular aldol reaction of 1,5-cyclononanedione catalyzed by (*S*)-proline, *trans*-4-fluoro-(*S*)-proline and *cis*-4-fluoro-(*S*)-proline. The simulations were performed in vacuum and with solvent models for dimethylformamide (DMF) and dimethylsulfoxide (DMSO). We set out to explain the enhancement in the stereo- and enantioselectivity observed when *trans*-4-fluoro-(*S*)-proline was used as a catalyst by analyzing the four competing catalysed pathways, which proceed through the key carbon–carbon bond forming transition structures identified by Houk (Scheme 3).



Scheme 3. Four products of the proline-catalysed transannular aldol reaction of 1, 5-cyclononadione.

2. Computational methods

The calculations have been carried out with Gaussian 03.[11] The geometries of all the stationary points were fully optimized at the B3LYP/6-31G**[12] level, and their nature (minimum or transition state) was determined by frequency analysis. The basis set was chosen since larger functionals do not lead to substantial differences in the geometries and energies of the transition states.[7b] The solvation energies in DMF and DMSO and the NBO analyses were performed with single point calculations using MO5-2X/6-31++G** as implemented in Jaguar version 4.2.[13] This functional was specially designed only for main group-chemistry providing a good accuracy in barrier heights and non-covalent interactions since the pure DFT methods overestimate bond energies and underestimate barrier heights.[14]

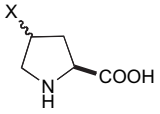
We have completed a full computational study of all possible transition states for the process in order to determine the details of the effect of placing a fluorine on carbon four of the proline. The conformational space of the system is small, because the diketone is cyclic, and the product has a conformationally restricted fused ring system. These constraints meant that we could be confident we had exhaustively surveyed the available conformation space.

3. Discussion

Tables 1 and 2 give the results of this survey of the potential energy surfaces for the reactions. Our calculations are in agreement with the experimental results for (*S*)-proline and its *cis*-fluoro derivative. Figure 1 shows the four most stable transition states (TS) for the key step in the aldol reaction for the *cis*-fluoro derivative. In all these TS a chair-shaped conformation is adopted by the six-membered ring and envelope conformations by both the proline and the five-membered ring, which forms by the development of the new C–C bond.

The most stable conformers of cyclopentane are the envelope and the half-chair or twisted form, and these interconvert readily. We have considered only the most stable transition states for each

Table 1
Energies (kcal/mol) relative to the most stable transition structures, including ZPE



X	H		*cis*-F		*trans*-F		
	Gas Phase	DMF	Gas Phase	DMF	Gas Phase	DMF	DMSO
TS1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS2	1.87	2.49	2.14	2.45	1.90	2.91	2.98
TS3	1.55	2.60	1.61	3.18	0.68	0.49	0.57
TS4	1.15	1.25	1.18	0.93	1.24	1.30	1.36

Table 2
Enantiomeric ratios from calculation and from experiment

X	H			*cis*-F			*trans*-F			
	Gas	DMF	Exp. (DMF) 60% yield	Gas	DMF	Exp. (DMF) 50% yield	Gas	DMF	DMSO	Exp. (DMSO) 75% yield
TS1	79.0	86.8	77	81.0	81.2	79	67.3	64.1	67.0	91
TS2	3.4	1.4	0	2.3	1.3	0	2.8	0.5	0.5	0
TS3	5.9	1.1	0	5.5	0.4	0	21.4	28.1	25.7	0
TS4	11.6	10.7	23	11.3	17.1	21	8.5	7.3	6.9	9
TS1+TS3	84.9	88.0	77	86.5	81.6	79	88.7	92.2	92.6	91
TS2+TS4	15.1	12.0	23	13.5	18.4	21	11.3	7.8	7.4	9

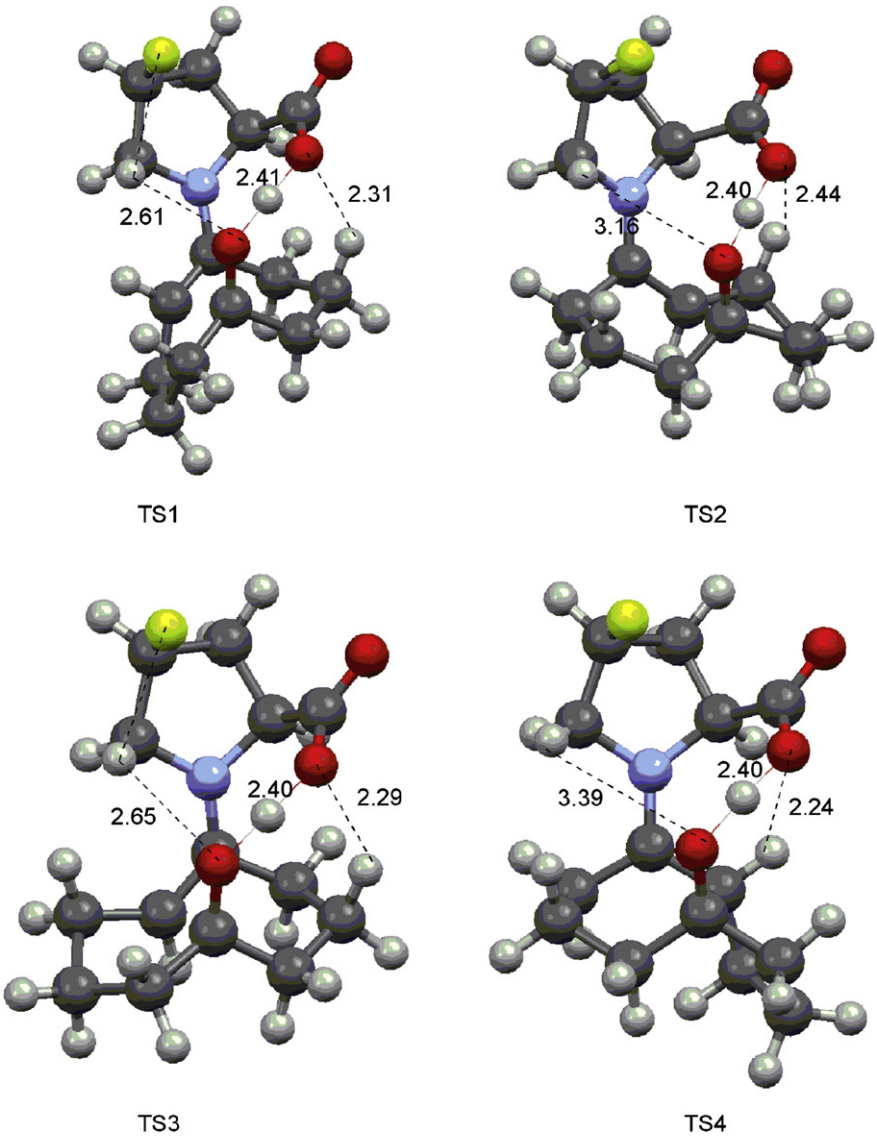


Figure 1. Geometries of the transition states for the aldol reaction of 1,5-cyclononadione catalysed by *cis*-4-fluoro-(*S*)-proline, with distances in Angstroms.

structure (TS1–TS4), but we have found in our conformational search at least two transition structures for each pathway with similar energies (see the Supplementary data). The main differences between these TSs are the conformations of the proline rings, which always have an envelope conformation. For the *cis* derivative the fluorine atom is axial in the most stable transition states (Fig. 1), and this leads to a large dipole moment, which is well stabilized by the polar solvent.

For proline and for *cis*-4-fluoro-(*S*)-proline, both the enantioselectivity and the diastereoselectivity show a close match between experiment and calculation. This is consistent with Houk's analysis of the Hajos–Parrish–Wiechert reaction, in which he concluded that the transition structures studied here control the stereochemistry of the reaction. This conclusion appears also to be true for the reactions of 1,5-cyclononadione.

The diastereomeric ratio increases when the solvent effects are introduced because TS3 is stabilised less well than the more polar TS1 and TS4. TS2 is the highest energy transition structure of all, and so corresponds to the least important reaction pathway. The slight enhancement of enantiomeric ratio when a *cis*-fluorine atom replaces the hydrogen can be explained by the increased dipole moments of all the TSs, which are stabilized for the high polarity solvent used in the reaction (DMF). TS4 is the most polar transition structure of all, and for this reason the use of a solvent decreases its energy more than the others. This further improves correlation between the experimental and the calculated diastereomeric ratios.

There are several factors that explain the greater stability of TS1 and TS4 over TS2 and TS3. In Houk's studies,[7,8,15] the most important reason for the stereocontrol is the effect on the geometry of transferring the hydrogen of the proline's carboxylic acid to the forming alkoxide and the electrostatic interactions between the proline iminium ion and the forming alkoxide. Our study is consistent with this conclusion, and also shows that the orientation of the carboxylic group with the forming alkoxide drastically affects the energies of transition structures and their geometries. At the optimum distance for hydrogen transfer between the two oxygen atoms (ca. 2.40 Å), the angle is forced to be 113° instead of the 120° of a typical carboxylic sp^2 group (Fig. 2). The carboxylic moiety and the forming alkoxide are in the same plane for the most stable transition structure found.

The close correspondence between calculation and experiment for proline and for *cis*-4-fluoro-(*S*)-proline reassured us that the computational approach was sufficiently powerful to analyse the reaction. The two competing geometries of TS4 for *trans*-4-fluoro-(*S*)-proline are quite different (Fig. 2) and this leads to the large energy difference between them (5.2 kcal/mol). In both, the proline has similar envelope shapes and the chair shape of the forming six-membered ring. The difference lies in the forming five-membered

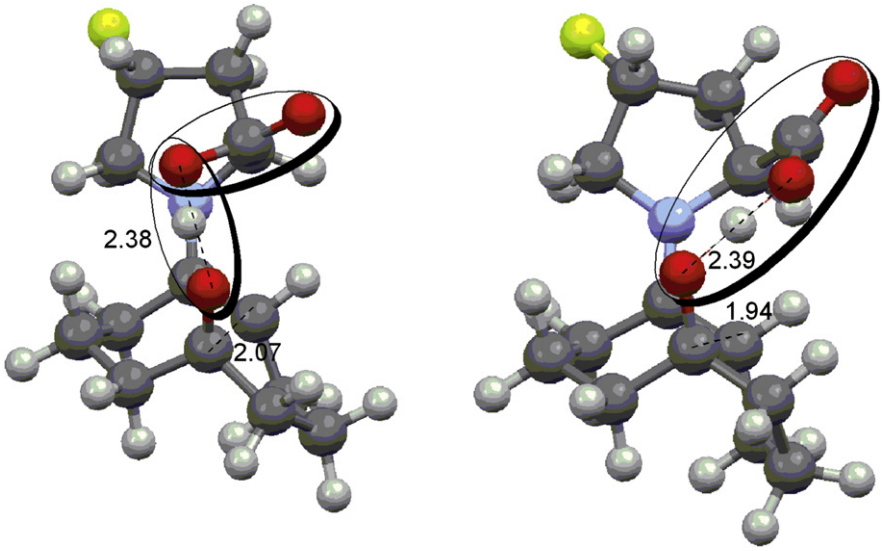


Figure 2. Different conformers of TS4 for *trans*-4-fluoro-(*S*)-proline. The right hand conformation is energetically preferred by more than 5 kcal/mol.

ring. In the most stable TS, where the carboxylic group and alkoxide are in the same plane, this ring has a more stable envelope conformation instead of the half-chair. The second reason for the greater stability of TS1 and TS4 than TS2 and TS3 is the electrostatic effect from the methylene group next to the forming iminium double bond of the proline with the forming alkoxide.

As in the cases of *cis* derivative and (*S*)-proline, we also found different transition structures for the trans stereoisomer where the variation is the conformation of the proline ring. In these cases the more stable transition states (Fig. 3) have the fluorine atom in an equatorial position except for TS3, where the fluorine is axial.

Single point calculations have been performed on these TSs where the fluorine atom has been substituted by hydrogen using the ONIOM option incorporated in Gaussian03 (see Supplementary data), to give us information about how the fluorine atom can affect the energy.

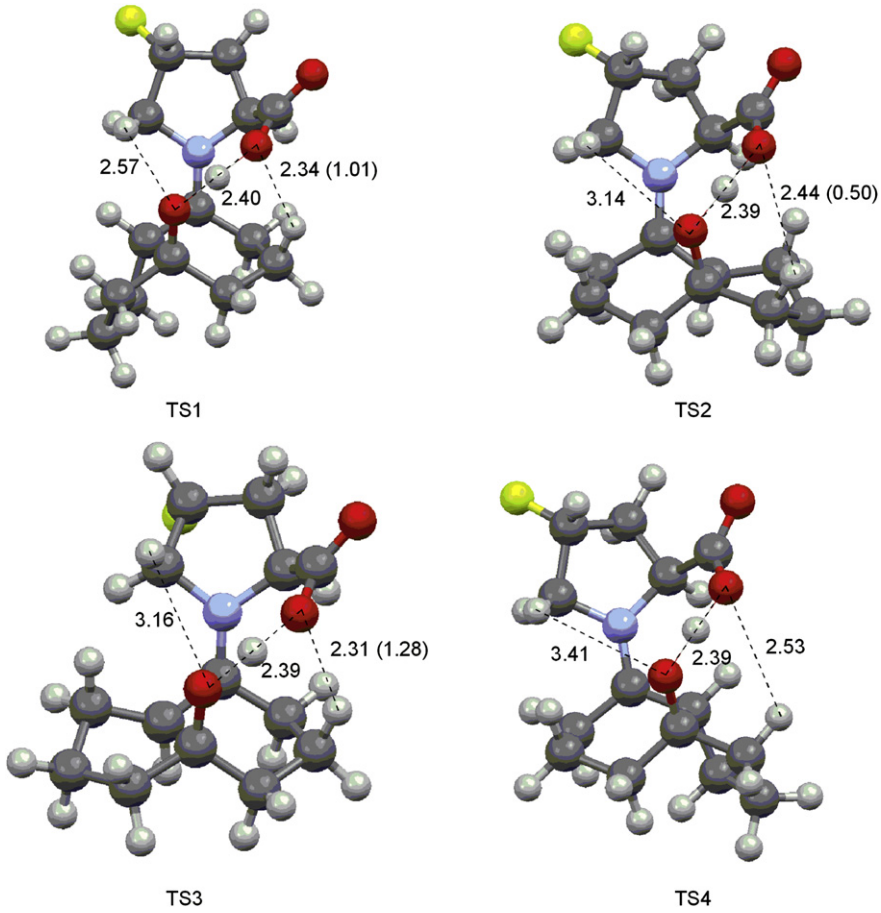


Figure 3. Geometries of the transition states for the aldol reaction of 1,5-cyclononadione catalysed by *trans*-4-fluoro-(*S*)-proline, with distances in Angstroms and NBO values in brackets.

Table 3 shows that the energies calculated when the fluorine atom replaces the hydrogen are similar to the ones for (*S*)-proline, except for TS3. This means that the strange conformation adopted for TS3 is not very stable for the TS of the unsubstituted (*S*)-proline. This different conformation in the forming five-membered ring is only favoured for the fluorine derivative with the fluorine in the trans position.

Table 3
Comparative energies of TS of (*S*)-proline and *trans*-4-fluoro-(*S*)-proline calculated using B3LYP, and ONIOM calculations on the unsubstituted geometries

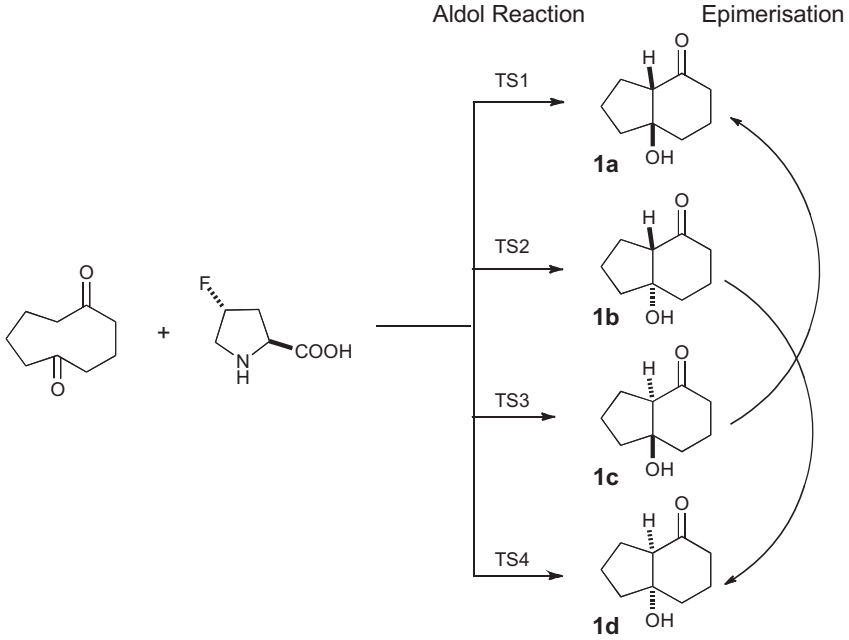
	(*S*)-Proline	*trans*-4-Fluoro-(*S*)-proline	ONIOM *trans*-4-fluoro-(*S*)-proline
TS1	0.0	0.0	0.0
TS2	2.2	2.1	2.0
TS3	1.8	0.90	3.0
TS4	1.4	1.43	1.10

Energies are relative to the most stable TS in each case and do not include the ZPE corrections.

be much lower than would be expected on the basis of the experimental results, and so the calculations suggest that the *trans*-fused six-five ring system, which is not observed experimentally, should be a significant proportion of the products. This is a major concern, because if the calculations do not correlate well with the experiments for *trans*-4-fluoro-(*S*)-proline, then it is possible that the good agreement for the other, very similar, reactions, could be fortuitous.

The high enantio- and diastereomeric ratio observed experimentally could be explained if the products of the transition states that we have investigated could epimerize. If the products from TS2 and TS3 could change to the more stable *cis*-fused six-five ring system through a pathway with low energy barriers, then the experimentally observed diastereomeric ratio would be high, even though TS3 has an important role in the reaction (Scheme 4).

The chiral centre adjacent to the carbonyl group in the products could, potentially, epimerise rapidly under acidic or basic conditions, transforming **1b** into **1d** and **1c** into **1a**. The thermodynamic



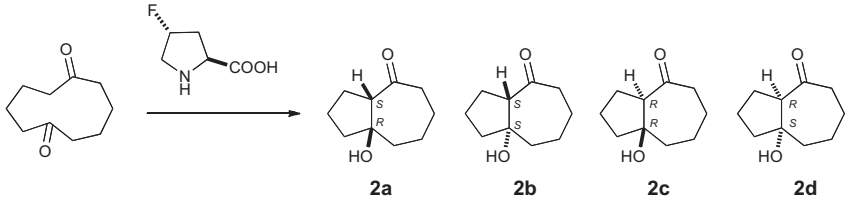
Scheme 4. Epimerisation pathways between pairs of reaction products could explain the differences between the experimental observations and the calculated pathways.

The enhancement of the stereocontrol for *trans*-4-fluoro-(*S*)-proline compared with the *cis*-4-fluoro-(*S*)-proline and unsubstituted proline can be explained by the proximity of the methylene group for TS1 (2.57 Å). We have not located a NBO relationship between these atoms, but we have found a relationship between the oxygen of the carboxyl group and the closest hydrogen of the 1,5-cyclononanedione (2.34 Å) for TS1. This coupling in the molecular orbitals also occurs in other TS (see Fig. 3). In the case of TS3 this NBO is also higher (1.28 for TS3 vs 1.01 for TS1).

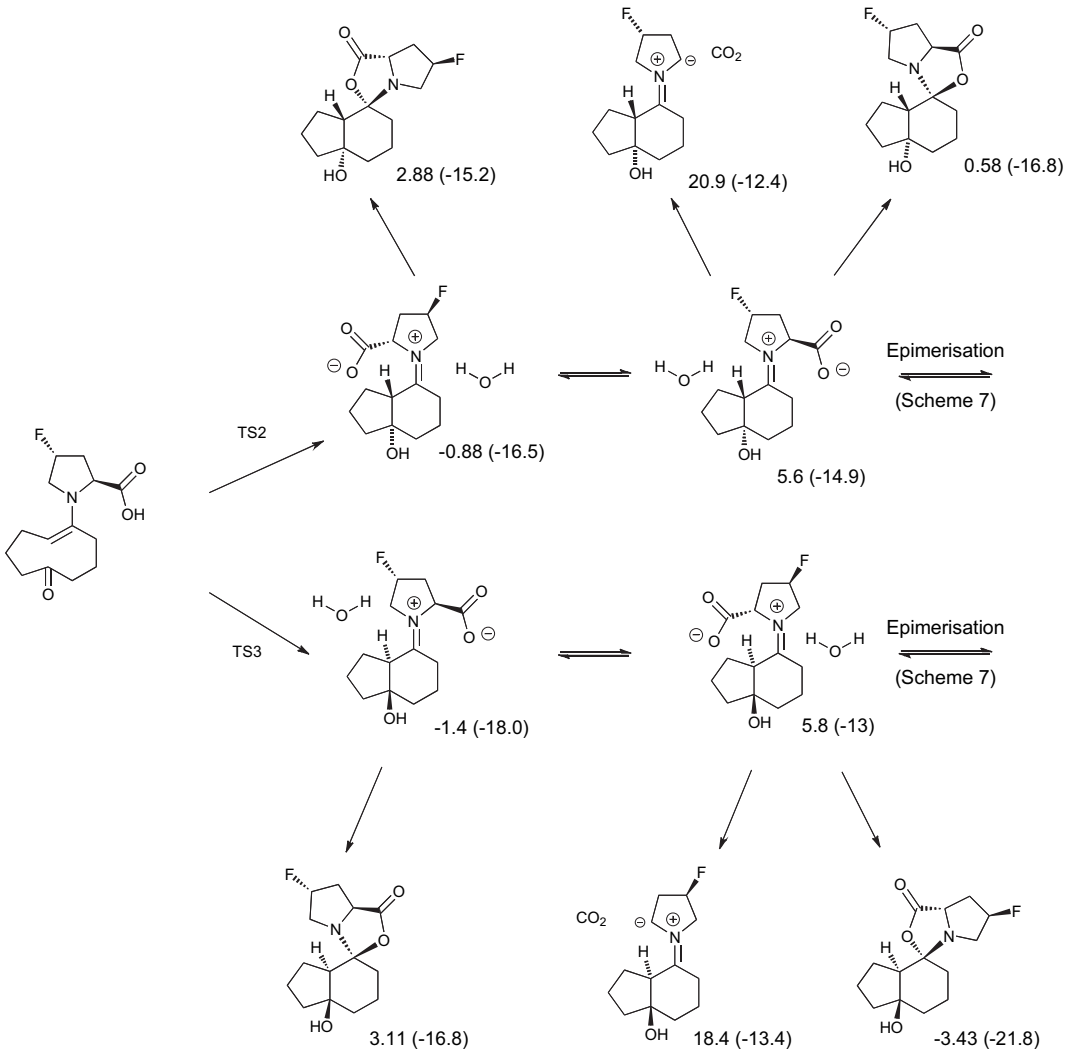
Whilst the experimental and the computational results for proline and for *cis*-4-fluoro-(*S*)-proline are in close agreement, the results for *trans*-4-fluoro-(*S*)-proline show substantial differences between the calculations and the experiments. The energy of TS3 is calculated to

preference for a *cis*-fused six-five ring system should drive the process towards the observed products, **1a** and **1d**, without affecting the enantioselectivity of the reaction. There are some experimental studies where the epimerization of an α-hydrogen to a carbonyl group is possible in mild conditions using a similar catalyst to proline.[16] When a secondary amine like proline reacts with a ketone, the zwitterionic intermediate makes the α-hydrogen more acidic since the positive nitrogen of the iminium group withdraws charge and the hydrogen can be easily removed.

This effect is not limited to 1,5-cyclononadione. In order to test its generality, we have also performed a computational study of hydroxyoctahydroazulen-4(5*H*)-one, Scheme 5, the experimental results for which have also been reported by List.[3] The details of this



Scheme 5. Products of the cyclisation of 1,6-cyclodecadione catalysed by *trans*-4-fluoro-(*S*)-proline. The observed ratio of **2a** to **2d** was 82:18. The diastereomeric ratio was 7: 1.



Scheme 6. This scheme shows how water interacts with the intermediate species in the pathways for the formation of the *trans*-fused rings. In the absence of water, the process is diverted to aminals or decarboxylation. With sufficient water epimerization is possible (Scheme 7). All energies in vacuum (DMSO values in brackets) are in kcal/mol and are relative to the energy of the reactants.

study are available in the Supplementary data. The major product, **2a**, was obtained as a diastereomeric mixture (dr=7:1). The calculated thermodynamic ratios of the products **2a** and **2c** (Scheme 5), which have the hydroxyl group as an *R* chiral centre give us a diastereomeric ratio of 6.7:1, which is similar to the 7:1 that List reported. The analogous thermodynamic analysis for **1a** and **1c**

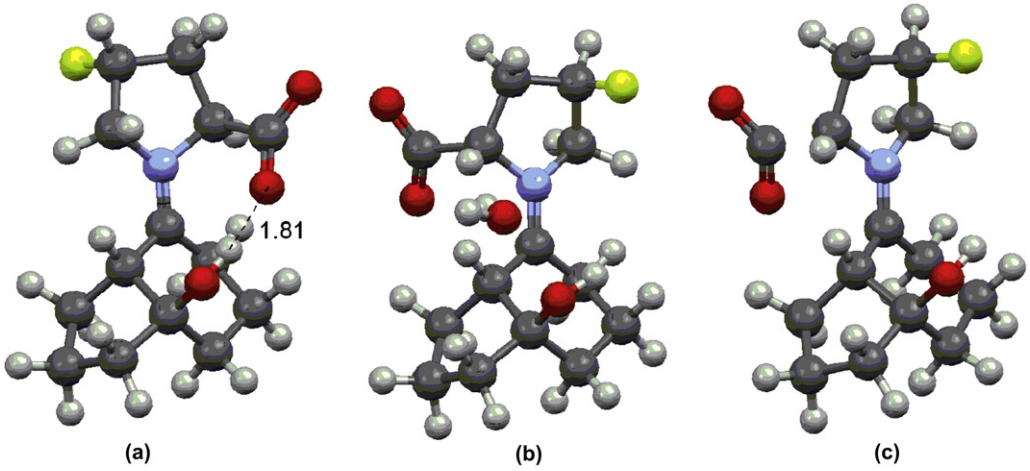
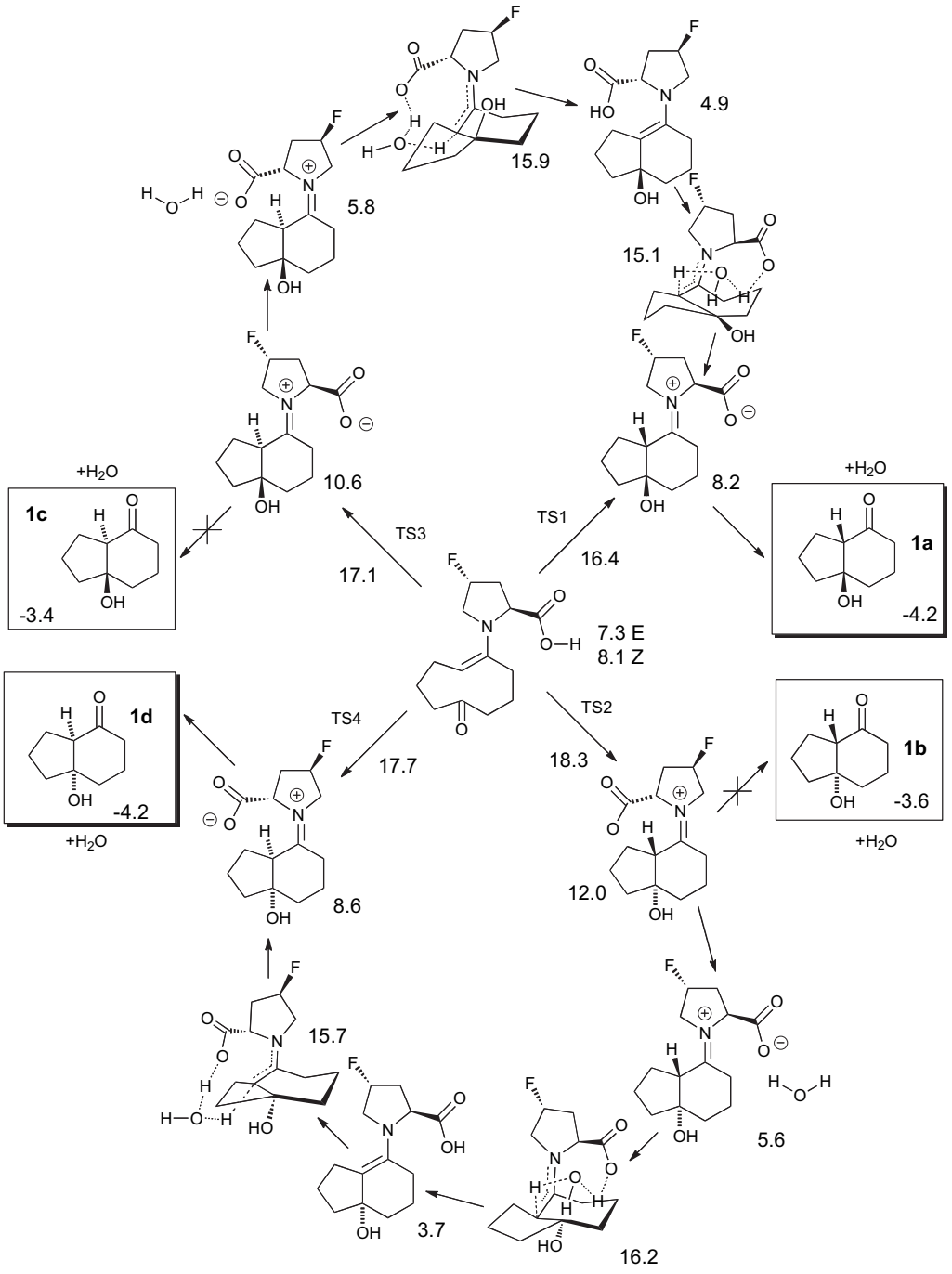


Figure 4. Structures of zwitterionic intermediates from TS1 with the carboxylic group and hydroxyl in the same face (a) and in the opposite face (b and c).

gives a strong preference for **1a** (99:1), as expected. This observation supports the suggestion that the epimerization of **1b** and **1c** leads to the more stable products, **1a** and **1d**. A conformational search and a full optimization of all conformers of both diastereomers gives the thermodynamic ratios of the products and these calculations are in agreement with the experimentally reported diastereomeric ratio. This is consistent with our hypothesis for the reaction of 1,5-cyclononadione: only one of the chiral centres in the product (the carbon which bears the hydroxyl group) is determined by the kinetically-controlled aldol reaction. The other chiral centre is formed through an epimerization process that leads to the final thermodynamic products.

Table 2 shows that the sums of the populations of the products from TS1+TS3 and TS2+TS4 give the experimentally observed enantiomeric ratio for *trans*-4-fluorine-(*S*)-proline reacting with 1,5-cyclononadione. For *cis*-4-fluorine-(*S*)-proline and (*S*)-proline, TS2 and TS3 are so high in energy that none of the products of these pathways form. There are, therefore, no substrates for an epimerization process in these cases. For the products of the *trans*-4-fluoro-(*S*)-proline catalysed reaction, an epimerization process could bring the calculations and experiments back into harmony.

How can the product of the reaction with *trans*-4-fluorine-(*S*)-proline catalysis undergo the epimerization process? We have carried out a computational study of several reasonable pathways. In the absence of water, epimerization processes seem to be inaccessibly high in energy. In the presence of a water molecule, however, the epimerization process becomes a competitive pathway (Scheme 6).



Scheme 7. Energies are in vacuo and are in kcal/mol relative to the reactants.

It has been demonstrated that the key carbon–carbon bond-forming step is independent of water. In studies by Blackmond et al.,[17] however, it was shown how the concentration of water can affect the rate of the reaction. In our studies we have observed that the zwitterionic intermediates are stabilized by either a hydroxyl group, which has been formed in the aldol reaction, or by a water molecule. In the absence of both these effects, a decarboxylation process leads to an azomethine ylide. Blackmond suggests this competing reaction can take place both in the presence or absence of water for the reactions of aromatic aldehydes with proline. Our calculations suggest that the process also applies to ketones.

After the zwitterionic compounds have been formed, a water molecule could hydrolyse the imine and give the aldol product. Alternatively, the imine double bond could isomerise (Scheme 6). This could lead to decarboxylation, the formation of an aminal (which have been detected in the first minutes of the reaction by NMR both with and without water)[17] or to epimerization. These equilibria between several species can coexist when the proline reacts with a ketone or aldehyde before and after the aldol reactions, and have been studied by Vilarrasa.[18] In all of the zwitterionic compounds there is an interaction between the oxygen of the carboxylate and the hydrogen of the hydroxyl group, since the distances between them is about 1.8 Å (Fig. 4). In the zwitterionic intermediates where the carboxylate group is on the opposite face, the hydroxyl group cannot stabilize them and the decarboxylation occurs leading an azomethine ylide.

The epimerization process could occur by intramolecular deprotonation of the imine by the nearby carboxylate anion. The energies found for this process, however, were too high to explain why this process would occur instead of the formation of the product **1c** (see Supplementary data). The addition of a molecule of water, however, leads to a low energy epimerization process, which is energetically preferable to the formation of **1c**. This is reasonable because the reaction was carried out with 20 mol % of catalyst, which means that there is at least 20 mol % of water in the reaction medium.[3]

The full reaction pathway is given in Scheme 7. The observed products, **1a** and **1d**, form directly, and also by water-catalysed epimerization of the zwitterions formed through TS2 and TS3. The enamines (*Z* or *E*) undergo an aldol reaction through TS1–TS4, forming zwitterionic intermediates. These structures could have the carboxylic moiety on either side of the iminium ion, but QRC[19] calculations confirm that the zwitterionic compounds formed after aldol reaction are those represented in the Scheme 7.

The most favourable pathway for two of these zwitterions is hydrolysis to form **1a** and **1d** directly. When a molecule of water is included in the system, the most favourable route for the other two is the epimerization process that also leads to the formation of **1a** and **1d**. All of the competing pathways in Scheme 7 need to be considered in order to get a computational result, that is, consistent with the experimental data. With this full analysis, the factors controlling the enantioselectivity and the stereoselectivity of the reaction become clear.

4. Conclusions

Experiments and calculations give consistent results for the intramolecular aldol reaction of 1,5-cyclononanedione catalyzed by (*S*)-proline, *trans*-4-fluoro-(*S*)-proline and *cis*-4-fluoro-(*S*)-proline. However, it is not sufficient simply to find the transition structures for the key carbon–carbon bond forming process. A low energy epimerization step can take place after the new carbon–carbon bond is formed, and this process is needed to make the experiments consistent with the calculations. This has implications for other studies of stereoselective processes in organic synthesis: analysis of the key transition structures may not give a complete explanation for the stereoselectivity.

Acknowledgements

We thank Unilever and the Ministerio de Ciencia e Innovación for a José Castillejo grant.

Supplementary data

Tables and comments are added to Supplementary data moreover the Cartesian coordinates of all reported structures, including the total electronic and zero-point vibrational energies. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.003.

References and notes

1. (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; Wiley-VCH: Weinheim, 1995; (b) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
2. (a) March, J. J.; Lebherz, H. G. *TIBS* **1992**, *17*, 110–113; (b) Rutter, W. J. *Fed. Proc. Am. Soc. Exp. Biol.* **1964**, *23*, 1248–1257; (c) Lai, C. Y.; Nakai, N.; Chang, D. *Science* **1974**, *183*, 1204–1206; (d) Morris, A. J.; Tolan, D. R. *Biochemistry* **1994**, *33*, 12291–12297.
3. Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737–6739.
4. (a) Hajos, Z.G.; Parrish, D.R. German Patent DE 2,102,623, July 29, 1971; (b) Hajos, Z. G.; Parris, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
5. (a) Eder, U.; Sauer, G.; Wiechert, R. German Patent DE 2,014,757, Oct. 7, 1971; (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.
6. List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839–5842.
7. (a) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766–5768; (b) Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294–11302; (c) Zhu, H.; Clemente, F. R.; Houk, K. N.; Meyer, M. P. *J. Am. Chem. Soc.* **2009**, *131*, 1632–1633.
8. Alleman, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569.
9. (a) Duarte, F. J. S.; Cabrita, E. J.; Frenking, G.; Santos, A. G. *Eur. J. Org. Chem.* **2008**, 3397–3402; (b) Duarte, F. J. S.; Cabrita, E. J.; Frenking, G.; Santos, A. G. *J. Org. Chem.* **2010**, *75*, 2546–2555.
10. Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785–2788.
11. Gaussian, R. D., 03; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T., Jr.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 98, Revision A.9*; Gaussian, Inc.: Wallingford CT, 2004.
12. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
13. *Jaguar 4.2*; Schrodinger: Portland, Oregon, 2002.
14. (a) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364–382; (b) Zhao, Y.; Gonzalez-Garcia, N.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 2012–2018.
15. Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.
16. (a) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591–9595; (b) Hedenstrom, E.; Andersson, F.; Hjalmarsson, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1513–1518; (c) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem.* **2008**, *6*, 719–726; (d) Ramachary, D. B.; Chowdari, S. N.; Barbas, C. F., III. *Synlett* **2003**, *12*, 1910–1914.
17. (a) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101; (b) Zotova, N.; Broadbelt, L. J.; Armstrong, A.; Blackmond, D. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3934–3937.
18. Isart, C.; Burés, J.; Vilarrasa, J. *Tetrahedron Lett.* **2008**, *49*, 5414–5418.
19. Silva, M. A.; Goodman, J. M. *Tetrahedron Lett.* **2003**, *44*, 8233–8236.