Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1631–1634

TETRAHEDRON: *ASYMMETRY*

Proline mediated asymmetric ketol cyclization: a template reaction †

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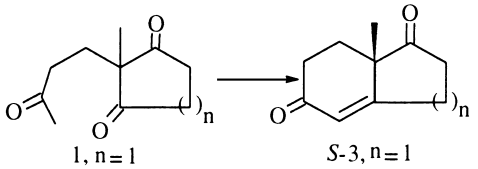
Received 30 March 1999; accepted 30 April 1999

Abstract

^{1}H, ^{13}C and ATR-FTIR spectroscopic studies reveal that the asymmetric cyclization of prochiral triones **1** and **2** in the presence of *S*-proline is a template reaction.

The prochiral triones **1** and **2** have been reported by us earlier[1] to give the diones *S*-**3** and *S*-**4**, respectively, when neat (in the absence of solvents) in the presence of *S*-proline.



1, n = 1
2, n = 2

S-3, n = 1
S-4, n = 2

This study suggested that the asymmetric cyclization of the above triones by the well-known literature[2–4] methods using solvents was also probably a surface reaction. In these methods, a solution of the trione **1** or **2** in a polar aprotic solvent was stirred with catalytic amounts of *S*-proline which remained mostly undissolved and was filtered before work-up. To our surprise, we found using trione **2** that there was no reaction (no λ_{max} at 247 nm) in the absence of the insoluble *S*-proline, i.e. when the stirred mixture of proline and solvent (CH_3CN or DMSO) was first filtered free of undissolved proline and the filtrate reacted with trione **2**. Evidently the cyclization was a surface reaction and we decided to probe into the mechanism of both cyclizations with the aid of high resolution ^{1}H and ^{13}C NMR and also ATR-FTIR techniques. In spite of several studies, the mechanism of chiral transfer in the above cyclizations is still not clear. Hajos and Parrish in their seminal paper[2a] proposed two mechanisms, one involving reaction of *S*-proline with one of the enantiotopic ring carbonyls to give an intermediate carbinol amine **5** followed

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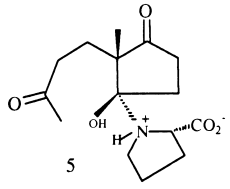
† A part of this work was presented at the 9th International Symposium on Chiral Discrimination (ISCD-97) held at Nagoya, Japan during September 1997.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00174-3

by cyclization and another involving the side chain carbonyl to give the protonated enamine **6** followed by cyclization with one of the diastereotopic ring carbonyls.



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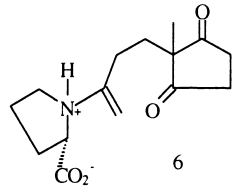


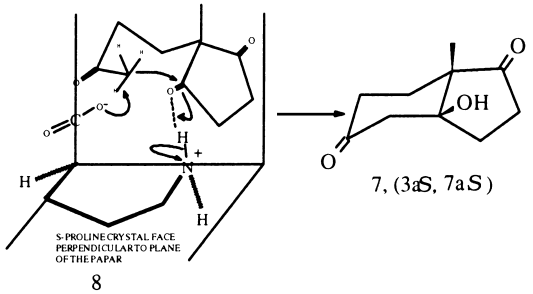
6

Subsequent studies[5] have mostly favoured initial reaction with the side chain carbonyl, though the work of Kasthuri et al.[6] based on some spectroscopic studies casts doubts on the enamine mechanism.

We report here results based on 400 MHz ^{1}H NMR and 100.40 MHz ^{13}C NMR spectra[7a] taken at intervals to follow the course of the reaction of equivalent amounts of triketones **1** (0.25 mmol) and **2** (0.25 mmol) in DMSO-d_6 (0.5 ml) with *S*-proline (0.25 mmol) at 23°C: (a) there is no evidence of the reaction of *S*-proline with the carbonyl groups in both triketones to give enamine or carbinol amine intermediates (in both ^{1}H and ^{13}C spectra); (b) *S*-proline is hardly soluble in DMSO at room temperature since no signals are seen for the proline carbons (weak proton signals are however seen for proline due to moisture associated with DMSO). Since there is no reaction as mentioned above in the absence of undissolved proline, it is obvious that the substrates **1** and **2** can react only on the surface of the insoluble crystalline proline;[8] (c) within 15 min of mixing trione **1** with *S*-proline, one observes carbon signals: ten for (3a*S*,7a*S*) ketol **7**, eight for unreacted trione **1** and seven for DMSO. In the proton spectrum also taken immediately on mixing the reactants and at intervals of 15 min over a 2 h period, only starting trione **1** and ketol **7** show up with no signals for proline as such or in a combined form. The formation of *cis*-ketol **7** is complete in 5 to 6 h with no trace of any other product.

With a view to detect intermediates, if any, which may have escaped detection in our NMR studies, we studied the ATR-FTIR spectra also.[7b] The liquid trione **1** was stirred with an equivalent amount of powdered dry *S*-proline and ATR-FTIR spectra were taken at regular intervals over a period of 40 h. Initially, one observes the twin 1,3 ring C=O absorptions at 1762 cm^{-1} (m) and 1700 cm^{-1} (s), the latter merging with the side chain C=O absorption in addition to proline peaks at 3500 cm^{-1} (NH str. br.), 1557 cm^{-1} (w) (NH_2^+ bending) and 1618 cm^{-1} (-CO_2^-). The C=O at 1762 cm^{-1} gradually disappears and product peaks OH at 3500 cm^{-1} (s), 6-membered C=O at 1701 cm^{-1} and 5-membered C=O at 1741 cm^{-1} show up. There is no absorption for an enamine double bond.

Evidently, ketol formation and transfer of chirality take place simultaneously on the surface of the bifunctional chiral catalyst[9] as pictured in Fig. 1. This shows preferential hydrogen bonding with the pro-*R* carbonyl group which attracts the substrate to the catalyst surface followed by synchronous protonation of the same C=O and deprotonation of the side chain CH_3 by -CO_2^- of proline[10] leading to cyclization.

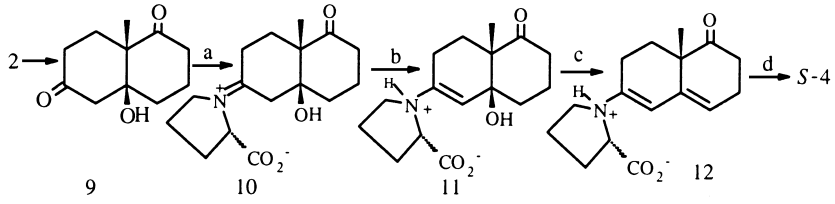


8

7, (3a*S*, 7a*S*)

Figure 1.

In **8** (Fig. 1), the trione is in the plane of the paper, the -CO_2^- and -NH_2^+ of proline are pictured to project from the crystal surface perpendicular to the plane of the paper, suitably aligned for reaction. After the ketol is formed, it is removed from the site by the solvent while the amino acid resumes its zwitterionic form and is ready to ketolize a second molecule of substrate. This process can repeat itself at a particular site a number of times. The crystal surface must function like a template as it contains a number of such active sites where ketolization can take place simultaneously and repeatedly, accounting for the high efficiency of the catalyst. The conformation of *cis*-ketol **7** with an axial -CH_3 and an equatorial -OH has been established by Hajos and Parrish.[2a] With catalytic amounts of proline, even after 10 h, unreacted trione **1** is still present and ketol formation is incomplete, due, no doubt, to the reduced number of active sites. In the heterogeneous system containing insoluble proline and triketone **1** in DMSO solution, the zwitterionic nature of proline must hold all the individual molecules of proline together in the crystal lattice. Only surface reactions[14] such as hydrogen bonding may be expected to lead to the one-step conversion of **8** to **7** (Fig. 1) with excellent enantioselectivity[2a] rather than a multi-step conversion involving intermediates **5** or **6** or their transformation products for none of which we have spectral evidence.[11] The reaction of trione **2** with *S*-proline is more complicated and takes a longer time to complete than in the case of trione **1**. The immediate product on mixing the reactants (within the first 15 min) is the dienamine **12** easily identified by strong signals for the two double bonds (δ 95.23 (C_4); δ 140.37 (C_{4a}); δ 111.07 (C_5) and δ 142.26 (C_6) ppm) besides unreacted trione **2**. A number of other very weak signals, four in the saturated C=O region and three in the -C–OH region, are seen indicating the presence of the known[2c] ketol **9** and other ketols (possibly **10** and **11**, Scheme 1).



Scheme 1.

Within the next 15 min the diketone *S*-**4** shows up besides dienamine **12** which at this stage has stronger signals than dione *S*-**4**. During the next 22 h, the signals for *S*-**4** become progressively stronger than those of **12** and also of starting trione **2**. On continued standing (a week) only signals for *S*-**4** are seen. The proton spectra also taken immediately on mixing the reactants and at intervals of 15 min over a period of 2.5 h and finally after 24 h, confirm the initial formation of dienamine **12** and *S*-**4** whose signals become progressively stronger. The dienamine has absorption at δ 5.2 (t, C_4 vinyl H), δ 4.7 (s, C_5, vinyl H) and δ 4.1 (t, C_2 proline protons); the formation of *S*-**4** is followed by its absorption at δ 5.8 (s, vinyl H). After standing for a week, only signals for *S*-**4** are seen as in the ^{13}C NMR. These data indicate: (i) that unlike in the case of trione **1** where the ketol **7** is the sole product, the ketol **9** is very reactive getting transformed to *S*-**4** via dienamine **12** formed via transformations a → b → c in Scheme 1; (ii) that the conversion of trione **2** to diketone *S*-**4** involves transformations partly on the surface of proline crystals and partly in solution. Scheme 1 is based on Spencer's[12] mechanism of amine-catalyzed β-ketol dehydration. The intermediates **10**, **11** and **12** must be formed on the surface of solid proline and held there because of their zwitterionic nature, limiting their detection in spectra. The ^{13}C NMR signals for **12** are stronger than those of **9**, **10** and **11**, probably because a second molecule of water becomes available after step c to dissolve the bonding of **12** to the proline surface before hydrolysis (step d).

The marked difference in reactivity of ketols **7** and **9** towards *S*-proline may be due to a steroid

conformation for ketol **9** in contrast to the non-steroid conformation for ketol **7**. Some related ketols with steroid-like conformation have been reported.[5]

In summary, spectroscopic studies reveal that the asymmetric cyclization of triones **1** and **2** in the presence of *S*-proline is a template reaction[13] and that the primary reaction products are the *cis*-ketols **7** and **9**, respectively, with different reactivities.

Acknowledgements

The authors thank the Dept. of Science and Technology, Govt. of India for financial assistance.

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7. (a) NMR spectra were recorded on a JEOL 400 MHz GSX model. (b) IR spectra were recorded on a NICOLET AVATAR 360 FTIR EST with Multi Bounce HATR.
8. Dr. Hajos has drawn our attention to US Patent 3975440, 1976 where the synthesis of *S*-**3** without using solvents was reported earlier.
9. Hajos and Parrish reported[2a] that there was no reaction between trione **1** and 2*S*-*trans*-4-hydroxy proline and ruled out any solid state reaction.
10. Similar deprotonation by crystalline salts of carboxylic acids occur in the Perkin reaction.
11. Also, ^{13}C NMR studies of reaction between ketones like cyclohexanone, cyclopentanone and ethyl methyl ketone in DMSO with *S*-proline did not show any evidence of reaction.
12. (a) Ferran Jr., H. E.; Drake, D. A.; Spencer, T. A. *J. Org. Chem.* **1975**, *40*, 2017. (b) Hupe, D. J.; Kendall, M. C. R.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 2271.
13. We can invoke this template mechanism also for the antibody catalyzed enantioselective conversion of trione **2** to *S*-**4** reported recently by Zhong, G.; Hofmann, T.; Lenner, R. A.; Danishefsky, S.; Barbas, C. *J. Am. Chem. Soc.* **1997**, *119*, 8131.
14. We are thankful to the referee for drawing our attention to the following two references where a similar surface reaction has been invoked: (a) Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911. (b) Thoen, J. C.; Lipton, M. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3947.