# A New Diagnostic Tool for Elucidating the Mechanism of Enantioselective Reactions. Application to the Hajos–Parrish Reaction

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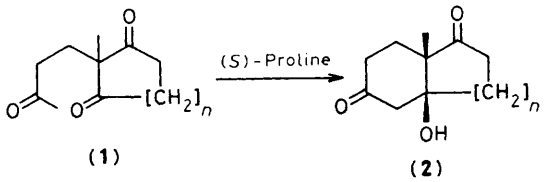
A dilution effect shows that the proline-catalysed Robinson cyclisation involves both enantioselective and non-enantioselective processes, with a different dependence on amino acid concentration.

The Hajos–Parrish reaction[1] presents a most interesting mechanistic problem in the field of enantioselective synthesis (Scheme 1), but only indirect mechanistic studies have been carried out so far, mainly through structural modifications of the catalyst[2] and/or the substrate.[3] We report here direct evidence which provides a clear answer to an essential question: does the transition state of the stereodifferentiating step involve only one molecule of proline?




(1) (2)

**Scheme 1**

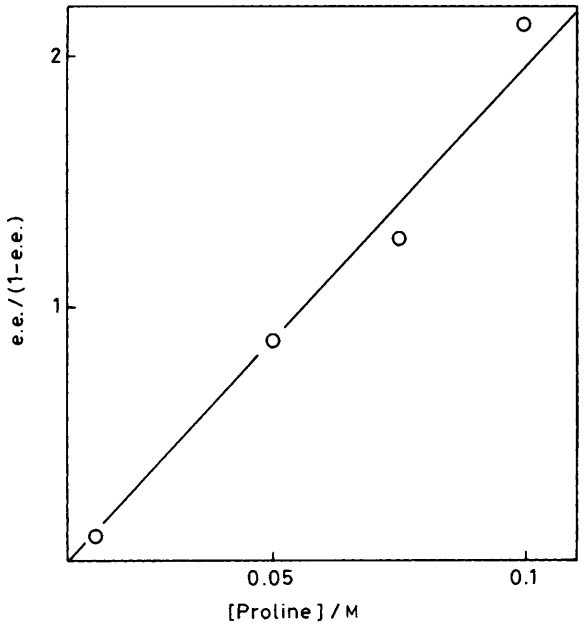



**Figure 1.** Relationship between enantiomeric excess and proline concentration.

**Table 1.** Influence of dilution on the enantioselectivity of the cyclization.[a]

| [(*S*)-proline]/M | % E.e of (**2**; $n$=2)[b] |
|---|---|
| 0.1 | 68 |
| 0.075 | 56 |
| 0.05 | 46 |
| 0.005 | 7 |

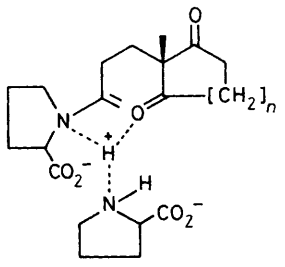
[a] [triketone (**1**)]/[proline] = 20, $Me_2SO$ solution, room temperature; (**2**) was purified by silica gel column chromatography; no crystallisation occurred at any stage. [b] E.e. (enantiomeric excess) values were determined from the specific rotation of the enantiomerically pure ketol (**2**);[1] the proportionality between specific rotations and concentrations was verified by plotting the optical rotations of samples whose optical purities were known *vs.* their corresponding enantiomeric excesses (these samples were obtained from racemic and enantiomerically pure ketol).

A dilution effect indicates that the catalysis by proline needs more than one proline molecule per triketone molecule. A decrease in enantioselectivity resulted from a dilution of both substrate (**1**; $n$ = 2) and catalyst at a constant substrate/catalyst ratio (see Table 1). This effect can be explained by assuming a competition between:
(i) a base- or acid-catalysed non-enantioselective (NE) process whose rate law (1) is first-order in proline concentration;
(ii) an enantioselective (E) cyclisation (2) involving several molecules of proline.

$$\text{rate}^{NE} = k^{NE}_{obs.}\,[\text{proline}]\,[\text{triketone}] \quad (1)$$

$$\text{rate}^{E} = k^{E}_{obs.}\,[\text{proline}]^{x}[\text{triketone}] \quad (2)$$

The possible occurrence of a non-enantioselective process, *i.e. via* the base or the acid properties of proline, is substantiated by the observation of sluggish formation of (±)-(**2**; $n$ = 2) when proline is replaced by either cyclohexylamine or maleic acid whose $pK_a$ values are similar to that of proline. Likewise catalysis by both (*S*)-proline and maleic acid



(A)

(1:1), other things being equal, provided the ketol (−)-(**2**) with very low enantioselectivity: 14% e.e. instead of 68% when (*S*)-proline was the only catalyst.

Plots of e.e./(1−e.e.) *vs.* [proline] are linear (see Figure 1). Assuming (i) that the ideal enantioselective process affords the pure (*S*)-ketol,† and (ii) that the ratio of products deriving from the enantioselective and from the non-enantioselective processes is equal to the ratio of the corresponding rates (both processes are pseudo-first-order in triketone concentration) equation (3) follows. Thus this correlation means that the rate law of the enantioselective process [equation (2)] is second-order in proline concentration ($x$ = 2).‡

$$\frac{\text{rate}^{E}}{\text{rate}^{NE}} = \frac{[(S)]-[(R)]}{2[(R)]} = \frac{\text{e.e.}}{1-\text{e.e.}} = k\,[\text{proline}] \quad (3)$$

These results disclose a fundamental parameter as far as the reaction mechanism is concerned. Obviously the fact that proline shows a multiple catalytic effect makes the enantioselection still more intricate. As hydrogen bonding is indicated by the data available so far,[3] we tentatively suggest that proline has a dual role, as in structure (A). The stereo-differentiation would occur in a three-centre[4] hydrogen-bonded structure involving: (i) the most reactive *pro-R* ring carbonyl group; (ii) an enamine moiety resulting from the reaction between the side-chain carbonyl group and the first proline molecule; (iii) a second proline molecule. This model accounts for the observed *si*-enantioface selectivity,[3] but other models might be equally valid. In the present state of our knowledge, it is probably premature to draw any definitive mechanistic conclusion.

We thank Professors H. B. Kagan and R.Noyori for helpful advice.

*Received, 19th December 1984; Com. 1773*

## References

1 Z. G. Hajos and D. Parrish, *J. Org. Chem.*, 1974, **39**, 1615; U. S. Pat. 3 975 442 (17th Aug., 1976).
2 K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, 1975, **95**, 33; P. Buschschacher, J. M. Cassal, A. Furst, and W. Meier, *Helv. Chim. Acta*, 1977, **60**, 2747; K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, and C. Kratky, *Helv. Chim. Acta*, 1978, **61**, 3108.
3 N. Cohen, *Acc. Chem. Res.*, 1976, **9**, 412; C. Agami and H. Sevestre, *J. Chem. Soc., Chem. Commun.*, 1984, 1385.
4 G. A. Jeffrey and J. Mitra, *J. Am. Chem. Soc.*, 1984, **106**, 5546.

† For brevity major enantiomer (−)-(**2**; $n$ = 2) which has the absolute configuration 4a*S*, 8a*S* is termed *S*.

‡ Strictly speaking, the validity of equation (3) shows that the difference between partial orders in proline concentration in equations (1) and (2) is unity. As suggested by a referee, it can be deduced from Figure 1 that the ratio $k^{E}/k^{NE}$ is about 17.