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STEREOCHEMISTRY-61[†]

AMINO ACID-CATALYZED ENANTIOSELECTIVE DEHYDRATION OF CYCLIC β-KETOLS

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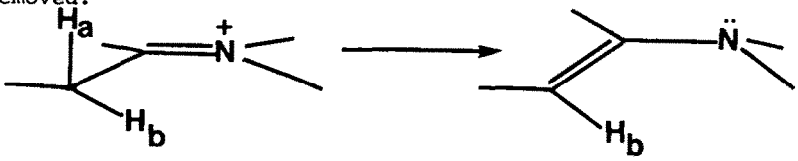
Abstract - Optically active octalones result from dehydration of the corresponding racemic β-ketols catalyzed by (S)-phenylalanine or (S)-proline. According to the nature of the amino acid, opposite enantioselectivities were observed during the kinetic resolutions. Catalysis by proline leads to higher enantiomeric excesses and occurs with greater discrimination between different substrates. A mechanism involving an intramolecular hydrogen transfer mediated by the amino-acid carboxylate group is consistent with the observed selectivities.

The formation of enamines from imine or iminium intermediates is a common process in enzymatic chemistry.[2] It is noteworthy that the corresponding hydrogen-transfers may occur in a stereospecific manner, one of the methylene enantiotopic protons being selectively removed.[3]



We wish to present here a full account of our study of the amino acid-catalyzed β-ketol dehydration which involves such an iminium-enamine conversion.[4] In this reaction, the chiral catalyst induces an enantioselective proton abstraction analogous to that shown by an enzyme-catalyzed reaction, albeit with a lower efficiency.

Catalysis by (S)-phenylalanine

In the course of their elegant synthesis of estrone,[6] Danishefsky and Cain reported that a (S)-phenylalanine-perchloric acid system induces the asymmetric dehydration of a racemic β-ketol: a 8% enantiomeric excess was observed for the enone produced. Pecher *et al.*[7] reported that the dehydration of an optically active β-ketol, whose ee was unknown, leads to an enone with different ee depending on the dehydration catalyst: 36% with (S)-proline and 8% with p-toluenesulfonic acid. These results can be recognized as kinetic resolutions occuring with a very low enantioselectivity.

[†] Previous part in this series, Ref. 1 .

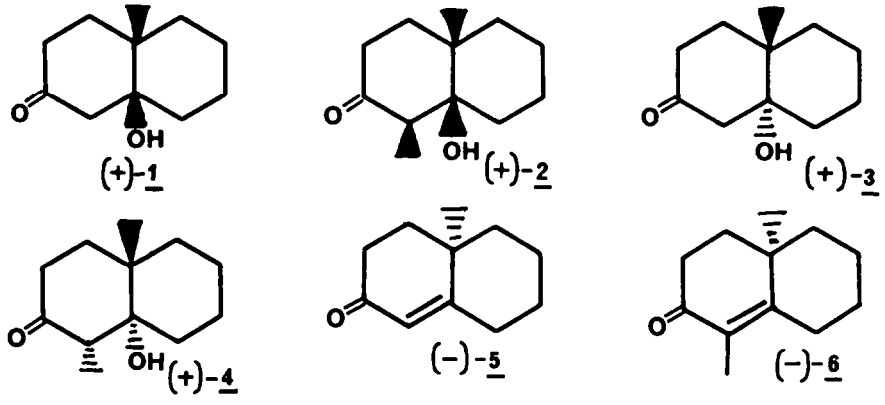
Table 1. Enantioselective ketol dehydrations

Entry	Ketol	Catalyst	Extent of reaction (%)	Enone (%ee)	ρ
1	(±)-1	(S)-Phenylalanine	45	(−)-5 (16)	0.63
2	(±)-2	"	24	(−)-6 (30)	0.50
3	(±)-3	"	22	(−)-5 (4)	0.91
4	(±)-4	"	20	(−)-6 (5)	0.97
5	(±)-2	(S)-Tyrosine	38	(−)-6 (29)	0.58
6	(±)-2	(S)-pNO_2 Phe	22	(−)-6 (27)	0.53
7	(±)-1	(S)-Proline	40	(±)-5	1
8	(±)-2	"	37	(+)-6 (87)	0.04
9	(±)-3	"	43	(±)-5	1
10	(±)-4	"	10	(−)-6 (39)	0.42

Mindful of the fact that the low efficiency of the Danishefsky and Cain experiment could be ascribed to the presence of perchloric acid, which is able to catalyse a non-enantioselective dehydration, we have submitted four racemic β-ketols to dehydration using (S)-phenylalanine as the only catalyst.

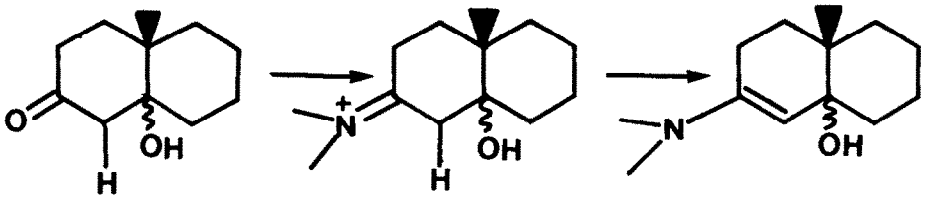
Thus, enone (−)-5 was obtained from ketols (±)-1 and (±)-3 and enone (−)-6 resulted from the dehydration of ketols (±)-2 and (±)-4. The dehydrations were conducted only partially; therefore, the recovered ketols {(+)-1 , (+)-2 , (+)-3 , and (+)-4 } were optically active. The results are summarized in Table 1 (entries 1-4) where the ρ values[8] ($\rho = k_{\text{less reactive enantiomer}}/k_{\text{more reactive enantiomer}}$) indicate the efficiency of the corresponding kinetic resolutions.

Enantiomeric excesses of the enones were determined either by comparing polarimetric measurements with a literature value[9] (enone (−)-5)or by ^{1}H NMR analysis using the chiral shift reagent Eu(dcm)$_3$ (enone (−)-6). Absolute configuration assignements are reported in the literature.[5,9]



According to Spencer's mechanism,[10] the amine-catalyzed ketol dehydration involves an iminium ion intermediate which leads to an enamine with an axial proton[11] being selectively abstracted (Scheme 1). In the amino acid-catalyzed dehydration, the hydrogen-transfer is intramolecularly catalyzed by the internal carboxylate ion. However no significant differences could be detected, as regards enantioselectivity, when phenylalanine (pK_a^{COOH} 1.83) was replaced by either

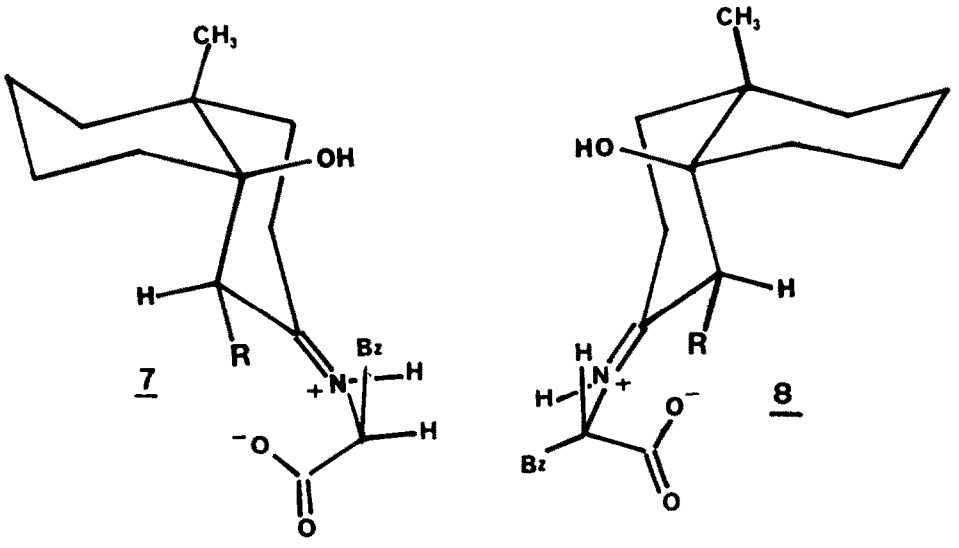
tyrosine (pK_a^{COOH} 2.20) or p-nitrophenylalanine (pK_a^{COOH} 1.60) (Table 1, entries 2,5 and 6). Since the carboxylate group is linked to a chiral center (C-2 of the amino acid) asymmetric induction is thus conceivable.



Scheme 1

The more efficient kinetic resolutions of ketols (±)-1 and (±)-2 deserve an interpretation : ketols (4aR,8aR)(−)-1 and (1R,4aR,8aR)(−)-2 are respectively more reactive than their enantiomers.

The iminium compounds 7 (R = H or Me) are intermediates during the conversion of ketols (−)-1 (R = H) or (−)-2 (R = Me) to the corresponding enones (−)-5 and (−)-6, whereas ketol (+)-1 and ketol (+)-2 led to enones (+)-5 and (+)-6 via the diastereoisomeric iminium compounds 8 .



The greater reactivity of the iminium structure 7 relative to 8 can be explained by assuming a conformational preference which agrees with many staggered models for asymmetric induction.[12] In these models, the reactive conformation is that in which the largest allylic substituent (in the present case, the benzyl group) is perpendicular to a C=C or C=O double bond (Felkin model). The reactive conformations are depicted in Figure 1 in which conformation A (iminium intermediates 7) is lower in energy than conformation B (iminium intermediates 8).

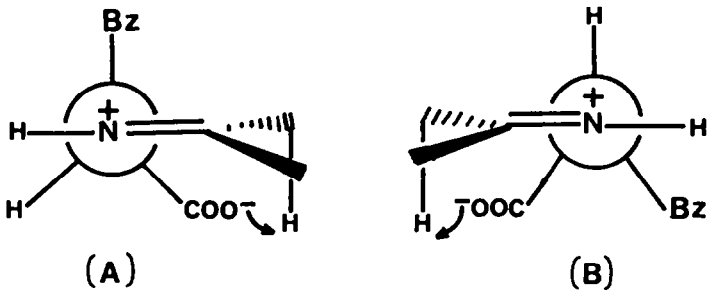
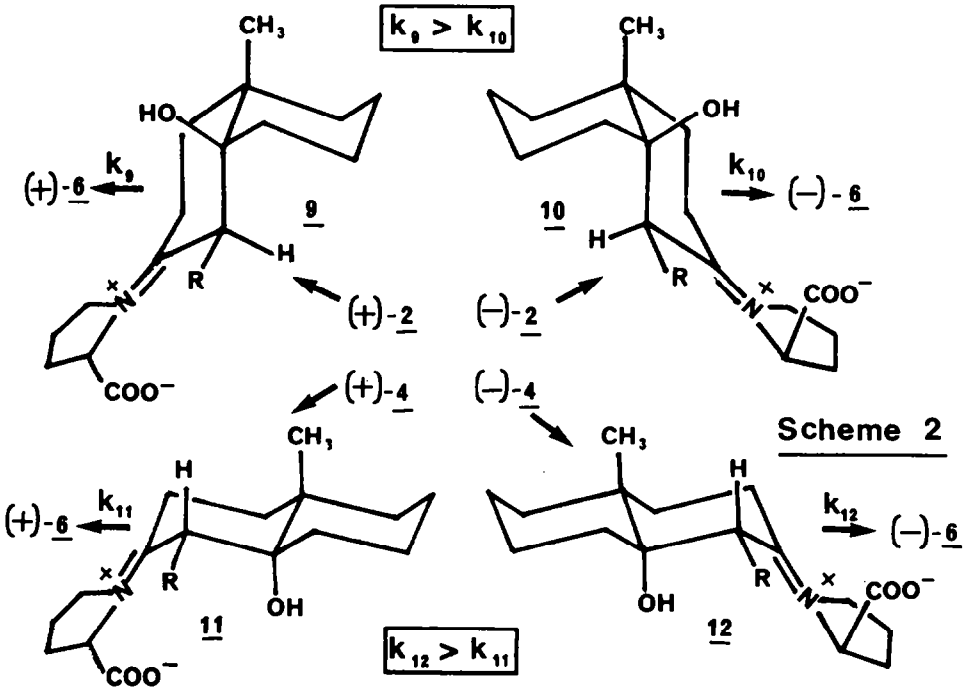


Figure 1. Staggered model depicting the reactive conformations of the phenylalanine moiety, associated with an intramolecular proton abstraction. (A) : Iminium ion intermediates 7 . (B) : Iminium ion intermediates 8 .

Catalysis by (S)-proline

Treated with (S)-proline, as dehydrating catalyst, ketols (±)-1 and (±)-3 gave the racemic enone (±)-5. On the other hand, efficient kinetic resolutions were observed with ketols (±)-2 and (±)-4 which led respectively to the optically active enones (+)-6 and (−)-6. Apart from the fact that phenylalanine and proline catalyzed the asymmetric dehydration of the racemic ketol (±)-2 with an opposite enantioselectivity (compare entries 2 and 8 in Table 1), two points stand out from these results : (i) a methyl group in an α position with respect to the carbonyl group is necessary for an enantioselective reaction to occur, (ii) the cis or trans nature of the ring junction of ketols (±)-2 and (±)-4 is of paramount importance as regards the outcome of the kinetic resolutions.

Owing to the more rigid structure of the proline moiety relative to the phenylalanine moiety in 7 and 8, a straightforward interpretation of the data stand out. Irrespective of the cis or the trans decaline-isomerism, the more reactive enantiomers (+)-2 and (−)-4 both exhibit a S absolute configuration at the C-1 center. Observation of the corresponding iminium intermediates 9 (R=Me) and 12 (R=Me) (compared with 10 (R=Me) and 11 (R=Me)) shows that the H to be abstracted and the COO^- group are in a favored syn relationship in 9 and 12 and in a disfavored anti relationship in 10 and 11 (Scheme 2).



Scheme 2

On the other hand, the proline-catalyzed dehydrations of ketols (±)-1 and (±)-3 occured without any enantioselectivity. This agrees perfectly with the preceding scheme since there are two hydrogen atoms at C-1 in the related iminium ions 9-12 (R=H) : the favored syn relationship can be found in each case between the carboxylate group and the pro S hydrogen of the prochiral methylene group (Scheme 2). It should be noticed that the stereoelectronically favored axial position for the pro S hydrogen to be abstracted can be attained easily from 10 (R = pro S H) by a steroid/non-steroid conversion and from 11 (R = pro S H) via a skew-boat conformation of the ring. Obviously such conformational changes do not modify the syn or anti relative configurations of any of the iminium compounds 9-12 (R=H or Me). Likewise a skew-boat form of the dehydroquinic acid ring was envisaged to explain the syn elimination of water during the dehydroquinase-catalyzed formation of dehydroshikimic acid.[13]

Therefore, in the case of the proline-catalyzed dehydration the enantioselectivity depends on a configurational difference (Figure 2), whereas the enantioselectivity induced by phenylalanine relies on conformational preferences (Fig.1).

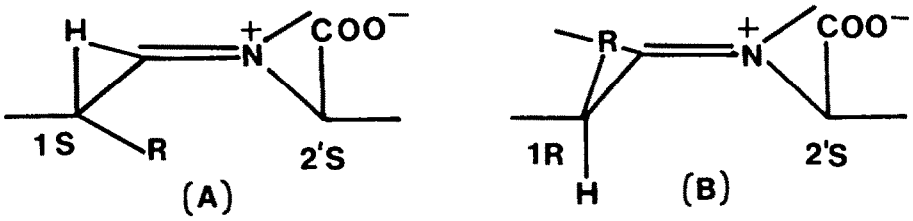


Figure 2. Relative configurations of the chiral C-1 and C-2' centers (proline-catalyzed dehydrations). (A): Syn relationship. (B): anti relationship.

The common mechanistic feature in the amino acid-catalyzed dehydrations reported above is an intramolecular proton transfer mediated by the carboxylate moiety. In a pioneering report, Bender et al.[14] studied the glycine-catalyzed enolization of acetone with the aim to decipher the proton-transfer which occurs during the rabbit muscle aldolase-catalyzed aldol reaction; these authors concluded that water is responsible for the acetone proton-transfer.[15] The difference between our conclusion and that of Bender can be ascribed to the greater rigidity of the decalinic substrates and to the chirality of the catalysts; these two parameters lay down the structural arrangements which are required for the enantioselective dehydrations to occur.

Acknowledgements

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EXPERIMENTAL

The racemic β-ketols 1, 2, 3 and 4 were synthesized according to published[16] procedures. Optical rotations (dioxan solution) were determined with a Perkin-Elmer 421 polarimeter. NMR analysis were performed with a Jeol FX 90 Q spectrometer ($CDCl_3$ solution).

The reported pK_a values of phenylalanine and tyrosine are literature values.[17] The pK_a of p-nitrophenylalanine was measured by titrating a 0.05 N solution of the hydrochloride derivative; owing to the low solubility of the zwitterionic form of the amino acid, the uncertainty raises to 1.60 ± 0.05 (25°C). Since the diacidic and the zwitterionic forms of p-nitrophenylalanine show identical electronic spectra (λ_{max} : 275 nm, ε : 9350, water solution) any spectrometric pK_a measurements

were impossible.

The dehydrations were achieved as follows : an equimolar amount of a given amino acid was added to the racemic β-ketol (0.2g) dissolved in dimethyl sulfoxide (10 mL). The reaction mixture was stirred under argon at 65°C and its evolution was monitored by t.l.c. The final mixture was cooled to room temperature and extracted with ether. The organic extracts were washed with water and dried with Na_2SO_4. The solvent was removed at reduced pressure. The crude material was dissolved in benzene and chromatographed on Merck Silica Gel 60. Elution with petroleum ether (bp 35-70°C) - ether mixtures gave the enone and the recovered ketol.

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