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On the mechanism of chiral aldol cyclization reaction

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Abstract. Spectroscopic studies (^1H and ^{13}C NMR, fluorescence and UV) of 2-[3-(*p*-methoxyphenyl)- 3-ketopropyl]- 2-methyl -cyclopentane-1, 3-dione in the presence of *l*-amino acids and *l*-N-acetylphenylalanine ethyl ester indicated the possible involvement of a molecular association complex in the transition state of the amino acid catalyzed chiral aldolization of prochiral triketones to yield useful steroidal intermediates.

Keywords. Chiral intramolecular aldolization ; molecular association ; bifunctional catalysis ; ^{13}C and ^1H NMR ; fluorescence quenching ; ultra violet ; hydrogen bonding ; noncovalent interaction.

1. Introduction

The chiral aldol cyclization of the prochiral triketone (1) to the chiral diketone (2) has been utilized in a number of recent steroid syntheses (Cohen 1976 and references therein : Shimizu *et al* 1980) employing naturally occurring amino acids and their derivatives as the chiral catalysts. The mechanism of the transformation is still uncertain, although a few probable modes have been suggested. In an earlier review, (Sarkar *et al* 1979) we pointed out the discrepancies in the postulated enamine intermediate (Danishefsky and Cain 1976) because it does not explain (a) lack of efficient chiral induction by amino acid derivatives * although they possess the same chirality as that of the parent amino acids ; (b) role of free carboxylic function in chiral recognition or participation in the chemical process and (c) enhanced chiral induction with amino acids possessing side chains of similar dimensions as that of the acyclic portion of the triketone. It was therefore conten-

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† Synthetic studies with *l*-histidine methylester hydrochloride, *l*-dehydroabietylamine and brucine as catalysts in the cyclization of 1 ($R = CH_3$) also indicated that a chiral amine providing a chiral environment is not sufficient for substantial chiral induction (Sarkar 1982).

ded that bifunctional catalysis involving a molecular association between the substrate and the catalyst would be a more probable mechanism ; the free energy of activation associated with the transition state could be largely compensated by molecular complexation (catalysis) and the chiral bias could be due to the chirality of the catalyst. The transition state has been schematically represented as 3. The mechanism accounts for (a) less degree of chiral induction with amino acid derivatives ; (b) role of the Zwitterionic structure of the amino acid in the catalytic function and (c) the recognition of residual (nonfunctional) segments of the amino acid and the substrate for greater chiral induction. This paper deals with the results of the spectroscopic studies carried out to investigate the presence and the nature of the intermediate species and their role in this chiral transformation.

2. Design of model substrate

It was recognized at the outset that while the structure of an intermediate could be studied conveniently by spectroscopic techniques, a transition state involving bifunctional catalysis would not be amenable for such direct observations. Hence a substrate (4) (Buchowieski and Zajac 1979) was synthesized such that the intermediate or molecular complex could be formed, but further reaction leading to the formation of the product was precluded by the absence of a centre for cyclization. The molecule (4) possessed all the functionalities of the triketone (1) to facilitate the formation of a related intermediate or molecular complex, while the aromatic group in the triketone (4) provided an ideal internal probe to be monitored by spectroscopic techniques. The tacit assumption was that the specific conformation of the intermediate or complex thus identified, would satisfactorily approximate the geometry of the transition state structure.

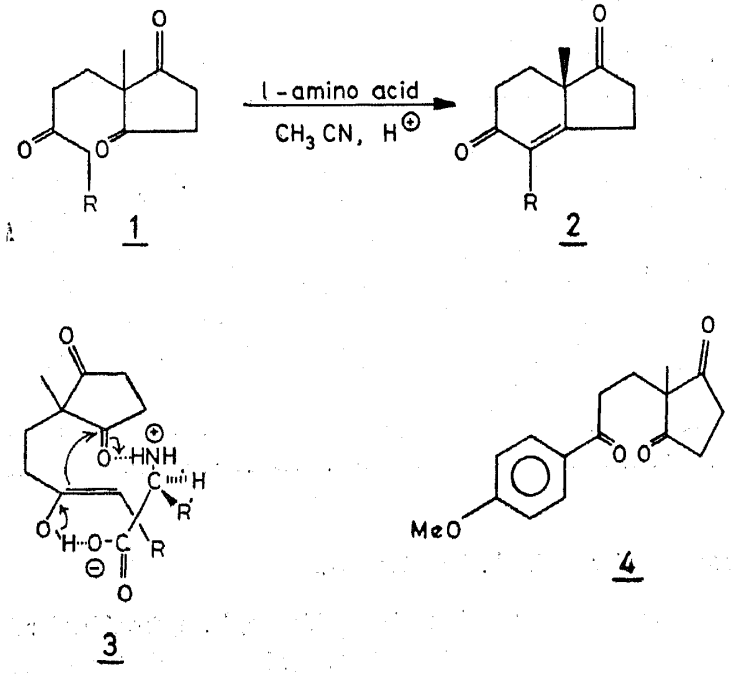

Chart 1

3. Experimental

3.1. *Preparation of* 2-[3-(*p-methoxyphenyl*)-3-*ketopropyl*]-2-*methylcyclopentane*-1, 3-*dione*

β-Diethylamino-*p*-methoxy-acetophenone (7·8 g) and 2-methylcyclopentane-1, 3-dione (4·2 g) in 40 ml of xylene containing 10 ml of pyridine was heated under reflux for 24 hr. The solution was cooled, diluted with chloroform, washed with dil. HCl, water, aq. $NaHCO_3$ and water and dried over anhydrous Na_2SO_4. The solvent was removed and the residue crystallized from hexane-benzene to furnish the triketone (4) as a white crystalline solid, m.p. 101° (6·3g, 69%). IR(nujol) : ν_{max} 1770, 1725, 1675, 1615 and 1580 cm^{-1}; NMR ($CDCl_3$): δ 1·20 (s, CH_3, 3H), 2·03 (t, $—COCH_2CH_2—$,2H,J = 7 Hz) 2·83 (*s*, ketomethylenes, 4H), 2.92 (*t*, $—COCH_2CH_2—$, 2H, J = 7 Hz), 3·83 (*s*, Ar—OCH_3, 3H), 6·90 (d, Ar—H, 2H, J = 9 Hz), 7·86 (d, Ar—H, 2H, J = 9 Hz). Concurrent to our work, a patent describing the preparation of this compound was published, which was quoted in a subsequent publication (Kasturi *et al* 1982) from our laboratory.) Analysis : C 69·68, H 6·87 ; $C_{16}H_{18}O_4$ requires C 70.05, H 6·61%.

3.2. *Spectroscopic studies*

Although the cyclization reactions were generally carried out in CH_3CN or DMF in the absence of water, an 80% (v/v) $CH_3CN—H_2O$ ($CD_3CN—D_2O$ for NMR) solvent mixture was used throughout the spectral study. The addition of water to the medium was necessary due to the low solubility of amino acids in organic solvents, while the possible disruption of the balance between the hydrogen bonding and the hydrophobic association restricted the amount of water added.

The ^{13}C NMR spectra were recorded in a Bruker 270-WH FT NMR machine (operating at 67·89 MHz) in CD_3CN-D_2O (80%, v/v) solution containing TMS as the internal standard. The broad-band decoupled spectrum was obtained with proton noise decoupling at 270 MHz while the off-resonance decoupled spectrum was recorded with single frequency irradiation at *ca.* -5δ (highfield region from TMS) with the decoupler power of *ca.* 2 watts and pulse interval of 3 sec.

The emission spectra of *l*-phenylalanine and *l*-N-acetylphenylalanine ethyl ester were recorded in the presence of various concentrations of the triketone (4) in a Perkin-Elmer fluorimeter Model MPF-44.

The ^1H NMR spectra were recorded on a Varian T-60 machine with CD_3CN-D_2O (80%, v/v) as the solvent using TMS as the internal standard.

The UV spectra were recorded in a Beckmann UV and visible recording spectrophotometer Model 26 using CH_3CN-H_2O (80%, v/v) as the solvent. The reference solution always contained equal amount of the amino acid component to cancel the additive contribution to the absorbance of the sample under study.

4. Results and Discussion

The ^{13}C NMR spectrum of the compound (4) exhibited two distinct carbonyl signals, well separated for identification. On addition of the amino acid, the formation of the intermediate should be directly observable by the emergence

of new peaks in the higher field at the expense of the carbonyl peak intensity. This would immediately indicate; (i) which carbonyl was affected and (ii) what type of intermediate was formed (this technique was successfully applied to a study of the interaction between pyridoxal and *l*-alanine and reported in the literal ture : see Jo *et al* 1977). In this case, a gradual downfield shift of the carbony carbon with the emergence of no new shielded carbon signal was observed for the triketone (4) in the presence of different quantities of *l*-phenylalanine (this amino acid was chosen for maximum nonbonding stabilizing interaction in the complex or the intermediate). It was confirmed from the peak print-out that the signals of all other carbons of the compound (4) remained almost unaltered while the carbonyl signals were shifted downfield consistently (table 1). Absence of new signals ruled out the presence of carbinolamine/Schiff's base/enamine in the solution—a fact also supported by the UV studies, as described later. The observed downfield shift was therefore attributed to hydrogen bonding (Stothers 1972) involving the carbonyl groups and the protonated amino function of the amino

Table 1. Changes in the chemical shifts of different carbons of (4) (0·9 M) in the presence of different concentrations of *l*-phenylalanine in CD_3CN–D_2O (80%, v/v) with TMS = 0 ppm.

Concentration of *l*-phenylalanine (M)	Δδ					
	5-membered ring carbonyl	P-OMe-Ar-CO	Ar–C–OMe	$Ar–OCH_3$	Ring methylenes	Angular methyl
	δ = 218·805	δ = 199·894	δ = 164·677	δ = 56·328	δ = 35·620	δ = 19·003
0·09	+ 0·496	+ 0·186	— 0·031	+ 0·032	— 0·031	0
0·12	+ 0·741	+ 0·378	+ 0·031	+ 0·029	0	+ 0·031
0·15	+ 1·674	+ 0·744	+ 0·062	+ 0·031	0	+ 0·093

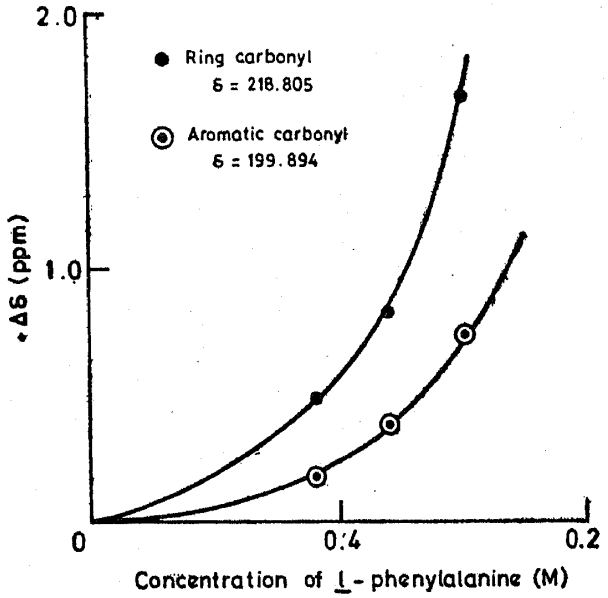

Figure 1. Change in the chemical shift of the carbonyl signals of the compound (4) with different concentrations of *l*-phe.

acid. This further indicated that the complexation is a fast exchanging process on NMR time scale. The comparatively large shift noticed for the cyclopentanedione carbonyl signal indicated a preferential binding at that site (figure 1).

If the hydrogen bonding envisaged above is significant in the stabilization of the complex, the prevention of efficient hydrogen bonding would definitely impair the complex formation. Thus, quenching (Udenfriend 1962) of an amino acid, *l*-phenylalanine (which permits both hydrogen bonding and nonbonding interaction) would proceed with a higher efficiency than an amino acid derivative, *l*-N-acetylphenylalanine ethyl ester (which permits nonbonding interaction but not hydrogen bonding) with the same substrate (4). The fluorescent properties of these two substances were studied in the presence of various concentration of the triketone (4) ,a nonfluorescent compound. The results are shown in figure 2. In both the cases, there had been progressive quenching with the increasing concentration of the triketone (4). The plots for the quenching process indicated comparable quenching efficiency in both the cases. This observation implied the formation of a charge-transfer complex in the excited state, probably resulting from the stacking of the aromatic rings. Such a position evidently called for a considerable proximity of the two aromatic rings in the complex, though the importance of hydrogen bonding for the complex formation was not definitively reflected in the above observations.

The 60 MHz ^{1}H NMR spectra of the triketone (4) in the presence of *l*-phenylalanine further corroborated the stacking phenomenon in the ground state. The stacking interaction results in an upfield shift of the aromatic proton signals (Chan *et al* 1964). This was observed for the aromatic signals of both the molecules (figure 3).

The decrease in the absorbance of the chromophoric group in the substrate in the presence of an added reagent had been used as a criterion for the complex

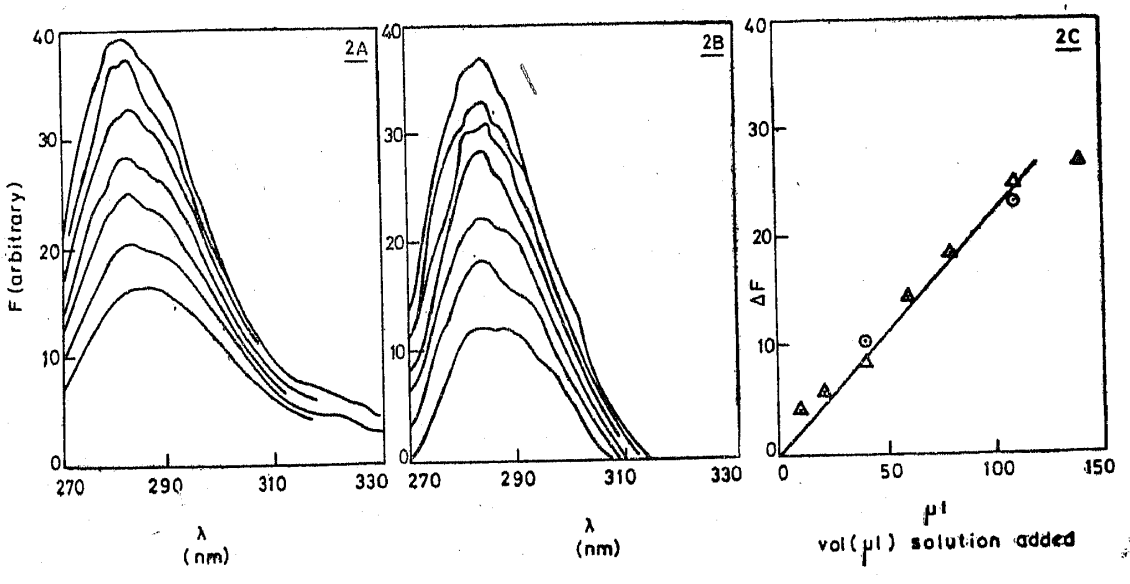

Figure 2. (A) The emission spectra of *l*-phe (3×10^{-4} M) excited at 257 nm in presence of various volumes of added (4) (B) The emission spectra of the *l*-phe ester amide (3×10^{-4} M) excited at 257 nm in presence of various volumes of added (4 (C) The plot of change of fluorescence intensity (–*l*-phe, △-ester) as the function of volume (μl) of (4) added; the conc. of (4) has been kept constant at 10^{-4} M throughout.

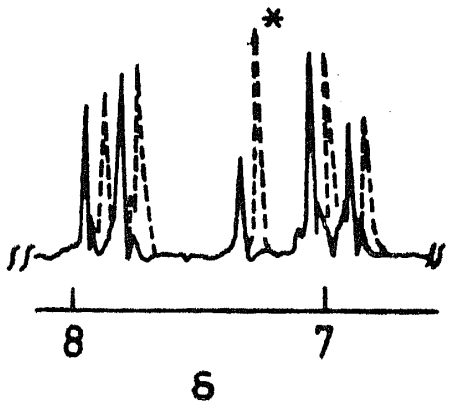

Figure 3. The 60 MHz ^{1}H NMR Spectra (low field region) of the triketone (4) (0·4 M) in CD_3CN–D_2O (80%, v/v) in the presence of (i) 0·05 M *l*-phe (- -) (ii) 0·15 M *l*-phe (- - -). The peak marked asterisk corresponds to the aromatic proton of *l*-phe.

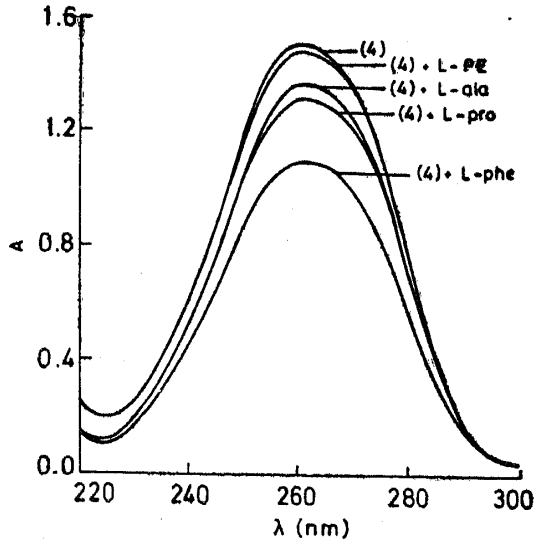

Figure 4. The UV spectra of the triketone (4) alone ($0·8 \times 10^{-4}$ M) and in the presence of amino acids ($2·0 \times 10^{-4}$ M). PE = *l* — N — acetyl phenyl alanine ethyl ester.

formation between the two (Eisenberg and Crothers 1979). To assess the relative importance of the hydrogen bonding and the nonbonding interaction in stabilizing the complex, a comparative study of the UV absorbance of different mixtures of triketone (4) with various amino acids and an amino acid derivative, was undertaken (1 : 2 M) (figure 4). The decrease in the absorbance without any significant change in the spectra recorded under identical conditions again confirmed the absence of a discrete intermediate and the presence of a molecular association complex. The decrease in the absorbance was maximum for l-phenylalanine, while for others it was much less significant. The greater change in the absorbance was indicative of a stronger complexation between the triketone (4) and l-phenylalanine, stabilized both by hydrogen bonding and nonbonding interaction.

5. Conclusion

The present investigation demonstrated (a) no intermediatec arbinolamine/Schiff's base/enamine was formed between the triketone (4) and the amino acid, (b) a molecular complex stabilized both by hydrogen bonding and nonbonding interactions was definitely formed under the reaction condition of aldol cyclization (such nonbonding interactions contributing to the specific orientation of the molecules in hydrogen bonded association complexes in nonpolar solvents, was demonstrated earlier; see Breslow 1972) and, (c) the hydrogen bonding was crucial for the formation of a stable complex, while the stacking interaction alone could not bring about a complexation of appreciable stability.

Thus, assuming the factors operative in the stabilization of the above molecular complex under the simulated reaction condition are practically the same as those relevant for the transition state of the chiral intramolecular aldolization, the above observation is in favour of the proposition of bifunctional catalysis as depicted in 3. The manifestation of a molecular complexation catalyzing intramolecular chiral cyclization, to the best of our knowledge, is identified for the first time in the present case.

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