# Asymmetric Transformations in Keto-Enol Systems

MOHSIN A. KHAN AND A. M. KHAN

*Chemistry Department, Karachi University, Karachi -32, Pakistan*

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**Summary:** Potentially optically active but labile compounds exhibiting keto-enol tautomerism are studied with a view to select suitable material for the realization of asymmetric transformations.

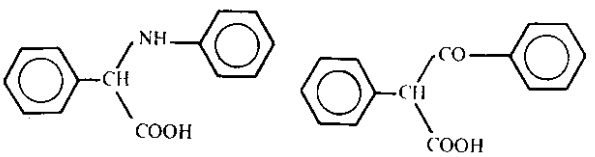
## Introduction

Asymmetric transformations are usually shown by compounds in which optical lability is due to either i) relaxation in restriction of rotation around a single bond or ii) keto-enol process. Although numerous compounds in which optical lability is of the former type (e.g. biphenyls, amine derivatives and related compounds) have been found to undergo asymmetric transformations, very few cases of asymmetric transformations are reported with those in which the optical lability is of latter type[1-5]. The explanation forwarded is that the selection of material is much easier in biphenyl and amine derivatives since asymmetric transformation is caused by a purely physical process. Therefore, a careful assessment of steric and electronic effects of substituents enables one to predict, with reasonable accuracy, the extent of optical lability in these compounds[2,3]. Such a prediction is not possible in keto-enol compounds since the process involved is dynamic.

During a study on optical induction of substituted malonamic and malonanilic acids it was, however, felt that the substituents do have some effect on the mobility of enolic hydrogen and, therefore, the optical lability of compounds exhibiting keto-enol tautomerism[5]. Support to this observation is available from the work of McKenzie[6] on similar compounds. In view of the meager data available on asymmetric transformations of keto-enol compounds, these observations cannot be used at this stage to make generalizations regarding the effect of substituents on the extent of optical lability and, therefore, the asymmetric transformation. It is clear that stronger the electron withdrawing effect of the groups attached to the asymmetric carbon, the greater will be the optical lability of the substance. The problem, however, is not only to determine if a compound is labile, but also to assess the *extent* of optical lability in these compounds. This would only be possible after sufficient data has been accumulated to make a generalization or hypothesis. The purpose of this study was to seek new keto-enol compounds and to see if our previous observations could be used to serve as a guideline in the selection of suitable materials for asymmetric transformations.

## Results and Discussion

In order to make meaningful comparisons with the past work on such compounds[5-10], compounds I and II were selected for trials:




I II

Equivalent quantities of acids (I) or (II) with quinine, cinchonine, cinchonidine and strychnine did not show any mutarotation in solvents in which either the acid or the base was soluble (e.g. acetone, chloroform, methanol, and dioxan). The alkaloidal salts being quite soluble in these solvents were, therefore, obtained either by the concentration or complete removal of the solvent at room temperature and in some cases by the addition of ligroin (40-60°). These salts did not exhibit any mutarotation when dissolved in solvents other than those from which they were originally obtained and gave back the original inactive acid on decomposition thus indicating that neither "asymmetric transformation by crystallization". nor "asymmetric transformation in solution" was taking place[2,4]. However, when the experiments were repeated with brucine using methanol and chlorofrom, similar results were obtained. In an acetone solution, however, equivalent amounts of the racemic acid (II) and brucine exhibited mutarotation which was not observed with the racemic acid (I). The mutarotated solution of (II) was evaporated off and the residue decomposed. The product was characterized (m.p. and mixed m.p.) and found identical to the original inactive acid thus proving that mutarotation is the

result of displacement of equilibrium of the diastereoisomers leading to "asymmetric transformation in solution" and not due to any other chemical change (e.g. decarboxylation[11]).

The failure of (I) to undergo asymmetric transformation is not very surprising since it was found optically stable enough to be resolved[12] through cinchonine in ethanol. Still this acid was selected for study because it seemed likely that it may be optically labile in other solvents and with other alkaloids. For example, the alkaloidal salts of phenylhalogenacetic acids are stable enough and may be resolved whereas their menthyl and bornyl esters undergo asymmetric transformations[13,14]. Here it may be argued that in the former case the labile acid and the activating agent are separated from each other (being ionic in nature) whereas in the latter case they are linked together. However, some formal bonding between them is not necessary for asymmetric transformation to take place[1-4] because asymmetric transformation takes place in ionic salts and also through the recrystallization of racemic labile compounds with optically active solvents[15,16].

The failure of (I) in responding to optical activation once again brings home the fact that for asymmetric transformation to occur, a compound should not only be labile (by virtue of a mechanism for the interconversion of the antipodal forms) but its optical lability should be of some exact order; a little less lability and the compound would be stable and, therefore, not suitable for these studies; a little more lability and the enantiomers would invert instantaneously making the detection of asymmetric transformation impossible.

The mutarotation (due to partial inversion) of brucinyl-II obeyed first-order kinetics so that the rate constant $k$ was obtained from the slope of log plot of $\alpha_t - \alpha_{\infty/t}$ and the Arrhenius parameters from the slope of log $k$ against $T^{-1}$ following the simplified form[17] of the absolute rate equation[18]. The rate constants and corresponding half-life periods are given in Table I and the Arrhenius and transition state functions are shown in Table II.

Table I *The Rate of Partial Inversion for Brucine-2-benzoyl-2-phenylethanoate in acetone*

| Temp (°C) | $k$ $min^{-1}$ | $t_{½}$(min) |
|---|---|---|
| 17 | $5.31 \times 10^{-4}$ | 1303 |
| 22 | $1.04 \times 10^{-3}$ | 624 |
| 27 | $2.03 \times 10^{-3}$ | 315 |

Table II *The Arrhenius and Transition-State Parameters for the Partial Inversion of Brucine-2-Benzoyl-2-phenylethanoate in acetone*

| | | |
|---|---|---|
| $E_A$ | = | 99.6 $JK^{-1}$ $mol^{-1}$ |
| log A | = | 14.6 $s^{-1}$ |
| $\Delta S^*$ | = | 16.7 $JK^{-1}$ $mol^{-1}$ |
| $\Delta H^*$ | = | 97.2 $JK^{-1}$ $mol^{-1}$ |
| $\Delta G^*$ | = | 102.0 $JK^{-1}$ $mol^{-1}$ |

## Experimental

(i) 2-Anilino-2-phenyl-ethanoic acid was obtained from the method of McKenzie and Bates[12]. Recrystallized from benzene, m.p. 174-5° (Found C, 74.0; H, 5.8; N, 6.2%. $C_{14}H_{13}O_2N$ requires C, 73.9; H, 5.8; N, 6.2%)

(ii) 2-Benzoyl-2-phenyl-ethanoic acid was prepared from the acylation of phenylacetonitrile followed by stepwise hydrolysis of the ester[19] and the cyano[20] groups, m.p. 134-5°. (Found C, 74.9; H, 5.0%. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%).

(iii) The solvents used in the experiments were the 'ANALAR' grade reagents.

(iv) The alkaloids used were the commercially available chemicals.

*Activation Experiments:*

The general procedure and techniques used are the same as described in the previous paper[5].

(i) *With Cinchonine:*

A solution of (±)-acid I (4.5 g). or (±)-acid II (4.8 g.) was treated with cinchonine (5.9 g.) in ethyl acetate (300 ml.) and dimethyl sulphoxide (20 ml.). No solid separated on usual work up. Addition of ligroin (40-60°) gave the solid salt (80-90%) with constant rotations $[\alpha]_D^{20}$ + 143° and + 140° (MeOH) respectively; and $[\alpha]_D^{20}$ + 80 and + 82° (acetone) respectively. Decomposition gave back the original inactive acid (m.p and mixed m.p.). Similar results were obtained on repeating the experiments in dioxan (200 ml.), chloroform (100 ml.), acetone (100 ml.) and ethanol (200 ml.)

(ii) *With Cinchonidine:*

The above experiments were repeated using cinchonidine (3.0 g.) and (±)-acid I (3.87 g.) or (±)-acid II (4.0 g.). Again the salts (80-90%) obtained had cons-

tant rotations $[\alpha]_D^{20}$ -74° and -78° (MeOH) repectively which gave back the original inactive acid on decomposition (m.p and mixed m.p.)

(iii) *With Quinine:*

Similar experiments as described in (i) were repeated using quinine (3.2 g.) and (±)-acid I (2.27 g.) or (±)-acid II (2.4 g.) in acetone (50 ml.) and chloroform (25 ml.). Again the alkaloidal salts (85-90%) were obtained which had constant rotations $[\alpha]_D^{20}$ -110° and -113° (MeOH) respectively. These salts on decomposition gave back the original inactive acids (m.p and mixed m.p.).

(iv) *With Strychnine:*

Experiments as in (i) were repeated with (±)-acid I (2.83 g.) or (±)-acid II (3.0 g.) and strychnine (4.2 g.) in acetone (200 ml.), chloroform (200 ml.) or dioxan (100 ml). The salt obtained (82-90%) had constant rotations $[\alpha]_D^{20}$ - 26° and -27° (MeOH) respectively which gave back the original inactive acid (m.p. and mixed m.p.) on decomposition in chilled ethyl alcohol (20 ml.) with 10% NaOH solution followed by filteration and acidification with 6N HCl.

(v) *With Bruchine:*

Experiments (i) were repeated using (±)-acid I (2.85 g.) or (±)-acid II (3.0 g.) and brucine (4.9 g.) in chloroform (200 ml.), methanol (150 ml.) or dioxan (100 ml.). The alkaloidal salts being highly soluble in these solvents were obtained by the addition of ligroin (40-60°). These salts did not exhibit any mutarotation in (a) methanol and (b) chloroform solutions and gave back the original inactive acid (m.p. and mixed m.p.) on decomposition.

Brucine (0.98 g.) and (±)-acid I (0.056 g.) were dissolved to 10 ml. in acetone. The solution had a constant rotation (α -0.05°). On repeating the experiment with (±)-acid II (0.06 g.) the solution containing the same amount of brucine and acetone showed an initial rotation of α -0.48° which changed to α -1.25° on standing overnight.

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