CHEMISTRY LETTERS, pp. 341-344, 1982. © The Chemical Society of Japan 1982

ALKYL-PHENYL INTERACTION IN ENANTIOMER DIFFERENTIATING ACYLATION

Yuji HIRAKI and Akira TAI
Institute for Protein Research Osaka University, Yamada-oka, Suita,
Osaka 565

The enantiomer-differentiating acylation (kinetic resolution) of α-substituted benzylamine with (*S*)-2-phenylbutyric acid anhydride was carried out in organic and aqueous media. (*R*)-Amines reacted in excess in organic media, while (*S*)-amines reacted in large excess in aqueous media. These differences in the chiral recognition were interpreted based on the idea that the attractive interaction took place between phenyl and alkyl groups in aqueous media.

We wish to report here a drastic change in the chiral recognition of the enantiomer-differentiating acylation (kinetic resolution) on changing the reaction media from organic to aqueous solvent systems, explicable by the specific interaction between phenyl and alkyl groups in the reactant molecules.

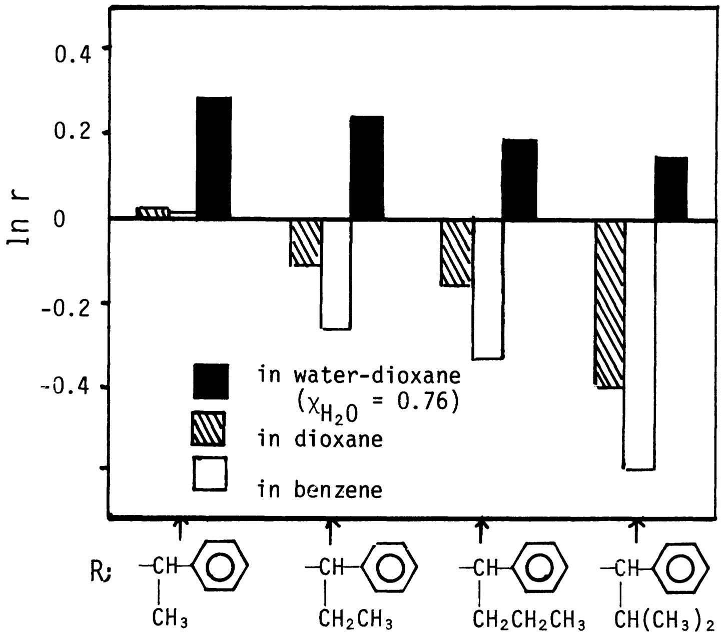

Fig. 1. Enantiomer-differentiating acylation of α-alkylbenzyl amines with (*S*)-2-phenylbutyric anhydride (R^0=$-CHPhCH_2CH_3$)

Racemic α-substituted benzylamine homologues(4 molar equivalent) were treated with (*S*)-2-phenylbutyric anhydride (1 molar equivalent) in dioxane, benzene, or water-dioxane mixture (χ_{H_2O} = 0.76) as shown in Eq. 1). The results of the chiral recognition were expressed by the logarithmeric molar ratio of the diastereomers produced.[1)]

As shown in Fig. 1, ln r values shifted from the almost zero to the appreciably negative values with increasing size of alkyl group from methyl, ethyl, n-propyl to iso-propyl group in organic media.[2)] The result is in the same line with those found in

$$\begin{array}{l} (R)\text{-R-NH}_2 \\ (S)\text{-R-NH}_2 \end{array} + (S)\text{-}(R^0\text{-CO})_2O \longrightarrow \begin{array}{l} (R,S)\text{-R-NHCOR}^0 \\ (S,S)\text{-R-NHCOR}^0 \end{array} \qquad (1)$$

$$\ln r = \ln([(S,S)\text{-R-NHCOR}^0]/[(R,S)\text{-R-NHCOR}^0]) \qquad (2)$$

the literatures[3)] indicating the contribution of steric effect of hydrocarbon residue to the chiral recognition.

However the chiral recognition in the aqueous media showed clear contrast to that in organic media. In all cases, the positive ln r values were obtained. The mode of interaction other than the steric interaction was expected to take major part in the chiral recognition in aqueous media.

In order to make clear the interaction between various types of hydrocarbon residues contained in the reagent and substrate, the competitive acylation of two monofunctional amines with acid anhydride was carried out in water-dioxane mixed solvent system as a model reaction (Eq. 3). The selectivity of the competitive reaction was expressed by logarithmeric molar ratio of the products (Eq. 4).[1)]

$$\begin{matrix} R^{1}NH_2\text{(2 molar equivalent)} \\ R^{2}NH_2\text{(2 molar equivalent)} \end{matrix} + (R^{0}CO)_2O\text{ (1 molar equivalent)} \longrightarrow \begin{matrix} R^{1}NHCOR^{0} \\ R^{2}NHCOR^{0} \end{matrix} \qquad (3)$$

$$\ln r' = \ln([R^{1}NHCOR^{0}]/[R^{2}NHCOR^{0}]) \qquad (4)$$

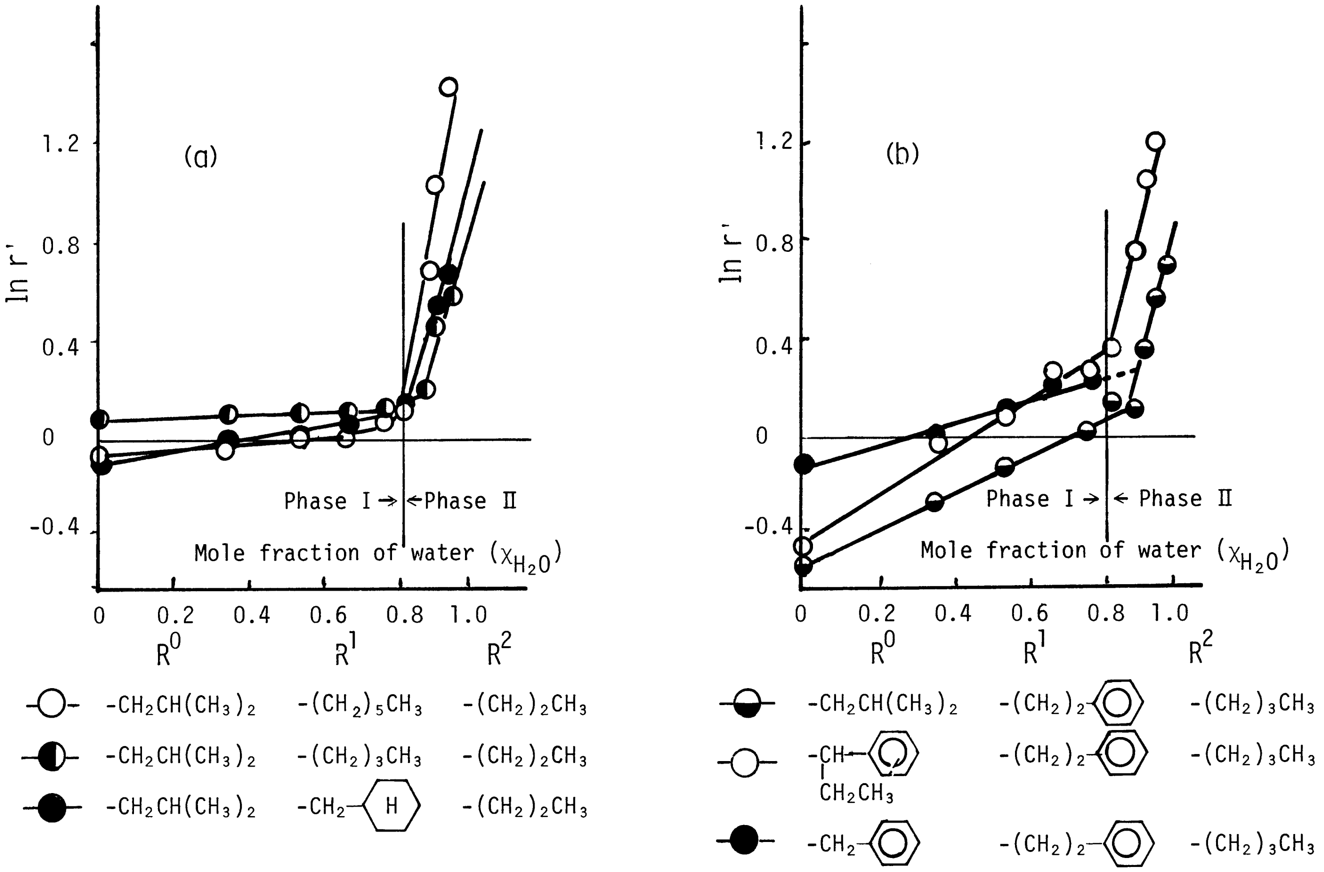

Fig. 2. The relationship between χ_{H_2O} and the ln r' value of the competitive reaction shown in Eq. 3.

As found in Fig. 2, the profile of plots was apparently composed of two phases; i. e., phase I ($\chi_{H_2O} < 0.83$) and phase II ($\chi_{H_2O} > 0.83$). In phase I, the reaction took place under homogeneous condition, while in phase II the phase separation of the reagent occured and the reaction proceeded heterogeneously. The reaction in phase I will be discussed here, because we are chiefly concerned with the molecule to molecular interaction between reagent and substrate under the homogeneous condition.

As found in Fig. 2a, the ln r' values stayed not far from zero within phase I so far as the reagent and substrates carried the saturated hydrocarbon residues, even if the plot —●— showed slight increase in ln r' from the negative to the positive values. The result suggested that there were no significant interactions between the saturated hydrocarbon residues of the reagent and competing substrates in aqueous solvent system as well as the organic solvent.

When an aromatic hydrocarbon residue was contained within one of the competing substrates, the ln r' was remarkably increased with the increase of χ_{H_2O} (Fig. 2b, plot —◒— and —○—). Thus, the amine carrying phenyl group was preferentially converted into amide in aqueous media. These characteristic changes of ln r' could be attributed to the alkyl-phenyl and phenyl-phenyl attractive interaction induced between the reagent and substrates in aqueous media. The gentle gradient of the slope of the plot —●— suggested that the participation alkyl-phenyl interaction was almost comparable to that of the phenyl-phenyl interaction.5) When the reagent carried both alkyl and phenyl group(plot —○—), the ln r' became more sensitive to the addition of water.

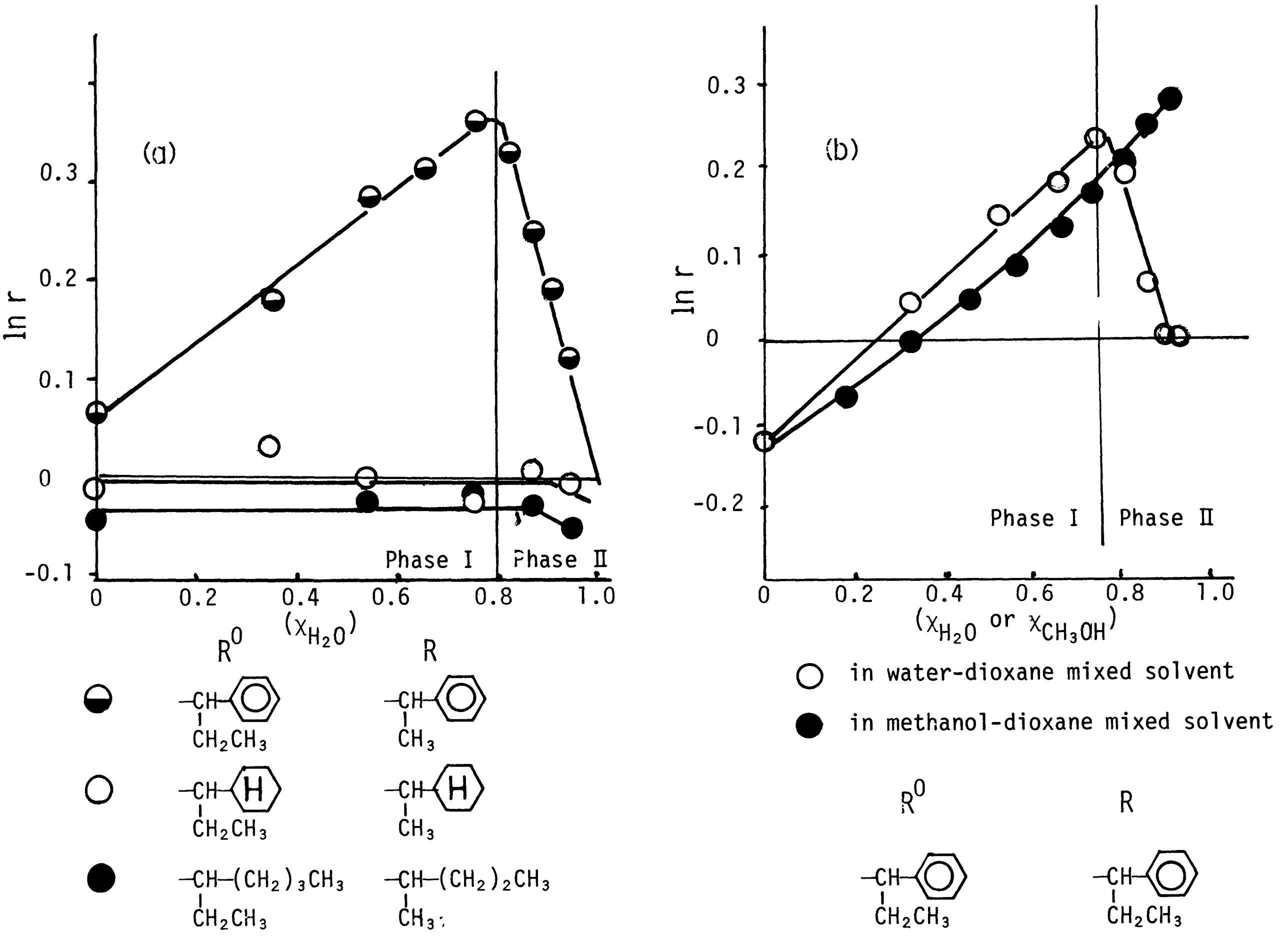

Fig. 3. The ln r values of enantiomer-differentiating acylation (Eq. 1) in the mixed solvent systems.

Assuming the participation of attractive alkyl-phenyl interaction in aqueous media, it was expected that the chiral recognition was sensitively affected by the addition of water in the case that the chirality was composed of alkyl and phenyl groups, compared with the case that it was composed of only alkyl groups. In this respect, the enantiomer-differentiating acylation was carried out with three different types of reagent and substrate. The plots of ln r against χ_{H_2O} were shown in Fig. 3. The results were quite resemble to that of the competitive acylation. In the reaction system of racemic 1-phenylethylamine and (*S*)-2-phenylbutyric anhydride (plot-◒- in Fig. 3(a)), ln r increased significantly with the increase of χ_{H_2O} up to 0.8 (phase I). The sharp decrease of ln r in phase II indicates that the effective chiral recognition is disturbed by the phase transfer process of substrate. As expected from the model reaction system, the absence of phenyl group in the reactant molecules resulted in no significant chiral recognition in either organic or aqueous solvent systems (plots-○-and -●- in Fig. 3(a)). Thus it was clearly shown that the phenyl group possessed a unique character in the distinction of substrate structure in aqueous media.

In the enantiomer-differentiating acylation of (*R*/*S*) 1-phenylpropylamine with (*S*)-2-phenylbutyric anhydride (Fig. 3b), ln r changed its sign from the negative to the positive by the addition of water or methanol, explicable with the operation of opposing effects, steric repulsion and the phenyl-alkyl attractive interaction, on the chiral recognition. The fact that methanol could be substituted in place of water indicated that phenyl-alkyl interaction is a kind of solvophobic interaction. Though it is difficult to answer why phenyl-alkyl interaction was stronger than alkyl-alkyl interaction at this stage, the proximity effect of CH-π[4)] interaction could function in chiral recognition of reactant molecule.

We wish to thank Professor Yoshiharu Izumi, Drs. Tadao Harada, and Hiroshi Ozaki of Osaka University for their valuable discussions. We also thank Miss Masako Yamashita and Mr. Yoichi Kuroda for their technical assistance.

References

1) The reaction readily proceeded to give the substantially quantitative yield in both organic and aqueous media. The products were analyzed quantitatively by GLPC with the internal standard method.

2) The good linear condition between the ln r value and the steric parameter, ν_x value of α-substituted alkyl group was also obtained.

3) O. Cervinka, L. Hub, J. Chem. Soc., Chem. Commun., 1966, 761; Collect. Czech. Chem. Commun., 32, 2295 (1967). A. Horeau, "Stereochemistry Fundamentals and Methods." H.B. Kagan, E.d., Georg Thieme Publishers, Vol. 3, Stuttgart (1977), p 70.

4) a. Y. Kodama, K. Nishihata, M. Nishio, and N. Nakagawa, Tetrahedron Lett. 1977, 2105.
   b. Y. Kodama, K. Nishihata, S. Zushi, M. Nishio, Jun Uzawa, K. Sakamoto, and H. Iwamura, Bull. Chem. Soc. Jpn., 52, 2661 (1979).

5) W.P. Jenks, Catalysis in Chemistry and Enzymology, McGraw-Hill, New York (1969) P. 415.

(Received December 17, 1981)