A Determination of the Free-energy Difference between Two Diastereomeric Ion-pairs

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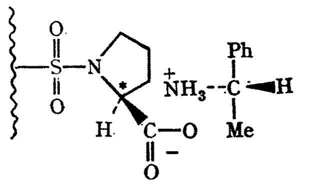
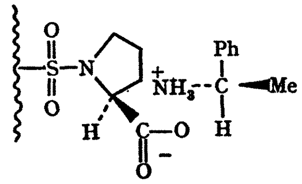
THE concept of separating enantiomers by the use of optically active resins has been described.[1-3] In particular, several workers have attempted to resolve amino-acids in aqueous solution by column chromatography.[2,3] Roberts *et al.*[2] incorporated L-(−)-cysteine on a polymer and partially resolved methionine. Losse *et al.*[3] copolymerized L-(−)-tyrosine and formaldehyde with various phenolic substrates and partially resolved the amino-acids. Neither group of workers determined the free-energy difference between the diastereomeric ion-pairs involved in these systems.





Such a determination could be made if (i) a model system were employed in which the optically active resin was fully characterized and (ii) the separation factor (β) were defined at equilibrium conditions such that it could be related to the free-energy difference as shown by the following equations:

$$\underset{(-)}{\mathrm{HA}} + \underset{(-)}{\mathrm{B}} \overset{K_1}{\rightleftharpoons} \underset{(-)\,(-)}{\mathrm{HB^+A^-}} \tag{1}$$

$$\Delta G^\circ_1 = \underset{(-)\,(-)}{G^\circ_{\mathrm{HB^+A^-}}} - \underset{(-)}{G^\circ_{\mathrm{HA}}} - \underset{(-)}{G^\circ_{\mathrm{B}}} \tag{2}$$

$$\Delta G^\circ_2 = \underset{(+)\,(-)}{G^\circ_{\mathrm{HB^+A^-}}} - \underset{(-)}{G^\circ_{\mathrm{HA}}} - \underset{(+)}{G^\circ_{\mathrm{B}}} \tag{3}$$

$$\Delta G^\circ_1 - \Delta G^\circ_2 = \delta(\Delta G^\circ) =$$

$$\underset{(-)\,(-)}{G^\circ_{\mathrm{HB^+A^-}}} - \underset{(+)\,(-)}{G^\circ_{\mathrm{HB^+A^-}}} - \underset{(-)}{G^\circ_{\mathrm{HA}}} - \underset{(-)}{G^\circ_{\mathrm{B}}} + \underset{(-)}{G^\circ_{\mathrm{HA}}} - \underset{(+)}{G^\circ_{\mathrm{B}}}\dagger \tag{4}$$

$$\Delta G_1^\circ = -\boldsymbol{R}T\ln K_1 \tag{5}$$

$$\delta(\Delta G^\circ) = -\boldsymbol{R}T\ln(K_1/K_2) \tag{6}$$

$$\beta = \frac{K_1}{K_2} = \frac{\left[\begin{smallmatrix}\mathrm{HB^+\,A^-}\\(-)\,(-)\end{smallmatrix}\right]}{\cancel{\left[\begin{smallmatrix}\mathrm{HA}\\(-)\end{smallmatrix}\right]}\left[\begin{smallmatrix}\mathrm{B}\\(-)\end{smallmatrix}\right]} \times \frac{\cancel{\left[\begin{smallmatrix}\mathrm{HA}\\(-)\end{smallmatrix}\right]}\left[\begin{smallmatrix}\mathrm{B}\\(+)\end{smallmatrix}\right]}{\left[\begin{smallmatrix}\mathrm{HB^+\,A^-}\\(+)\,(-)\end{smallmatrix}\right]} \tag{7}$$

$$\beta = \frac{\left[\begin{smallmatrix}\mathrm{HB^+\,A^-}\\(-)\,(-)\end{smallmatrix}\right]\text{Resin}}{\left[\begin{smallmatrix}\mathrm{HB^+A^-}\\(+)\,(-)\end{smallmatrix}\right]\text{Resin}} \times \frac{\left[\begin{smallmatrix}\mathrm{B}\\(+)\end{smallmatrix}\right]\text{Supernatant}}{\left[\begin{smallmatrix}\mathrm{B}\\(-)\end{smallmatrix}\right]\text{Supernatant}} \tag{8}$$

We report that the free-energy difference ($T = 25°$) between the diastereomeric ion-pairs shown is 4 ± 1 cal. mole^{-1}. The equilibrium data are summarized in the Table. It is significant that such a small energy difference exists, that it can be experimentally determined, and that the energy differences in both the protic and aprotic solvents are virtually identical. The last point may be a consequence of the very small energy differences which are involved in this particular system.

The system chosen consisted of L-proline which had been incorporated on an Amberlyst-15‡ ion exchange

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† Standard state defined as $T = 25°$, $P = 1$ atmos., and molar concentrations of the species involved.

‡ Purchased from the Rohm and Haas Company.

Determination of the separation factors for the resolution of α-methylbenzylamine by a prolinated resin at 25°

Solvent	Resin (g.)	Amine (g.)	Amine (g.) recovered from supernatant liquid	$(\alpha)_{\text{obs}}$ of amine[a, b] (neat) in supernatant liquid ($l = 2$)	Amine (g.) recovered from resin	$(\alpha)_{\text{obs}}$ of amine (neat) recovered from resin ($l = 2$)	Separation factor (β)
Methylene chloride	25	6·6	2·9	(+) 0·066°	2·0	(−) 0·140°	1·006
Methylene chloride	25	6·6	4·25	(+) 0·081	1·25	(−) 0·254	1·009
Methanol	44	6·3	2·0	(+) 0·166	2·1	(−) 0·127	1·008
Methanol	44	6·3	2·0	(+) 0·123	2·0	(−) 0·109	1·007

[a] Optical rotations were measured with an O. C. Rudolph and Sons Model 80 polarimeter.

[b] α-Methylbenzylamine (neat; $[\alpha]_D^{25}$ − 39·4°; d_4^{24} 0·950) (A. W. Ingersol, *Org. Synth.*, **1943**, Coll. Vol. II, 506; W. Theilacker and H. G. Winkler, *Chem. Ber.*, 1954, **87**, 690).

resin and racemic α-methylbenzylamine. Control experiments and extensive analytical data indicated that (i) L-proline was incorporated without racemization; it was cleaved from the resin and found to be >90% optically pure; parallel control experiments indicated <1% racemization when L-proline was subjected to the reaction conditions employed to incorporate it on the resin; (ii) the resin consisted of 64% of the sulphonate moieties in the prolinated form while the remaining 36% were in the form of the sodium salt. Equilibration was accomplished by shaking a solution of α-methylbenzylamine with the resin. The α-methylbenzylamine was distilled before use and its purity established by g.l.c. α-Methylbenzylamine in the supernatant liquid was isolated by decantation followed by distillation. The amine on the resin in the form of the ammonium salt was displaced from the resin with pyrrolidine and isolated by distillation. The separation factor (β) was calculated by use of equation (8). The ratio of the concentrations of the enantiomers in the supernatant liquid was calculated by use of the value for the rotation of pure α-methylbenzylamine indicated in the footnote of the Table. The ratio of the concentrations of α-methylbenzylamine associated with the resin was determined in a similar fashion.

These experiments suggest the possibility of thermodynamically defining what is meant by a loose or a tight ion-pair in terms of the energy difference which exists between diastereomeric ion-pairs.

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