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ASYMMETRIC SYNTHESIS—IV

QUANTITATIVE INTERPRETATION OF STEREOSELECTIVITY IN THE REACTION OF HYDRATROPIC ANHYDRIDE WITH OPTICALLY ACTIVE AMINES

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Abstract—The extent of kinetic resolution in the reaction of hydratropic anhydride with seven optically active amines was determined. Experimental results are in good agreement with values calculated from the Ugi equation. Modification of the definition of "positive" and "negative" diastereomers is suggested.

THE USE of symmetrical anhydrides of amino acids in the synthesis of peptides is rather scarce,[1] as compared to the wide-spread method of mixed anhydrides.[2] The main disadvantage of symmetrical anhydrides is the loss of one of the aminoacyl residues during the synthesis. This behaviour of symmetrical anhydrides can in turn be exploited advantageously for the determination of the extent of stereoselectivity in acylation reactions.

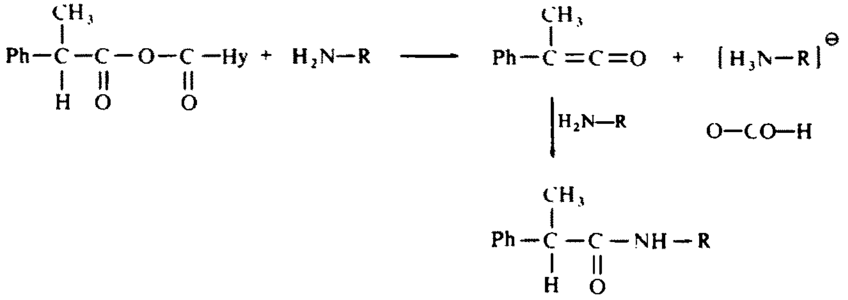
Ugi and coworkers[3] have recently determined the extent of kinetic resolution brought about by a series of mixed anhydrides of carbonic acid and chiral carboxylic acids. Quantitative valuation of the data hit against difficulties because of the transient existence of a new chirality centre in the transition state.

RESULTS

The symmetrical anhydride prepared from racemic hydratropic acid with either Ac_2O or dicyclohexylcarbodiimide (DCC) was reacted with 2 to 3 fold molar excess of the optically active amines listed in Table 1. To avoid the possibility of resolution no purification of the acylamines formed in the reaction was undertaken, apart from washing their ethereal solutions with N HCl. N Na_2CO_3 solution and water. Drying and concentration of the solution afforded crystalline acylamines, the optical properties of which are collected in Table 1. The portions of Na_2CO_3 washing were separately collected, acidified with conc. HCl and extracted with ether. Drying and evaporation of the solvent, followed by distillation of the residue gave pure hydratropic acid. The specific rotation of these products is shown in Table 2.

The fact that the optical yield data calculated from the specific rotation of acylamines and hydratropic acid, respectively, agree reasonably well within the limits of experimental error suggests that the mechanism involving the formation of ketene can not be of importance in the acylation reaction.

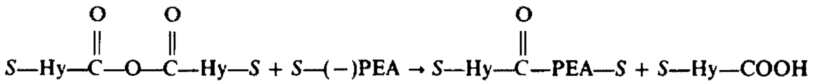
The formation of ketene before acylation would involve extensive racemization of the hydratropoyl group which takes part in the amide bond whereas the hydratropoyl



$$\mathrm{Ph{-}\overset{CH_3}{\underset{H}{C}}{-}\underset{O}{\overset{}{\underset{\|}{C}}}{-}O{-}\underset{O}{\underset{\|}{C}}{-}Hy} + \mathrm{H_2N{-}R} \longrightarrow \mathrm{Ph{-}\overset{CH_3}{C}{=}C{=}O} + [\mathrm{H_3N{-}R}]^{\ominus}\ \mathrm{O{-}CO{-}H}$$

$$\mathrm{Ph{-}\overset{CH_3}{C}{=}C{=}O} \xrightarrow{\mathrm{H_2N{-}R}} \mathrm{Ph{-}\overset{CH_3}{\underset{H}{C}}{-}\underset{O}{\underset{\|}{C}}{-}NH{-}R}$$

group which gives rise to the acid would preserve its stereochemistry. Direct evidence for the exclusion of the "ketene mechanism" was provided by the aminolysis of *S*-(+)-hydratropic anhydride with *S*-α-phenylethylamine.



$$S\text{—Hy—}\overset{O}{\overset{\|}{C}}\text{—O—}\overset{O}{\overset{\|}{C}}\text{—Hy—}S + S\text{—}(-)\text{PEA} \rightarrow S\text{—Hy—}\overset{O}{\overset{\|}{C}}\text{—PEA—}S + S\text{—Hy—COOH}$$

The optical purity of the hydratropic acid recovered after the aminolysis was identical to that of the starting material used for the preparation of S-(+)-hydratropic anhydride from triethyl ammonium *S*-(+)-hydratropate and *S*-(+)-hydratropoyl chloride. Similarly, the specific rotation of *S*-(+)-hydratropoyl-*S*-(−)-α-phenylethylamide formed was identical to that calculated from known optical purity of the starting materials. No racemization could be detected during the reaction.

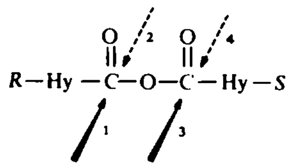
From the optical purity data referring to the hydratropic acid recovered, from the aminolysis of the meso anhydride (Table 3, rows 3, 4 and 5, respectively), and from the optical yields given in the 1st, 2nd and 4th rows of Table 2 we calculated the molar ratio of the meso diastereomer present in hydratropic anhydride prepared from racemic acid. In this way we obtained that hydratropic anhydride prepared from racemic acid contains 54·2 ± 3% meso diastereomer. Consequently, multiplication of the average optical yield data in Table 2 by a factor 1·84 (100/54·2) gives optical yields referring to the aminolysis of the pure meso anhydride (*cf.* Table 4).

DISCUSSION

The extent of kinetic resolution observed in the complete aminolysis of hydratropic anhydride with optically active amines may vary from 0 to a maximum value depending upon the molar ratio of the meso diastereomer present. The maximum value is obtained in the case of pure meso anhydride, provided that optically pure amine is used. The aminolysis of meso hydratropic anhydride with optically active amine, B_S, involves four, more or less probable, transition states (the arrows represent the directions of attack of B_S leading to the various transition states)

If k is the experimental rate constant of the reaction, the following relation holds:

$$k = k_1 + k_2 + k_3 + k_4 \qquad (1)$$



$$R{-}Hy{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}Hy{-}S$$

where k_1, k_2, k_3 and k_4 are the rate constants of the particular reactions corresponding to the indices. The four k_i values are, in principle, different, since the four directions of attack represent different magnitudes of chirality[4] (χ_1, χ_2, χ_3 and χ_4, respectively) of the anhydride. We define these chiralities by the following relation:

$$k_i = wke^{c\chi_i\chi_S^B} \tag{2}$$

where w is a statistical factor ($=\frac{1}{4}$, in the case), χ_S^B represents the chirality of B_S and c is a proportionality factor depending upon the conditions of the reaction (temperature, solvent, etc.).

The transition states concerning the direction of attack 1 and 3, as well as 2 and 4 represent corresponding pairs of reactions, for which the Ugi equation[4] holds:

$$\ln\frac{k_1}{k_3} = (\rho_2\chi_{\mathbf{R}}^{\mathrm{Hy}} + \rho_1\chi_{\mathbf{R}}^{\mathrm{CO}} + \rho_3\chi_{\mathbf{S}}^{\mathrm{Hy}})\,\chi_{\mathbf{S}}^{\mathbf{B}} \tag{3a}$$

$$\ln\frac{k_2}{k_4} = (\rho_2\chi_{\mathbf{R}}^{\mathrm{Hy}} + \rho_1\chi_{\mathbf{S}}^{\mathrm{CO}} + \rho_3\chi_{\mathbf{S}}^{\mathrm{Hy}})\,\chi_{\mathbf{S}}^{\mathbf{B}} \tag{3b}$$

where χ^{Hy} is the chirality determinant of the asymmetric carbon of the hydratropoyl group (the lower index refers to the absolute configuration). χ^{CO} is the chirality determinant of the carbonyl group being attacked in the transition state (the index referring to the absolute configuration is arbitrarily chosen). The proportionality factors ρ_1, ρ_2 and ρ_3 refer to interactions of the chirality centres separated by 1, 2 and 3 atoms, respectively.

It is obvious that $\chi_i = \chi_{i+2}$ ($i = 1, 2$), because 1 and 3 represent enantiotopic faces. Thus, we obtain from equations (2) and (3) relation (4):

$$c\chi_i = \tfrac{1}{2}\,v_i(\rho_2\chi_{\mathbf{R}}^{\mathrm{Hy}} + \varepsilon_i\rho_1\chi_{\mathbf{R}}^{\mathrm{CO}} + \rho_3\chi_{\mathbf{S}}^{\mathrm{Hy}}) \tag{4}$$

where

$$v_i = \begin{cases} +1 & i = 1, 2 \\ & \text{if} \\ -1 & i = 3, 4 \end{cases}$$

and

$$\varepsilon_i = \begin{cases} +1 & i = 1, 4 \\ & \text{if} \\ -1 & i = 2, 3 \end{cases}$$

As the reactions defined by the directions of attack 1 and 2 lead to identical stereochemical results and the same holds true for reactions 2 and 4. we actually determine the ratio $k_1 + k_2/k_3 + k_4$. by measurement of the specific rotation of the products. For this ratio we obtain from equations (2) and (4) the following expression:

$$\log\frac{k_1 + k_2}{k_3 + k_4} = \tau \,.\, \chi_R^{Hy} \,.\, \chi_S^{B} \tag{5}$$

where

$$\tau = (\rho_2 - \rho_3)\log e$$

Equation (5) does not contain the chirality determinant of the carbonyl group that becomes transiently asymmetric in the transition state. On this basis we may expect that the Ugi equation is valid for the quantitative interpretation of the stereochemistry of the aminolysis of meso anhydrides by optically active amines. The agreement between experimental and calculated values shown in Table 4 bears out this view.

TABLE 1. SPECIFIC ROTATION OF ACYLAMINES AND THE EXTENT OF STEREOSELECTIVITY IN THE AMINOLYSIS OF HYDRATROPIC ANHYDRIDE

No.	Amine	optical purity %	Acylamine (major diastereomer)	$[\alpha]_{546}$[b] in MeOH	optical[c] yield %
1	S—PEA[a]	97·5	S—HyCO—S—PEA	−89·21	6·7
2	R—PEA[a]	95·2	R—HyCO—R—PEA	+87·85	6·7
3	S—Ala—OEt	100	R—HyCO—S—AlaOEt	−59·3	0·9
4	S—Val—OEt	100	R—HyCO—S—Val—OEt	−45·73	11·4
5	S—Leu—OEt	100	R—HyCO—S—Leu—OEt	−54·9	9·1
6	R—PhGly—OEt	100	S—HyCO—R—PhGly—OEt	−110·75	9·1
7	S—Phe—OEt	100	R—HyCO—S—Phe—OEt	−10·26	7·3

[a] PEA = α-phenylethylamine

[b] specific rotation of the diastereomeric mixture of acylamines formed

[c] data refer to optically pure amines and are calc on basis of the $[\alpha]_{546}$ values given by Ugi and coworkers[3]

[d] HyCO stands for hydratropoyl. R and S indicate the absolute configuration

In addition to the quantitative aspects of stereochemistry, Table 1 contains important information concerning the configuration of the hydratropoyl group incorporated. Before dealing with the regularities of the preferential formation of diastereomers a brief discussion concerning the definitions included by the original form of the Ugi equation[4] seems to be appropriate.

In the Ugi equation

$$\log\frac{D_p}{D_n} = \chi_p \tau \sigma_p \qquad \sigma_p = \pm 1$$

where D_p and D_n represent molar fractions of the "positive" and "negative" diastereomer, respectively, the p- and n-diastereomers are defined by the *atomic number sequence* of the ligands attached to the chiral atoms Z and Z' in the product state, χ_p is defined by the *steric size* (magnitude of ligand constants) of the ligands attached to Z either in the transition or product state, whereas σ_p is defined again by the *atomic number sequence* of the ligands attached to Z' in the product state. Accordingly, the Ugi equation claims for a relationship between quantities of incomparable physical meaning. To avoid this inconsistency, we propose the following definitions for the cases of kinetic resolution that obey the Ugi equation

TABLE 2. SPECIFIC ROTATION OF HYDRATROPIC ACID AND THE EXTENT OF STEREOSELECTIVITY IN THE AMINOLYSIS OF HYDRATROPIC ANHYDRIDE

No.[a]	$[\alpha]^D$ in EtOH	optical yield[b] %	optical yield[c] (average) %
1	−5·29	6·68	6·7
2	+5·04	6·84	6·7
3	+1·22	1·5	1·2
4	+9·25	11·4	11·4
5	+7·22	8·9	9·0
6	−7·38	9·1	9·1
7	+6·08	7·5	7·4

[a] Nos correspond to aminolysis reactions given under the same No. in Table 1

[b] Data refer to optically pure amines

[c] Mean values derived from the optical yield data in Tables 1 and 2

i. Those diastereomers should be considered as "positive" (D_p) for which the multiplication product of $\chi^Z . \chi^{Z'}$ ($= \chi^{Hy} . \chi^B$ in this paper) is positive.

ii. The chirality function should be described in the form

$$\chi = (\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)$$

where λ_i represents the ligand constant of the substituents attached to the chirality centre concerned apart from the group which is involved in chemical bonds that join the chirality centres. The chiral atom is viewed down according to the arrangement of the Gahn–Ingold–Prelog convention, provided that the group joining the chirality centres is replaced for the atom of smallest atomic number. Numbering may start with any substituent, however, it must proceed in a righthanded sense.

According to these definitions equation (5) may be rewritten in the form

$$\log \frac{D_p}{D_n} = \tau . \chi_p^{Hy} . \chi_p^B \qquad D_p + D_n = 1$$

where χ_p^{Hy} and χ_p^B refer to the corresponding chirality centres as they occur in the "positive" diastereomer.

It is easy to see that *R*—HyCO—PEA—*R* or *S*—HyCO—PEA—*S* and *R*—HyCO—AmOEt—*S* or *S*—HyCO—AmOEt—*R* are those ones which represent "positive" diastereomers (D_p). Configuration of the major diastereomer (D_m) formed is given in Table 4 in parentheses. The 1st letter refers to the configuration of Hy and the 2nd one to that of PEA or AmOEt in HyCO—PEA or HyCO—AmOEt, res-

TABLE 3. AMINOLYSIS OF ACTIVE AND MESO DIASTEREOMERS OF HYDRATROPIC ANHYDRIDE WITH OPTICALLY ACTIVE AMINES

No.	Anhydride	enantiomeric purity of *S* moiety. %	enantiomeric purity of *R* moiety. %	Amine $[\alpha]_D$	Amine opt. purity %	Acylamine $[\alpha]_{546}$ calc	Acylamine $[\alpha]_{546}$ found	Opt. purity of Hy-COOH[b] recovered %
1	*S*-HyCO—O—COHy-*S*	90·5	—	−37·36[a]	97·5	−48·26	−47·1	(*S*) 89·8
2	*S*-HyCO—O—COHy-*S*	90·5	—	+36·48[a]	95·2	+115·1	+116·0	(*S*) 89·2
3	*S*-HyCO—O—COHy-*R*[c]	90·5	93·2	−37·36[a]	97·5	−85·83[d]	−89·5	(*R*) 12·95
4	*S*-HyCO O—COHy-*R*[c]	90·5	93·2	+36·48[a]	95·2	+94·26[d]	+93·4	(*S*) 12·33
5	*S*-HyCO—O—COHy-*R*[c]	90·5	93·2	+6·6[e]	100	−48·04[d]	−48·2	(*S*) 20·24

[a] PEA

[b] *S* or *R* in parentheses denotes configuration of Hy-COOH

[c] calc to contain 95·93% meso and 4·07% active (*RR* and *SS*) isomer of hydratropic anhydride

[d] calc on basis of the optical purity of HyCOOH recovered

[e] L-Val-OEt.HCl

pectively. The consequent stereochemistry of the reaction is shown by the fact that the "positive" diastereomer is the major product in each case.

TABLE 4. PER CENT RATIO OF THE MAJOR DIASTEREOMER (D_m) OF THE ACYLAMINE FORMED IN THE REACTION OF MESO-HYDRATROPIC ANHYDRIDE WITH OPTICALLY ACTIVE AMINES

Amine	χ_p^B	$D_m \cdot 100$		optical yield	
		calc[a] ($\tau \cdot \chi_p^{Hy} = \pm 0{\cdot}42$)	found[b]	found[c]	calc[d]
S—PEA	−0·2829	56·80 (*S*—*S*)	56·16 (*S*—*S*)	12·33	13·60
R—PEA	0·2829	56·80 (*R*—*R*)	56·16 (*R*—*R*)	12·33	13·60
S—Ala—OEt	0·0900	52·17 (*R*—*S*)	51·11 (*R*—*S*)	2·21	4·34
S—Val—OEt	0·4229	60·08 (*R*—*S*)	60·49 (*R*—*S*)	20·98	20·16
S—Leu—OEt	0·3240	57·77 (*R*—*S*)	58·28 (*R*—*S*)	16·56	15·54
R—PhGly—OEt	−0·3653	58·78 (*S*—*R*)	58·37 (*S*—*R*)	16·74	17·56
S—Phe—OEt	0·2587	56·22 (*R*—*S*)	56·81 (*R*—*S*)	13·62	12·44

[a] $D_m = \dfrac{10^{\chi_p^B \cdot \chi_p^{Hy}}}{1 + 10^{\chi_p^B \cdot \chi_p^{Hy}}}$ as expressed from equation (6)

[b] Calc. from optical yield data estimated to pure hydratropic anhydride (*cf.* next column on the right)

[c] Obtained from the average optical yields in Table 2 by multiplication with the factor 1·84 (*cf.* text)

[d] Obtained from the calc. value of D_m

EXPERIMENTAL

Hydratropic anhydride from racemic acid. 15·7 g (0·1 mole) racemic hydratropic acid was dissolved in 20 ml Ac_2O and the mixture heated 8 hr at 140°. AcOH and excess Ac_2O were removed *in vacuo*. The residue was fractionally distilled to give a pale yellow liquid, b.p. 169–171°/1 mm, which became colourless on standing for a short period. ν_{max}: 3·4, 5·55, 5·75, 6·25, 13·2 and 14·3 μ. No absorption due to hydrogen bond could be observed.

S-(+)-*Hydratropic anhydride.* Et_3N (3·3 ml) was added dropwise to a soln of 3·74 g (23·8 mmole) *S*-(+)-hydratropic acid ($[\alpha]_D$ +73·4° (*c* 1·913, EtOH) in 30 ml dry THF at 0°. After stirring 15 min, 4·0 g (23·8 mmole) *S*-(+)-hydratropoyl chloride, freshly prepared from the above acid with $SOCl_2$ and distilled, was added dropwise. After standing overnight at 0° the crystalline $Et_3N.HCl$ was filtered and the soln conc *in vacuo*. The residue was dissolved in ether, quickly washed with 0° H_2O and dried over Na_2SO_4. Removal of the ether gave a colourless liquid (6·82 g, 96·7%). Its IR spectrum was identical with that of the racemic anhydride.

Hydrolysis of *S*-(+)-hydratropic anhydride (774 mg in aqueous THF (10 ml THF and 2 ml H_2O) yielded *S*-(+)-hydratropic acid (750 mg), $[\alpha]_D$ 72·9° (*c* 1·956, EtOH).

meso-Hydratropic anhydride. It was prepared similarly from *R*-(−)-hydratropic acid ($[\alpha]_D$ −75·58° (*c* 1·370, EtOH) and *S*-(+)-hydratropoyl chloride (the same compound used in the preceding example).

Hydrolysis of the anhydride in aqueous THF afforded hydratropic acid of $[\alpha]_D$ −2·21° (*c* 7·533, EtOH), expected value: $[\alpha]_D$ −2·18°.

General procedure for the aminolysis. A soln of 10 mmole hydratropic anhydride in 25 ml dry THF was cooled to 0° and a soln of 20–30 mmole amine or amino acid ethyl ester in 25 ml dry THF added. The mixture was kept 24 hr in the cold and conc *in vacuo*. The residue was dissolved in 100 ml ether and successively extracted with *N* HCl, *N* Na_2CO_3 soln and H_2O. After drying over $MgCO_3$ the solvent was removed to give a crystalline residue. Polarimetric measurements were carried out with 2% solns in MeOH, unless otherwise stated (*cf.* Tables 1 and 3). Acidification of the Na_2CO_3 washing afforded hydratropic acid, isolated by known manner (Table 2).

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