BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1426—1432 (1968)

Mechanism of Asymmetric Reactions. II.*[1] Kinetical Resolution of Racemic Primary Amines by Means of Sulfonylation with (+)-Camphor-10-sulfonyl Chloride—Preferential Conservation of an Absolute Configuration in the Asymmetric Sulfonylation of Racemic Amines

Kunio OKAMOTO, Etsuo MINAMI and Haruo SHINGU

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto

(Received December 26, 1967)

α-Phenylethylamine (I), α,β-diphenylethylamine (II), α-(β-naphthyl)-ethylamine (III) α-(α-naphthyl)-benzylamine (IV), α-pipecoline (V), 2-aminobicyclo[2.2.2]octane (VI), and methylamine (VII) have been partially sulfonylated by (+)-camphor-10-sulfonyl chloride in benzene (or toluene); the optical rotations for the unsulfonylated amines, partially resolved, have been measured. Examination of absolute configurations for the amines indicates that the (R) enantiomers of these amines (I, II, V and VII, including neomenthylamine (VIII)[3] and isomenthylamine (IX)[3]) react faster than the respective (S) enantiomers, with exception of III. The rate for the sulfonylation of (−)-menthylamine with (+)-camphor-10-sulfonyl chloride have been determined in toluene at the temperatures ranging from −20 to −40°C; the rate ratio of the (+)-menthylamine to the (−)-amine has been estimated from the extent of the kinetical resolution of the (±)-menthylamine. Kinetical implication of the coincidence of the preferred absolute configurations has been discussed.

A number of studies[1] concerned with the kinetic method of resolution have been reported since the beginning of this century. However, relatively few data[2] are available for a systematic scrutiny of the correlation between the structural factors of the racemic substrate and the extents or the directions of the resolution.

One of the purposes of this study was to provide additional examples of the kinetical resolution in the partial sulfonylation of a series of racemic primary amines (heretofore only three isomers of menthylamines[3] had been examined) by means of (+)-camphor-10-sulfonyl chloride as an asymmetric reagent.

Another purpose was to scrutinize steric factors which characterize the extent and the direction of such kinetical resolutions, and to discuss its mechanistic implication.

Results

The Partial Sulfonylation of Several Racemic Amines with (+)-Camphor-10-sulfonyl Chloride. Equal molar quantities of racemic amine and (+)-camphorsulfonyl chloride were allowed to react in benzene (or toluene). Since the reaction proceeds following the stoichiometric relation shown below, after the completion of this reaction the half of the starting amine was recovered as the hydrochloride. The amounts of one enantiomer enriched in

*1 Presented at the 9th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1956; Part I. K. Okamoto, K. Takeuchi and H. Shingu, This Bulletin, **34**, 1137 (1961).

1) For a summary, see a) J. R. Partington, "An Advanced Treatise of Physical Chemistry," Vol. 4, Longmans, Green and Co., London (1953), pp. 298—300; b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York (1962), pp. 67—75.

2) a) R. Wegler, *Liebigs Ann. Chem.*, **506**, 77 (1933); b) F. Hawthorne and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5859 (1952); c) G. Pracejus, *Liebigs Ann. Chem.*, **622**, 10 (1959); d) O. Cervinka and L. Hub, *Chem. Commun.*, **1966**, 761; e) F. Akiyama, K. Sugino and N. Tokura, This Bulletin, **40**, 359 (1967); f) H. Herlinger, H. Kleimann and I. Ugi, *Liebigs Ann. Chem.*, **706**, 37 (1967).

3) J. Read and R. A. Story, *J. Chem. Soc.*, **1930**, 2761.

Table 1. Optical rotations and the extents of kinetical resolution (α%) for unsulfonylated amines[a)]

Amine	Temp. °C	$[\alpha]_D$ (c, solvent, temp.) for unsulfonylated amine or derivatives of the amine	α%[b)]
α-Phenylethylamine (I)	27—30	−0.057°[c)] (29.0, water, 32°C)	0.69%
α, β-Diphenylethylamine (II)	25—30	−1.83°[c)] (0.87, water, 31°C)	2.61%
α-(β-Naphthyl)-ethylamine (III)	28—30	+2.04°[d)] (1.5, ethanol, 30°C)	3.0%
α-(α-Naphthyl)-benzylamine (IV)	25	−0.94° (9.68, benzene, 22°C)	1.48%
α-Pipecoline (V)	23—25	+0.43° (13.3, benzene, 24°C)	1.44%
2-Aminobicyclo[2.2.2]octane (VI)	15	0.00° (3.0, benzene, 15°C) 0.00°[c)] (5.0, water, 15°C)	0.00%
Menthylamine (VII)[f)]	−6.0	+7.27°[c)] (1.0, water, 25°C)	19.9%
Menthylamine (VII)[f)]	−40.0	+10.73°[c)] (1.0, water, 25°C)	29.3%
Menthylamine (VII)	room temp.	+10.7°[c,e)] (water)	29.2%[e)]

a) All reactions were conducted in benzene except when otherwise noted.
b) The rotations, $[\alpha]_D$, of the optically pure materials are taken to be −8.27° (c 31.45, water)[4)] for the hydrochloride of I, 70° (c 0.7, water, 15°C)[5)] for the hydrochloride of II, +67.9° (c 1.12, water, 17°C)[6)] for carbamide of III, +63.6° (p 4.76, benzene, 15°C)[7)] for IV, +30.0° (c 20, benzene, 15°C)[8)] for V, +36.6° (water, 15°C)[9)] for the hydrochloride of VII, respectively.
c) For the hydrochloride. d) For the carbamide.
e) Data given by Read and Story.[3)] f) In toluene.

the unsulfonylated amine were determined by the measurement of the optical rotation of the recovered amine.

$$2RNH_2 + (+)\text{-}RSO_2Cl = RNH_2\cdot HCl + (+)\text{-}RSO_2NHR$$

The extents (α%) of the resolution for the unsulfonylated amines were estimated by the comparison of their rotations with those of the optically pure amines (or hydrochlorides).[4-9)] The reaction conditions, the otpical rotations and the extents of the resolution (α%) are listed in Table 1. Among several amines examined, menthylamine (VII), which seems to be the most dissymmetric with regards to the reaction center, has been resolved in the greatest extent, and, in contrast, for 2-aminobicyclo[2.2.2]octane (VI), which is relatively symmetric because of its ball-like structure, there is no rate difference between the (R)- and the (S)-enantiomer.

Rate Measurements for the Sulfonylation of (−)-Menthylamine with (+)-Camphor-10-sulfonyl Chloride in Toluene. In order to compare the activation parameters for the sulfonylation of (+)- and (−)-menthylamine, first, the rates of the reaction of (−)-menthylamine with (+)-camphor-10-sulfonyl chloride were measured at the temperatures ranging from −20 to −40°C. The reaction was started by a rapid mixing of the toluene solutions (0.1 M for each) of the (−)-amine and the (+)-sulfonyl chloride; after an appropriate reaction time the reaction was stopped by adding a cold toluene solution of formic acid. The liberated chloride ion was extracted with

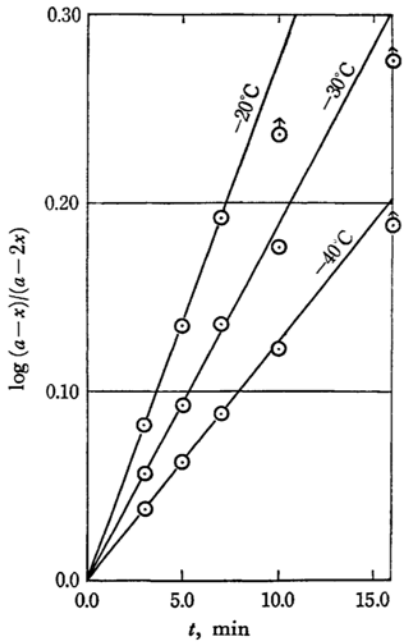


Fig. 1. Rates of the sulfonylation of (−)-menthylamine with (+)-camphor-10-sulfonyl chloride in toluene.

4) W. Marckwald and A. R. Meth, *Ber.*, **38**, 806 (1905).
5) R. Söderquist, *J. prakt. Chem.*, [2] **101**, 300 (1921).
6) E. Samuelsson, Thesis Univ. Lund, 1923, 75; *Chem. Abstr.*, **18**, 1833 (1924).
7) S. Berlingozzi, *Gazetta Chim. Ital.*, **50**, II, 57 (1920); *Chem. Zentr.*, **92**, I, 84 (1921).
8) W. Leithe, *Monatsh.*, **50**, 45 (1928).
9) J. Read, C. C. Steele and P. G. Carter, *J. Chem. Soc.*, **1929**, 28.

water and titrimetrically determined. Since the reaction was started with the equimolar quantities of the substrate and the reagent, we interpreted the rate data by a modified second-order kinetic equation (Eq. (1)), which was derived on the basis of the stoichiometry of this reaction:

$$k_2 = \frac{1}{at} \ln \frac{a-x}{a-2x} \quad (1)$$

where a is the initial concentration of the amine or the sulfonyl chloride, and x is the instantaneous concentration of the chloride ion at time t. The rate constants were calculated graphically by plotting $\log (a-x)/(a-2x)$ against time, and the results are illustrated in Fig. 1.

Secondly, the rate ratio of (+)- to (−)-menthylamine was estimated from the extent of the kinetical resolution of the racemic menthylamine with the (+)-sulfonyl chloride in toluene, as is described in the following.

The reaction of the racemic menthylamine and (+)-camphor-10-sulfonyl chloride is expressed as a competitive reaction of the (+)- and (−)-amine toward the sulfonyl chloride. So that, we obtain the following rate expression.

$$\frac{d[(+)\text{-RNHSO}_2\text{R}']}{dt} = k_{(+)\text{-Amine}}[\text{R}'\text{SO}_2\text{Cl}][(+)\text{-RNH}_2]$$

$$\frac{d[(-)\text{-RNHSO}_2\text{R}']}{dt} = k_{(-)\text{-Amine}}[\text{R}'\text{SO}_2\text{Cl}][(-)\text{-RNH}_2]$$

or when the reaction is conducted with the equal molar quantities of the racemic amine and the chloride,

$$\frac{dx}{dt} = k_{(+)\text{-Amine}}(a-x-y) \times \left\{0.5a - x - (x+y)\frac{(0.5a-x)}{(a-x-y)}\right\} \quad (2)$$

$$\frac{dy}{dt} = k_{(-)\text{-Amine}}(a-x-y) \times \left\{0.5a - y - (x+y)\frac{(0.5a-y)}{(a-x-y)}\right\} \quad (3)$$

where $x = [(+)\text{-RNHSO}_2\text{R}']$,

$y = [(-)\text{-RNHSO}_2\text{R}']$, $a = [\text{R}'\text{SO}_2\text{Cl}]_0$,

$0.5a = [(+)\text{-RNH}_2]_0 \equiv [(-)\text{-RNH}_2]_0$,

$(x+y) = \{[(+)\text{-RNH}_2\cdot\text{HCl}] + [(-)\text{-RNH}_2\cdot\text{HCl}]\} \equiv \{[(+)\text{-RNHSO}_2\text{R}'] + [(-)\text{-RNHSO}_2\text{R}']\}$,

$(a-x-y) = [\text{R}'\text{SO}_2\text{Cl}] \equiv \{[(+)\text{-RNH}_2]_0 + [(-)\text{-RNH}_2]_0\} - \{[(+)\text{-RNHSO}_2\text{R}'] + [(-)\text{-RNHSO}_2\text{R}']\}$,

$(0.5a-x) = \{[(+)\text{-RNH}_2]_0 - [(+)\text{-RNHSO}_2\text{R}']\}$, and

$(0.5a-y) = \{[(-)\text{-RNH}_2]_0 - [(-)\text{-RNHSO}_2\text{R}']\}$.

From Eqs. (2) and (3), dx/dy is expressed as:

$$dx/dy = k_{(+)\text{-Amine}}(0.5-x)/k_{(-)\text{-Amine}}(0.5a-y) \quad (4)$$

The integration of Eq. (4) gives:

$$k_{(+)\text{-Amine}}/k_{(-)\text{-Amine}} = \log\left(\frac{0.5a-x}{0.5a}\right)\Big/\log\left(\frac{0.5a-y}{0.5a}\right) \quad (5)$$

Since $x_{t=\infty} = [(-)\text{-RNH}_2\cdot\text{HCl}]_\infty$ and $y_{t=\infty} = [(+)\text{-RNH}_2\cdot\text{HCl}]_\infty$, the Eq. (5) is expressed as:

$$\frac{k_{(+)\text{-Amine}}}{k_{(-)\text{-Amine}}} = \frac{\log\left\{\dfrac{[(-)\text{-RNH}_2]_0 - [(-)\text{-RNH}_2\cdot\text{HCl}]_\infty}{[(-)\text{-RNH}_2]_0}\right\}}{\log\left\{\dfrac{[(+)\text{-RNH}_2]_0 - [(+)\text{-RNH}_2\cdot\text{HCl}]_\infty}{[(+)\text{-RNH}_2]_0}\right\}} \quad (6)$$

When $[(-)\text{-RNH}_2\cdot\text{HCl}]_\infty > [(+)\text{-RNH}_2\cdot\text{HCl}]_\infty$, the Eq. (6) can be expressed as the Eq. (7), which indicates the relation between $k_{(+)\text{-Amine}}/k_{(-)\text{-Amine}}$ and $\alpha\%$ of the unsulfonylated menthylamine.

$$\frac{k_{(+)\text{-Amine}}}{k_{(+)\text{-Amine}}} = \log\left(\frac{100-\alpha}{200}\right)\Big/\log\left(\frac{100+\alpha}{200}\right) \quad (7)$$

Using the rate ratio (Eq. (7)) and the rate constant observed for the (−)-amine, the rate constant for the (+)-menthylamine can be estimated.

Table 2. Rates and activation parameters for the sulfonylation of (−)- and (+)-menthylamine by (+)-camphor-10-sulfonyl chloride in toluene

Temp. °C	(−)-Menthylamine[a] 10^2k_2 ($\text{sec}^{-1}\,\text{M}^{-1}$)	(+)-Menthylamine 10^2k_2, calcd.[c] ($\text{sec}^{-1}\,\text{M}^{-1}$)
−6.0	3.20[b]	2.50[d]
−20.0	2.07	—
−30.0	1.44	—
−40.0	0.965	0.656[d]
E_A (kcal/mol)	4.40	4.84
$\Delta S^\ddagger$ (e.u.) at −40°C	−50.2	−49.1

a) The initial concentrations of the amine and the sulfochloride was 0.0500 M for each run.
b) Extrapolated from the data at other temperatures.
c) Calculated from the k_2 for the (−)-amine and the rate ratio, $k_{(+)\text{-Amine}}/k_{(-)\text{-Amine}}$ (*cf.* Eq. (7)).
d) $k_{(+)\text{-Amine}}/k_{(-)\text{-Amine}} = 0.78$ (at −6.0°C) and 0.68 (at −40°C).

In Table 2, the rate constants for the (−)- and the (+)-menthylamine are tabulated along with the respective activation parameters. In view of the observation that the reaction does not obey good second-order kinetics (*vide infra*), obviously the values for $k_{(+)\text{-Amine}}$ should be condisered as approximate ones.

As is shown in Table 2, (−)-menthylamine is sulfonylated 1.3 to 1.5 times as fast as (+)-menthylamine in the temperature range −6 — −40°C. The slower rate for the (+)-amine is attributed to the higher activation energy for the (+)-amine sulfonylation.

Discussion

The Mechanism of the Sulfonylation of the Primary Amines. The kinetics of the sulfonylation of the various amines have been studied by Litvinenko and his collaborators;[10] the second-order kinetics of an arylsulfonylation of a primary amine in nitrobenzene[10a] was interpreted by a two-step mechanism, which was composed of a rapid reversible formation of an adduct and a subsequent slow splitting of the adduct into *N*-alkylarylsulfonamide and hydrogen chloride; this is shown as in the following.

$$RNH_2 + ArSO_2Cl \overset{\text{rapid}}{\rightleftharpoons} ArSO_2Cl\cdot NH_2R \overset{\text{slow}}{\longrightarrow} HCl + ArSO_2NHR$$

In benzene, however, they found the reaction of *n*-butylamine (R=*n*-Bu) and 2,4-dinitrobenzenesulfonyl chloride (Ar=2,4-$(NO_2)_2C_6H_3$) to be the 2.6 order,[10b] and explained this order assuming the parallel paths. Namely, for both paths an adduct was formed rapidly and reversibly; the adduct then splits into HCl and $ArSO_2NHR$ by the second-order path as is in nitrobenzene, but this decomposition (*i. e.*, dehydrochlorination) is accelerated by a second RNH_2 in the third-order path.

$$RNH_2 + ArSO_2Cl \rightleftharpoons ArSO_2Cl\cdot NH_2R \rightarrow HCl + ArSO_2NHR \quad \text{(2nd-order path)}$$
$$ArSO_2Cl\cdot NH_2R \xrightarrow{+RNH_2} RNH_2HCl + ArSO_2NHR \quad \text{(3rd-order path)}$$

In a similar fashion, Ebel[11] proposed a two-step mechanism for the sulfonylation of aniline with *p*-toluenesulfonyl chloride in ether. However, in this case the reaction was found to obey the fifth-order kinetics, and this was attributed to the formation of an intermediate between one mole of the sulfonyl chloride and three moles of aniline at the first step of this reaction, this being shown as follows:

$$3C_6H_5NH_2 + ArSO_2Cl \rightleftharpoons ArSO_2Cl\cdot 3C_6H_5NH_2 \xrightarrow{+C_6H_5NH_2} ArSO_2NHC_6H_5 + C_6H_5NH_2HCl + 2C_6H_5NH_2$$

Such association of amines has been proposed in the case of the Menschutkin reaction of alkyl halides with diethylamine in cyclohexane.[12]

In our experiments carried out in toluene, the sulfonylation of (−)-menthylamine obeyed fairly good second-order kinetics, as is shown in Fig. 1. However, in view of a downward drift of the linear plot, the incursion of the third-order process (proposed by Litvinenko[10b]) or of the association of the amines might be considerable at least after the completion of 60% or more.

For the amines other than menthylamine we have not carried out kinetic measurements. However, it seems reasonable to consider that the reactions of these amines proceed through an amine-adduct to the sulfonyl chloride, as is considered in the case of sulfonylation with arylsulfonyl chloride.[10,11]

The Absolute Configuration of the Unsulfonylated Amines. In Table 3 the absolute

Table 3. Absolute configurations of unsulfonylated amines in the partial sulfonylation by (+)-camphor-10-sulfonyl chloride[a]

Amines	Signs of rotation[b] and absolute configurations[c] for unsulfonylated amines
α-Phenylethylamine (I)	(−)-S
α,β-Diphenylethylamine (II)	(−)-S
α-(β-Naphthyl)-ethylamine (III)	(+)-R
α-(α-Naphthyl)-benzylamine (IV)	(−)-?[g]
α-Pipecoline (V)	(−)-S
Menthylamine (VII)	(+)-S[d,f]
Neomenthylamine (VIII)	(+)-S[e,f]
Isomenthylamine (IX)	(+)-S[e,f]

a) In benzene.
b) The optically active hydrochlorides or carbamides possess the same signs of rotation as those for the respective amines of the same absolute configurations.
c) For the absolute configuration of I, III, V and methylamines (VII, VIII and IX), confer the Refs. 13, 2f, 14 and 15, respectively. The absolute configuration of II was deduced from the configuration of phenylbenzylcarbinol.[16]
d) The amines with the same configuration were obtained in toluene and in benzene (see Table 1).
e) The results obtained by Read and Story.[3]
f) The absolute configuration of the asymmetric carbon atom attached to the amino group.
g) The absolute configuration is not known.

10) a) L. M. Litvinenko and V. A. Dadali, Reaktsionnaya Sposobnost Organicheskikh Soedineni (Organic Reactivity), Tartu, Vol. 4, No. 2, 258 (1967); b) L. M. Litvinenko and A. F. Popov, *Dokl. Akad. Nauk SSSR*, **160**, 1124 (1965); *Chem. Abstr.*, **63**, 452e (1965).
11) F. Ebel, *Ber.*, **60**, 2079 (1927).

Table 4. Absolute configurations of unacylated alcohols in the partial acylation of racemic alcohols in the presence of brucine or strychinine[a)]

R, R′>CHOH		Unacylated alcohol (sign of rotation[2a)] and absolute configuration[16)])		
R	R′	Acetic anhydride + Brucine	Benzoyl chloride + Brucine	Benzoyl chloride + Strychinine
Me	Et	—	(−)-R	—
Me	*i*-Pr	—	(−)-R	(+)-S
Me	*n*-Bu	(−)-R	(−)-R	(−)-R
Me	Ph	(+)-R	(+)-R	(+)-R
Me	*cyclo*-Hex.	(−)-R	(−)-R	(−)-R
Me	Benzyl	(+)-S	(−)-R	(−)-R
t-Bu	Ph	(+)-?	(+)-?	(+)-?
n-Bu	Ph	—	(+)-R	(+)-R
n-Bu	*cyclo*-Hex.	—	(+)-?	(−)-?
Et	*n*-Pr	—	—	(−)-R
Et	*n*-Bu	—	—	(−)-R
Et	Ph	(+)-R	(+)-R	(+)-R
Et	*cyclo*-Hex.	—	(+)-R	(+)-R
Et	Benzyl	—	—	(−)-R
i-Pr	Benzyl	(+)-?	(−)-?	—
n-Bu	*i*-Pr	—	(−)-S	(−)-S

a) Data were taken from the experimental results of Wegler.[2a)]

configurations[2f,13-15)] of unsulfonylated amines are listed along with the observed signs of rotation; the signs of rotation for neomenthylamine (VIII) and isomenthylamine (IX) were cited from the data reported by Read and Story.[3)]

It is immediately obvious from Table 3 that the amine, with (R)-carbon atom attached to the amino-group, reacts faster than the (S)-enantiomer, with exception of III.

In a similar fashion, we can point out that in the benzoylation or the acetylation of various secondary alcohols, which were conducted in the presence of brucine or strychinine by Wegler,[2a)] the (S)-alcohols react faster than the (R)-alcohols, This is illustrated in Table 4; among 27 examples of the alcohols with known configurations,[16)] four examples seem to be the exceptions.

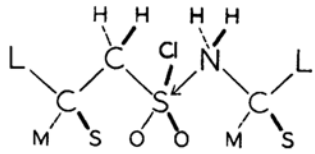
Recently, the similar coincidence of preferred absolute configurations has been disclosed for the kinetical resolution in some amidation reactions. For example, in amidation with (S)-(+)-2-methylamino-1-phenylpropane in the presence of dicyclohexylcarbodiimide,[2d)] six (R)-alkylphenylacetic acids, with excption of two, were found to react faster than respective (S)-enantiomers. Furthermore, the *N*-substituted amides of (−)-hydratropic acid were found to be formed in the presence of ethyl carbonate preferentially from (R)-primary amines (ten examples with exception of one), in comparison with the respective (S)-amines.[2f)]

In general, the enantiomeric rate ratio in these kinetical resolutions depends on the free-energy difference between the diastereomeric intermediates. Therefore, the simple coincidence of the preferred absolute configurations may suggest that the free-energy difference in these cases may be controlled phenomenally by the combinations (*e. g.*, dextro+dextro and levo+dextro) of the arrangements of three (large-, medium- and small-sized) groups attached to the respective asymmetric carbons of the diastereometric intermediates. This coincidence seems to be a general trend in the kinetical resolution, so far as it has been explored. However, we should find more examples available in order to confirm its conclusive generality.

In connection with an interpretation of the preference in configuration, examination of the most preferred constellation in the diastereomeric intermediates seems to be successful for several examples[2b,2d,17)] on the basis of a "rigid" model, which was proposed in the case of asymmetric "synthesis" of carbonyl-addition type.[18,19)] However, in the present case of asymmetric sulfonylation with (+)-camphor-10-sulfonyl chloride, in a

12) R. F. Hudson and I. Stelzer, *J. Chem. Soc. (B)*, **1966**, 775.
13) H. E. Smith, S. L. Cook and E. Warren, Jr., *J. Org. Chem.*, **29**, 2270 (1964).
14) W. Leithe, *Ber.*, **65**, 929 (1932).
15) See J. L. Simmonsen, "The Terpenes," Vol. II, Cambridge Univ. Press, London (1949), p. 242.
16) K. Freudenberg, "Stereochemie," Vol. II, Franz Deuticke, Leipzig (1932), p. 696.
17) H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 276 (1965).
18) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); see also Ref. 1b, p. 69.
19) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); see also Ref. 1b, p. 71.

supposed intermediate (see below) the two asymmetric groups lie so remote from each other that it seems difficult to apply a "rigid" model similar to the one proposed by Cram[18] or Prelog.[19] A reasonable elucidation of the preferred configuration in these sulfonylations should be postponed in the future study.



With respect to the extent of these kinetic resolution, we can point out the following factors which may affect the extent of resolution. First, the more tightness of the bonds between the substrate and the reagent in the supposed intermediate may cause the greater degree of inhibition of the free rotation of the respective asymmetric groups, and result in the more extent of resolution. Secondly, the greater degree of the polymolecular association of amines may require their more specific orientation[12] in the intermediate, and cause an enlarged difference in the free energies of diastereomeric intermediates. Thirdly, the multiplicity of the reaction step may enlarge the extent of resolution, since in the multi-step reaction the substrate is kinetically resolved at least twice, or more, until it is converted to the product. The exderimental verification of these factors will be a subject of the future study.

Experimental

Materials. (+)-Camphor-10-sulfonyl chloride was prepared according to Smiles and Hilditch[20] from thionyl chloride and (+)-camphor-10-sulfonic acid, and recrystallized twice from ether; mp 67.0—68.0°C, corr.; $[\alpha]_D^{29}$ +36.5° (*c* 7.72, chloroform). (±)-α-Phenylethylamine (bp 74.0°C/15 mmHg) and (±)-α-pipecoline (bp 128°C) were purified by fractional distillation. (±)-α,β-Diphenylethylamine (bp 165—170°C/15 mmHg), (±)-α-(β-naphthyl)-ethylamine (bp 160°C/13 mmHg; mp 198—199°C, uncorr., for the hydrochloride), and (±)-α-(β-naphthyl)-benzylamine (bp 200—206°C/5 mmHg, mp 119—120°C) were prepared from the respective ketones by the method described by Ingersoll.[21] (±)-Menthylamine (bp 70.0°C/7 mmHg) and (−)-menthylamine (bp 80°C/12 mmHg) were prepared from the respective menthone oximes according to the method of Wallach.[22] (±)-2-Aminobicyclo[2.2.2]octane (mp 138—140°C, decomp.) was prepared by the method described by Seka and Tramposch.[23]

The Recovery of Unsulfonylated Amines from the Products of the Sulfonylation (General Procedure). The sulfonylation was carried out by mixing the sulfonyl chloride with the equal molar quantity of the racemic amine in dry benzene (or toluene). After standing overnight at room temperature, the hydrochloride of the unchanged amine was filtered, and its optical rotation was measured in aqueous solution, or else it was measured in an appropriate solvent after isolation as a free amine or a carbamide. No characterization of the sulfonamide so produced was carried out. The details of the isolation procedures for the respective sulfonylations are cited below.

Isolation of Unsulfonylated α-Phenylethylamine (I). To a solution of (+)-camphor-10-sulfonyl chloride (40.0 g, 0.155 mol) in benzene (50 cc), 20.0 g (0.164 mol) of (±)-I in 50 cc of benzene was added. After standing overnight at 27—30°C, α-phenylethylamine hydrochloride (9.0 g, mp 155—159°C, 34.7% of the starting amine), which separated from the reaction mixture, was filtered; a part of the hydrochloride was dissolved into an appropriate amount of water for the measurement of the optical rotation; $[\alpha]_D^{32}$ of the hydrochloride, −0.038±0.004° (*c* 20.0, water); lit.[4] $[\alpha]_D$ for the optically pure hydrochloride, −6.20° (*c* 20.0, water).

In a duplicate run, 15.2 g (0.125 mol) of (±)-I and 31.4 g (0.125 mol) of (+)-camphor-10-sulfonyl chloride afforded 6.0 g (30.5% of the starting amine) of (−)-phenylethylamine hydrochloride (mp 156—159°C; $[\alpha]_D^{32}$ −0.057°±0.005° (*c* 29.0, water); lit.[4] $[\alpha]_D$ for the optically pure hydrochloride, −8.27° (*c* 31.45, water)).

Isolation of Unsulfonylated α,β-Diphenylethylamine (II). A mixture of (±)-II (10.5 g, 0.0537 mol) and (+)-camphor-10-sulfonyl chloride (13.5 g, 0.0538 mol) in 100 cc of dry benzene was allowed to react overnight at 25—30°C. The crystals (15.0 g, 42.2% yield) of α,β-diphenylethylamine hydrochloride (mp 220—230°C), which precipitated in the reaction mixture, was filtered, and washed with 20 cc of benzene; $[\alpha]_D^{31}$ −1.83±0.15° (*c* 0.87, water); lit.[4] $[\alpha]_D^{15}$ for the optically pure hydrochloride, −70° (*c* 0.7, water). After evaporation of a part of the filtrate, the second crop (1.0 g) of the hydrochloride (total yield 50.7%) was obtained. No characterization of the product from the mother liquors was undertaken.

Isolation of Unsulfonylated α-(β-Naphthyl)-ethylamine (III). A mixture of (±)-III (10.0 g, 0.0588 mol) and (+)-camphor-10-sulfonyl chloride (14.8 g, 0.0588 mol) in benzene (100 cc) was allowed to stand overnight at 28—30°C. The crystals of α-(β-naphthyl)-ethylamine hydrochloride (5.5 g, 45.4% of the starting amine, mp 200—210°C), which precipitated during the reaction, was filtered. A part (2.7 g) of the hydrochloride was converted to its carbamide (2.5 g) by mixing aqueous potassium cyanate with the chloride. The carbamide was recrystallized from 95% ethanol giving 2.3 g of pure carbamide (mp 197—198°C; $[\alpha]_D^{30}$ +2.04±0.03° (*c* 1.5, ethanol), +2.03° (*c* 0.96, ethanol); lit.[6] $[\alpha]_D^{17}$ for the optically pure carbamide, +67.9° (*c* 1.12, ethanol).

20) S. Smiles and T. P. Hilditch, *J. Chem. Soc.*, **91**, 522 (1907).
21) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. 2, p. 503 (1943); see also M. L. Moore, "Leuckart Reaction," in "Organic Reactions," Vol. 5, p. 320 (1949).
22) O. Wallach, *Liebigs Ann. Chem.*, **276**, 300 (1893).
23) R. Seka and O. Tramposch, *Ber.*, **75**, 1379 (1942).

Isolation of Unsulfonylated α-(α-Naphthyl)-benzylamine (IV). A mixture of (±)-IV (4.45 g. 0.0192 mol) and (+)-camphor-10-sulfonyl chloride (4.80 g, 0.0191 mol) in 130 cc of benzene was allowed to stand overnight at 25°C. The crystals (2.50 g) of α-(α-naphthyl)-benzylamine hydrochloride, which separated from the reaction mixture, was filtered, and shaken with 30% aqueous sodium hydroxide and ether. From the ethereal solution 2.0 g (45.0% of the starting amine) of the amine (IV) (mp 116—118°C) was recovered; $[\alpha]_D^{22}$ −0.94±0.04° (*c* 9.68, benzene); lit.[7] $[\alpha]_D^{15}$ for the optically pure IV, +63.6° (*c* 4.8, benzene).

Isolation of Unsulfonylated α-Pipecoline (V). A mixture of (±)-V (4.6 g, 0.0464 mol) and (+)-camphor-10-sulfonyl chloride (12.0 g, 0.0478 mol) in 100 cc of benzene was kept overnight at 23—25°C. The hydrochloride (3.0 g) of α-pipecoline, separated as a slightly hygroscopic crystals, was shaken with 20% aqueous sodium hydroxide and ether. The ethereal solution was dried with potassium hydroxide, and fractionated to give α-pipecoline (2.0 g; 43.4% of the starting amine; bp 110—120°C; $[\alpha]_D^{24}$ +0.43±0.01° (*c* 13.3, benzene); lit.[8] $[\alpha]_D^{15}$ for the optically pure V, 30.0° (*c* 20, benzene).

Isolation of Unsulfonylated 2-Aminobicyclo-[2.2.2]octane (VI). A mixture of (±)-VI (6.0 g, 0.0480 mol) and (+)-camphor-10-sulfonyl chloride (12.0 g, 0.0478 mol) in 110 cc of benzene was allowed to react for two days at 15°C. The hydrochloride (3.5 g; 45.7% of the starting amine) of VI was filtered, and showed no optical rotation within the experimental error ($[\alpha]_D^{15}$ 0.00+0.01° (*c* 5.0, water) for the hydrochloride, $[\alpha]_D^{15}$ 0.00±0.05° (*c* 3.0, benzene) for the free amine).

Isolation of Unsulfonylated Menthylamine (VII). A solution of (+)-camphor-10-sulfonyl chloride in toluene was prepared by dissolving about 6 g of the chloride into 100 cc of toluene; the concentration (0.213 M) was determined by the analysis of chloride ion liberated after 2 hr refluxing of an aliquot (1 cc) with 15 cc of 0.05 N ethanolic potassium hydroxide. The (±)-VII solution (100 cc) was prepared by dissolving 3.30 g of the amine into dry toluene (100 cc). The toluene solutions (80 cc for each) of the chloride and the amine were cooled at −40.0°C, and mixed with each other in one portion. After standing for 5 hr at −40.0°C, the unsulfonylated menthylamine was isolated following the method described by Read and Story.[3] The reaction mixture was made slightly alkaline with 5% sodium hydroxide and shaken until no further reaction occured. The toluene solution was washed with two 100-cc portions of water and extracted with two 100-cc portions of 10% aqueous hydrochloric acid. The hydrochloric acid solution of the amine was evaporated to afford 1.1 g (34.1%) of menthylamine hydrochloride ($[\alpha]_D^{25}$ +10.73±0.18° (*c* 1.0, water); lit.[9] $[\alpha]_D^{15}$ +36.6° (water)).

In the succeeding run carried out for 5 hr at −6.0°C, from a 0.23 M solution (80 cc) of (+)-camphor-10-sulfonyl chloride and a 0.23 M solution (80 cc) of (±)-menthylamine 1.8 g of menthylamine hydrochloride ($[\alpha]_D^{25}$ +7.27±0.10° (*c* 1.0, water)) was obtained.

Kinetic Measurements. A solution (0.1 M, 2.0 cc for each) of (+)-camphor-10-sulfonyl chloride and of (−)-menthylamine in toluene were placed in a Y-shaped tube, and kept at an appropriate reaction temperature in a thermostatted ethanol bath, which was cooled in another carbon dioxide - ethanol bath kept at about −45°C. The two 0.1 M solutions (2 cc for each) were mixed in one portion under nitrogen atmosphere; after appropriate reaction time, the reaction was stopped by adding 1 cc of cold toluene, saturated with formic acid; the solution was extracted with 10 cc of water. From the aqueous extracts 5 cc of an aliquot was titrated by the Volhard method. The rate data were treated graphically by the plot described in text; the results are shown in Table 2 and Fig. 1. In each case the reaction was followed to at least 60% completion.