

## The Resolution and Rotations of *trans*-2-Aminocyclohexanecarboxylic Acids and Derivatives

Hiroyuki NOHIRA, Kenji EHARA and Akira MIYASHITA

*Department of Applied Chemistry, Faculty of Science and Engineering, Saitama University, Urawa, Japan*

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Optically active *trans*-2-aminocyclohexanecarboxylic acids [(+)-**1** and (−)-**1**] have been prepared by a preferential crystallization of racemic *N*-benzoyl *trans*-2-aminocyclohexanecarboxylic acid [(±)-**2**]. Active **2** have been used for preparation of such active *trans*-1,2-disubstituted cyclohexanes as (+)-, and (−)-ethyl *trans*-2-aminocyclohexanecarboxylate [(+)-**3** and (−)-**3**], (+)-, and (−)-*trans*-2-aminocyclohexanemethanol [(+)-**4** and (−)-**4**], (+)-*trans*-2-bromomethylcyclohexylamine hydrobromide [(+)-**5**], and (+)-*trans*-2-methylcyclohexylamine [(+)-**6**]. Amine-nitrous acid reaction of these cyclohexylamines to give the corresponding hydroxy compounds (**7**, **8**, **9**) has also been examined. It was confirmed that the signs of optical rotations of these hydroxy compounds are the same as those of the starting amines. It has been shown that observed molecular rotations of these active 1,2-disubstituted cyclohexanes are in agreement, in sign and order of magnitude, with those calculated following Brewster's procedures presented in 1959 and in 1967.

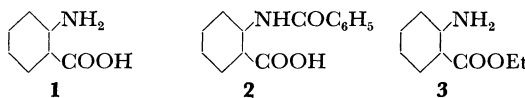
In 1959, Brewster<sup>1)</sup> presented a useful model for the calculation of optical rotations which has been applied to various types of optically active organic compounds.<sup>2)</sup> Recently a more theoretical treatment has been proposed by the same author.<sup>3)</sup> In this treatment the calculation is relatively simple in the case of 1,2-disubstituted cyclohexane systems. In this connection, Pascual<sup>4)</sup> has reported that the observed rotation of optically active 2-hydroxycyclohexanecarboxylic acids was in good agreement with that calculated by Brewster's earlier procedure.

We also became interested in correlations between observed and calculated rotations for 2-aminocyclohexanecarboxylic acids (**1**) and their derivatives, especially rotations calculated by the procedure proposed recently. Although the racemic isomers of *cis*- and *trans*-2-aminocyclohexanecarboxylic acid are known,<sup>5,6)</sup> there has been no investigation of their resolution.

In the present investigation, resolution of *trans*-2-

aminocyclohexanecarboxylic acid [(±)-**1**] has been first realized by fractional crystallization of diastereoisomeric salts of *N*-benzoyl *trans*-2-aminocyclohexanecarboxylic acid [(±)-**2**] and an active amine, such as quinine or ephedrine. Preferential crystallization initiated by inoculation has now been found to be more convenient. When a saturated solution of (±)-**2** is carefully inoculated with a pure crystal of one of the enantiomers obtained by fractional crystallization of the diastereoisomeric salts, the crystal grows and an appreciable amount of pure crystals are separated from the racemic solution. The resulting filtrate is then saturated with addition of the racemate, and inoculation with the antipode gives another good crop of active crystals. The process can be repeated, and the optically active acids [(+)-**2** and (−)-**2**] have been prepared in large quantities.

Various optically active 1,2-disubstituted cyclohexanes have been prepared from active **2**. For example, hydrolysis of active **2** with concentrated hydrochloric acid, and then esterification with ethanol gave the active esters [(+)-**3** and (−)-**3**]. The active free amino acids [(+)-**1** and (−)-**1**] have been prepared by hydrolysis of active **3**.



Active *trans*-2-aminocyclohexanemethanols [(+)-**4** and (−)-**4**], *trans*-2-bromomethylcyclohexylamine [(+)-**5**], and *trans*-2-methylcyclohexylamine [(+)-**6**] have been prepared by the following reaction sequence.

1) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475, 5483, 5493 (1959).

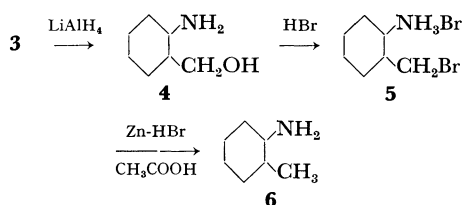
2) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y. (1962), p. 401.

3) J. H. Brewster, "Helix Models of Optical Activity" in "Topics in Stereochemistry," Vol. II, ed. by N. L. Allinger and E. L. Eliel, Interscience Publishers, Inc., New York, N. Y. (1967), pp. 1—72.

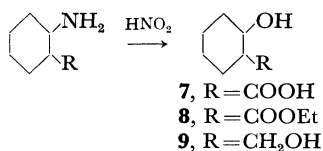
4) J. Pascual, *An. Real. Soc. Espan. Fis. Quim. Ser. B*, **63**, 727 (1967).

5) S. Hünig and H. Kahaneck, *Chem. Ber.*, **86**, 518 (1953).

6) E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966).



Treatment of these amines with nitrous acid gave the corresponding hydroxy derivatives:



The stereochemistry of the amine-nitrous acid reaction in cyclohexane systems has been investigated extensively. It has been shown that equatorial amines react with nitrous acid to give mainly equatorial alcohols without any alteration of configuration.<sup>7)</sup>

In the present investigation, it was also confirmed that the signs of observed optical rotations of the hydroxy compounds obtained by the amine-nitrous acid reaction are the same as those of the starting amines. The absolute configuration of (–)-7 has been determined by Faixat *et al.*,<sup>8)</sup> and

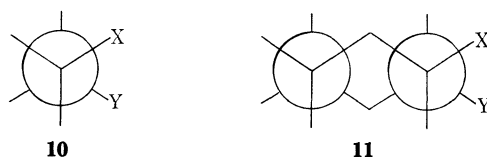


Fig. 1. Dextrorotatory conformations of 1,2-disubstituted ethane and cyclohexane.

the result is consistent with Brewster's model. In view of this, we might conclude that (+)-1 and (–)-1 have absolute configurations of 1(S), 2(S) and 1(R), 2(R), respectively.

Calculation of molecular rotations  $[M]_D$  of these 1,2-*trans*-disubstituted cyclohexanes was performed using Brewster's theory. According to his theory, a right-handed helical chain as X–C–C–Y in Fig. 1 makes a dextrorotatory contribution to  $[M]_D$ . From a summation of these conformational units, a skewed conformation of 1,2-disubstituted ethane (10) and 1,2-diequatorially substituted cyclohexane (11) give the same  $[M]_D$  value. In the present calculation, it has been assumed that these 1,2-*trans*-disubstituted cyclohexanes exist in the diequatorial conformation as shown in 11.

Table 1 shows the calculated  $[M]_D$  of several 1,2-*trans*-disubstituted cyclohexanes along with observed  $[M]_D$ . The procedures A and B are so-called semi-

TABLE 1. Mp, bp AND MOLECULAR ROTATIONS OF *trans*-1,2-DISUBSTITUTED CYCLOHEXANES

Compd.	Substituents		Mp or bp/mmHg, °C		Molecular rotations, $[M]_D$ , deg			
	X	Y	racemate	enantiomers	observed value (solvent)	calculated value A	calculated value B	calculated value C
1	COOH	NH <sub>2</sub>	274 <sup>a)</sup>	264	95 (H <sub>2</sub> O)	69	71	82
2	COOH	NHCOC <sub>6</sub> H <sub>5</sub>	227 <sup>a)</sup>	258	110 (EtOH)	—	—	—
3	COOEt	NH <sub>2</sub>	103–104/11 <sup>a)</sup>	109–110/13	85 (ether)	70	71	—
4	CH <sub>2</sub> OH	NH <sub>2</sub>	83–85/1 <sup>a)</sup>	106–108/6	28 (EtOH)	59	52	—
5	CH <sub>2</sub> Br	NH <sub>3</sub> Br	—	207–208	98 (EtOH)	108	—	—
6	CH <sub>3</sub>	NH <sub>2</sub>	150/760 <sup>c)</sup>	142–144/758	35 (ether)	59	52	55
7	COOH	OH	111 <sup>d)</sup>	107–109 110–111 <sup>f)</sup>	70 (EtOH) 77 (CHCl <sub>3</sub> )	52	31	75 <sup>e)</sup>
8	COOEt	OH	130–132/25 <sup>d)</sup>	130–132/23	64 (ether)	53	31	—
9	CH <sub>2</sub> OH	OH	111–113/3 122–124/2 <sup>g)</sup>	119–120/4 128–130/2.3 <sup>h)</sup>	27 (ether) 28 (EtOH) <sup>h)</sup>	42	23	—

A: Calcd from the theoretical equation,  $[M]_D = 251d_1d_2d_3/(d_1+d_2+d_3)^2(\sum AR_D)f(n)$ , using  $f(n) = 1.33$ , in Ref. 3, p. 29.

B: Calcd from the semi-empirical equation,  $[M]_D = 160(R_1^{1/2} - R_H^{1/2})(R_1^{1/2} - R_H^{1/2})$ , in Ref. 2, p. 404.

C: Calcd from the semi-empirical equation,  $[M]_D = k(X-H)(Y-H)$ , using empirical values of conformational rotatory powers in Ref. 2, p. 404.

a) Refs. 5 and 9. b) Ref. 6. c) Ref. 10. d) J. Pascual, J. Sistare and A. Regas, *J. Chem. Soc.*, **1949**, 1943. e) Ref. 4. f) M. A. Ferrer, P. Gomis and J. Pascual, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **63**, 499 (1967). g) L. J. Dolby, C. N. Lieske, D. R. Rosencrantz and M. J. Schwarz, *J. Amer. Chem. Soc.*, **85**, 47 (1963). h) L. J. Dolby, F. A. Meneghini and T. Koizumi, *J. Org. Chem.*, **33**, 3060 (1968).

7) a) J. A. Mills, *J. Chem. Soc.*, **1953**, 260; b) W. Hüchel, *Ann.*, **533**, 10 (1938); c) W. Hüchel and K. D. Thomas, *ibid.*, **645**, 177 (1961) and Ref. 2, pp. 226–

227.

8) J. E. Faixat, M. A. Febrer and J. Pascual, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **57**, 705 (1961).

empirical.<sup>1,2)</sup> Procedure C is a more exact theoretical treatment based on physical laws which govern the interaction between a helical conductor and electro-magnetic waves.<sup>3)</sup>

It is worth noting that in this experiment our observed results of  $[M]_D$  are in rough agreement with the results obtained by following Brewster's treatment, in which such a drastic model is assumed for molecular asymmetry as to consider a skewed chain of four atoms as a helical conductor.

### Experimental

**( $\pm$ )-*N*-Benzoyl-*trans*-2-aminocyclohexanecarboxylic Acid [( $\pm$ )-2].** ( $\pm$ )-*trans*-2-Aminocyclohexanecarboxylic acid [( $\pm$ )-1] was prepared from anthranilic acid by the action of metallic sodium in isoamyl alcohol.<sup>5,9)</sup> ( $\pm$ )-2 was prepared by the reaction of ( $\pm$ )-1 and benzoyl chloride in the usual way.

**(-)-*N*-Benzoyl-*trans*-2-aminocyclohexanecarboxylic Acid [(-)-2].** To a mixture of 3.71 g (0.015 mol) of ( $\pm$ )-2 and 5.18 g (0.016 mol) of quinine was added 130 ml of 70% methanol (methanol 70 and water 30 in volume). The mixture was briefly heated on a steam bath to dissolve all solid, then allowed to stand at room temperature. After 10 hr, the resulting fluffy needles were collected by filtration to give 6.0–6.5 g of salt, mp 125–130°C. Two or three recrystallizations of this material using 13–15 ml of 70% methanol per gram of salt gave 1.2–1.8 g of material whose properties did not change upon further recrystallization, mp 143–145°C,  $[\alpha]_D^{25}$  –111.6° (*c* 2.5, ethanol).

With 3*N* hydrochloric acid the salt was converted into crude (–)-2, which was purified by recrystallization from 70% methanol to give 0.22–0.37 g (12–20%) of (–)-2, mp 257–258°C (in a capillary tube), subliming at near 240°C on an open plate,  $[\alpha]_D^{25}$  –44.5° (*c* 0.67, ethanol).

Found: C, 68.26; H, 7.11; N, 5.71%. Calcd for  $C_{14}H_{17}NO_3$ : C, 67.99; H, 6.93; N, 5.66%.

*l*-Ephedrine salt of (–)-2 melts at 186–188°C,  $[\alpha]_D^{25}$  –39.7° (*c* 2.5, ethanol).

**(+)-*N*-Benzoyl-*trans*-2-aminocyclohexanecarboxylic Acid [(+)-2].** To a mixture of 3.71 g (0.015 mol) of ( $\pm$ )-2 and 2.75 g (0.015 mol) of *l*-ephedrine monohydrate was added 20 ml of 70% methanol. The mixture was heated on a steam bath to dissolve all solid. The solvent was then evaporated to dryness. The residue was recrystallized from 10 ml of 30% methanol to give 4.0–4.3 g of salt, melting at 160–175°C. Two or three recrystallizations of this material using 1.0–1.5 ml of 30% methanol per gram of salt gave 0.9–1.3 g of a material melting at above 190°C. With 3*N* hydrochloric acid the salt was converted into crude (+)-2, which was purified by recrystallization with 70% methanol, yielding 0.20–0.30 g (11–16%) of (+)-2, mp 257–258°C (in a capillary tube), subliming at near 240°C on an open plate,  $[\alpha]_D^{25}$  +44.5° (*c* 0.67, ethanol).

Found: C, 68.13; H, 7.08; N, 5.75%. Calcd for  $C_{14}H_{17}NO_3$ : C, 67.99; H, 6.93; N, 5.66%.

The pure salt of *l*-ephedrine and (+)-2 melts at 195–197°C,  $[\alpha]_D^{25}$  +10.0° (*c* 2.5, ethanol). Quine salt of

(+)-2 melts at 122–123°C,  $[\alpha]_D^{25}$  –72.3° (*c* 2.5, ethanol).

**Resolution of ( $\pm$ )-2 by the Preferential Crystallization.** A mixture of 10 g of ( $\pm$ )-2 and 800 ml of 70% methanol was heated on a steam bath to dissolve all crystals, then cooled to a temperature of 50–60°C, and it was inoculated with 0.1 g of pure crystals of (–)-2. After standing at room temperature for about 10 hr, the inoculated solution was decanted and residual crystals were washed with 70% methanol to yield 0.5–0.8 g (10–14%) of (–)-2, mp 255–257°C,  $[\alpha]_D^{25}$  –41±2° (*c* 0.67, ethanol).

The decanted solution was heated again with addition of 0.5–0.7 g of ( $\pm$ )-2, then inoculated with pure crystals of (+)-2, antipode of the seeds used in the preceding crystallization, to yield 1.1–1.6 g (20–30%) of (+)-2, mp 254–257°C,  $[\alpha]_D^{25}$  +41±2° (*c* 0.67, ethanol).

The process was repeated in this way. Crystals separated by each inoculation were then put together and recrystallized from 95% ethanol to yield a pure sample of each enantiomer of 2.

**(+)-Ethyl-*trans*-2-aminocyclohexanecarboxylate [(+)-3].** A mixture of 24.7 g (0.1 mol) of (+)-2 and 750 ml of concentrated hydrochloric acid was heated under reflux until crystals of (+)-2 had completely dissolved (for 56–72 hr). The mixture was then cooled, and the resulting benzoic acid was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was esterified by means of absolute ethanol and dry hydrogen chloride, and worked up in a known manner<sup>9)</sup> to yield 14.9 g (87%) of (+)-3, bp 109–110°C/13 mmHg,  $[\alpha]_D^{25}$  +49.7° (*c* 4, ether).

Similarly, (–)-3 was prepared from (–)-2 in 75–90% yield, bp 109–110°C/13 mmHg, 113–114°C/16 mmHg,  $[\alpha]_D^{25}$  –49.8° (*c* 4.5, ether).

Found: N, 8.05%. Calcd for  $C_{16}H_{21}NO_2$ : N, 8.18%. *N*-Benzoyl derivative of (–)-3 had a mp 146°C and  $[\alpha]_D^{25}$  –38.5° (*c* 2, ethanol).

Found: N, 5.17%. Calcd for  $C_{16}H_{21}NO_3$ : N, 5.09%.

**(+)-*trans*-2-Aminocyclohexanecarboxylic Acid [(+)-1].** A sample of (+)-3 (1.0 g) was refluxed with 10 times its quantity of water (10 ml) for 10 hr. The solvent was then evaporated to dryness under reduced pressure. The residue was recrystallized from 70% ethanol, and dried over phosphorous pentoxide to yield a pure sample of (+)-1 (0.5 g), mp 264°C,  $[\alpha]_D^{25}$  +66.5° (*c* 2, water).

Found: N, 9.54%. Calcd for  $C_7H_{13}NO_2$ : N, 9.78%.

Similarly, (–)-1 was prepared from (–)-3, mp 264°C,  $[\alpha]_D^{25}$  –65.5° (*c* 2, water).

Found: N, 9.63%.

(+)-, (–)-, and ( $\pm$ )-*trans*-2-aminocyclohexanemethanol [(+)-4, (–)-4, and ( $\pm$ )-4] were prepared in 75–80% yield from (+)-3, (–)-3, and ( $\pm$ )-3, respectively, by the action of lithium aluminum hydride in ether<sup>6)</sup> or tetrahydrofuran. (+)-4, bp 106–108°C/6 mmHg, mp 36–37°C,  $[\alpha]_D^{25}$  +21.2° (*c* 5, ethanol). (–)-4, bp 98–102°C/3.5 mmHg, mp 37–38°C,  $[\alpha]_D^{25}$  –21.6° (*c* 5, ethanol). ( $\pm$ )-4, bp 125–127°C/15 mmHg, mp 65–67°C (lit.<sup>6)</sup> bp 83–85°C/1 mmHg).

*N*-Benzoyl derivative of (+)-4 had a mp 151°C and  $[\alpha]_D^{25}$  +41.2° (*c* 3.4, ethanol).

Found: N, 6.13%. Calcd for  $C_{14}H_{19}NO_2$ : N, 6.00%.

*N*-Benzoyl derivative of ( $\pm$ )-4 had a mp 145°C.

Found: N, 5.95%.

**(+)-*trans*-2-Bromomethylcyclohexylamine Hy-**

9) A. Einhorn and A. Meyerberg, *Chem. Ber.*, **27**, 2467 (1894).

**drobromide [(+)-5].** A mixture of 2.58 g (0.02 mol) of (+)-**4** and 10 ml of 47% hydrobromic acid was heated on an oil-bath at 160–170°C for 1 hr with bubbling dry hydrogen bromide gas. The temperature was finally raised to 200°C. The resulting material was purified by dissolving with ethanol and then precipitating with ether, giving 5.2 g (95%) of (+)-**5**, mp 207–208°,  $[\alpha]_D^{20} +36.0^\circ$  (*c* 3, ethanol).

Found: N, 5.33%. Calcd for  $C_7H_{15}NBr_2$ : N, 5.13%.

**(+)-trans-2-Methylcyclohexylamine [(+)-6].** To a mixture of 4.1 g (0.015 mol) of (+)-**5**, 15 ml of acetic acid, and 15 ml of fuming hydrobromic acid was added slowly 2.5 g (0.038 atom) of zinc dust with stirring. The mixture was then heated under reflux for 2 hr. After removal of solvent under reduced pressure, the residue was dissolved in 10 ml of water. The resulting solution was treated with 12 g of sodium hydroxide and 20 ml of water, and extracted with three 4 ml portions of ether. The ethereal extract was dried (KOH), concentrated, and distilled giving 1.1 g (65%) of (+)-**6**, bp 142–144°C/758 mmHg,  $[\alpha]_D^{19} +30.8^\circ$  (*c* 10, ether).

Hydrobromide of (+)-**6** had a mp 299–301°C and  $[\alpha]_D^{20} +23.0^\circ$  (*c* 3, ethanol).

Found: N, 7.16%. Calcd for  $C_7H_{16}NBr$ : N, 7.22%.

*N*-Benzoyl derivative of (+)-**6** had a mp 164°C (lit.<sup>10</sup>) (racemate) mp 146°C], and  $[\alpha]_D^{20} +48.0^\circ$  (*c* 5, ethanol).

Found: N, 6.22%. Calcd for  $C_{14}H_{19}NO$ : N, 6.45%. (–)-*trans*-2-Hydroxycyclohexanecarboxylic acid [(–)-**7**], (–)-ethyl *trans*-2-hydroxycyclohexanecarboxylate [(–)-**8**], and (–)-*trans*-2-hydroxymethylcyclohexanol [(–)-**9**] were prepared from corresponding amines, that is, (–)-**1**, (–)-**3**, and (–)-**4**, respectively, according to a conventional method<sup>7,8,11</sup> in 50–60% yields. Their physical properties are listed in Table 1.

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10) A. Skita, *Ber.*, **56**, 1014 (1923).

11) M. Mousseron, J. Jullien and F. Winternitz, *Compt. Rend.*, **226**, 1909 (1948).