during storage at room temperatures. Aqueous solutions of sodium borohydride, stabilized with a few drops of concentrated sodium hydroxide solution, show much greater stability at room temperature, and therefore were employed in the subsequent reductions. The sodium borohydride solutions were prepared in beakers and added to the reaction mixture with a dropper; when a dropping funnel, buret, etc., was used, in which the wetted surface was large, the evolution of hydrogen was excessive. All reductions were conducted in aqueous methanol, the quantity of methanol being just sufficient to keep the nitro compounds in solution. The reduced products were contaminated with traces of the initial carbonyl compounds (determined by infrared analysis). The initial nitrocarbonyl compounds were removed by washing ethereal solutions of the product with several portions of saturated sodium bisulfite solution. It is especially necessary to shake the mixture thoroughly for at least five minutes with each portion of bisulfite solution; a long contact time is necessary to remove the contaminating compound.

4,4-Dinitro-1-pentanol.—Sodium borohydride solution (0.795 g., 0.021 mole, in 10 ml. of water containing one drop of 6 *N* sodium hydroxide) was added dropwise (15 minutes) to a stirred solution of 4,4-dinitro-1-pentanal (7.27 g., 0.0413 mole), methanol (25 ml.) and water (10 ml.) cooled in an ice–water mixture. The *p*H of the mixture, after the reaction was completed, was 9.2. The solution was partially neutralized with urea–acetic acid solution (10 ml., 0.028 mole, each of acetic acid and urea; the *p*H after the addition was 6); the *p*H was then adjusted to 3 by addition of 18 *N* sulfuric acid (2 ml.). The blue-green acidic solution was extracted with ether; the ether extract was dried with sodium sulfate and distilled to give **4,4-dinitro-2-pentanol** (4.97 g., 67.6% yield) (Table II), b.p. 114–118° (1.2 mm.).

5-Nitro-2-pentanol.—A solution of sodium borohydride (2.8 g., 0.075 mole), water (50 ml.), and concd. sodium hydroxide (one drop) was added dropwise in one hour to a slowly stirred mixture of 5-nitro-2-pentanone (19.7 g., 0.15 mole) and methanol (50 ml.). The temperature of the mixture was maintained at 20–25° by external cooling and its *p*H was kept at 3–4 (determined by *p*H meter) by the continuous addition of 3 *N* sulfuric acid. Hydrogen was evolved during addition of the sodium borohydride, and a white precipitate formed. After addition was completed, the mixture was allowed to stand for 5 minutes; excess sodium borohydride was then destroyed by adding concd. sulfuric acid (1 ml.). After the reaction mixture had been diluted to 350 ml. with water and neutralized with concd. sodium hydroxide, the homogeneous solution was extracted with ethyl ether. The ether extracts were combined, washed with saturated sodium bisulfite solution (3 × 150 ml., 5 minutes with each portion) and saturated sodium chloride solution, and filtered through anhydrous sodium sulfate. Benzene was added, and the solvents were removed by distillation. Distillation of the product, after a few crystals of boric acid had been added, gave **5-nitro-2-pentanol** (11.3 g., 0.1 mole) as a colorless liquid in 86.6% yield, b.p. 101–102.5° (2 mm.).

Because of the difficulty of preparing a solid derivative of the nitro alcohol, 5-nitro-2-pentanol was characterized by conversion into 4-hydroxy-1-pentanal 2,4-dinitrophenylhydrazone in the following manner. A solution of 5-nitro-2-pentanol (1 g.), sodium hydroxide (0.4 g.), methanol (5 ml.) and water (10 ml.) at 0–5° was added dropwise to a mixture of concd. sulfuric acid (2.5 ml.) in water (12 ml.) at 0–5°. The mixture was extracted with ethyl ether and the combined extracts were filtered through anhydrous sodium sulfate. The ether was removed by evaporation in a stream of air; crude 4-hydroxy-1-pentanal remained as a colorless oil. The hydroxyaldehyde was converted into its 2,4-dinitrophenylhydrazone by reaction with an ethanolic mixture of 2,4-dinitrophenylhydrazine and concd. sulfuric acid. The resulting precipitate was recrystallized 4 times from hot ethanol to give **4-hydroxy-1-pentanal 2,4-dinitrophenylhydrazone** in 37.3% yield, as fine yellow needles, m.p. 124.0–125.5°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: N, 19.85. Found: N, 19.92.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Problem of the Configurations of Hydratropic Acid and Atrolactic Acid. Application of the Method of Melting Point–Composition Diagrams

BY KURT MISLOW AND MILTON HEFFLER

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The solid–liquid phase relationships of (+)-hydratropamide and the enantiomorphous (+)-2-chloro-2-phenylacetamides have been found to differ, in that (+)-hydratropamide forms solid solutions with (+)-2-chloro-2-phenylacetamide but an immiscible mixture with (−)-2-chloro-2-phenylacetamide. This result, considered in context with the fact that (+)-2-chloro-2-phenylacetamide was obtained from L(+)-mandelic acid *via* the use of thionyl chloride, independently confirms prior conclusions regarding the configuration of (+)-hydrotropic acid relative to that of glyceraldehyde. The solid–liquid phase relationships of (−)-atrolactic acid and the enantiomorphous mandelic acids have been investigated and found to be of the same type. An attempt to confirm the configuration of atrolactic acid by the method of melting point–composition diagrams was thus rendered ineffective.

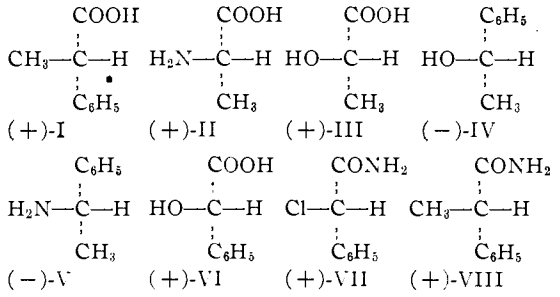
Optically active substances may exhibit a variety of phase relationships with their enantiomers; thus racemic mixtures ("conglomerates"), compounds ("racemates") and solid solutions ("pseudo-racemates") are encountered. Differences in phase behavior have often been utilized in the problem of relating the configurations of similarly constituted substances.[1] The basis for such correlations rests on the premise that a significance, capable of being rationalized in terms of molecular configuration, may be attached to any *difference* in the phase behavior of mixtures of configurationally related substances, Cabcx and Cabcy (or xcbaC and ycbaC, the corresponding enantiomers), and in the phase behavior of mixtures of configurationally quasi-enantiomorphous substances, Cabcx and ycbaC (or xcbaC and Cabcy). In practice, only three types of such *differences* in behavior have been noted. As of type 1 one may consider instances where mixtures of Cabcx and Cabcy form solid solutions while mixtures of Cabcx and ycbaC form a compound. The very reasonable conclusion that Cabcx and Cabcy are configurationally related while Cabcx and ycbaC are quasi-enantiomorphous follows from the premise that solid solution formation may be regarded as a consequence of a similarity in over-all geometry (and therefore mutual replaceability in the crystal lattice), while compound formation may be viewed as a phenomenon, *i.e.*, quasi-racemate

(1) For excellent reviews of such work, *cf.* H. Lettré, *Erg. Enzymforsch.*, **9**, 1 (1943), and A. Fredge, in "The Svedberg," Almqvist and Wiksells, Uppsala (Sweden), 1944, pp. 261 ff.

formation, closely allied to that of racemate formation between true enantiomers. In cases where mixtures of **C**abcx and **C**abcy form solid solutions while mixtures of **C**abcx and ycba**C** exhibit a simple eutectic (type **2**), or in cases where mixtures of **C**abcx and **C**abcy exhibit a simple eutectic while mixtures of **C**abcx and ycba**C** form a quasi-racemate (type **3**), the interpretation is the same as in type **1**; the absence of quasi-racemate formation in type **2** and of solid solution formation in type **3** does not detract from the usefulness of the general concept. In strong support of these arguments, it should be remarked that in those instances where verification through independent evidence has been applicable, the configurational assignments adduced from a *difference* in phase behavior have, without exception, been found correct. Stress has been put on *differences* in phase behavior, for in the event that both mixtures of **C**abcx and **C**abcy and mixtures of **C**abcx and ycba**C** show *similar* phase behavior (*e.g.*, if both mixtures form simple eutectics, compounds, or solid solutions), factors other than those governing the difference in symmetry of the component substances have evidently become of overriding importance; such cases cannot in consequence be used in configurational studies.

The work here reported is concerned with attempts further to clarify the relative configuration of hydratropic acid (2-phenylpropanoic acid) and that of atrolactic acid (2-hydroxy-2-phenylpropanoic acid) through the use of melting point–composition diagrams.

The relative configuration of hydratropic acid is of some interest, in view of the frequent use of the acid and its derivatives in stereochemical problems.[2] Bernstein and Whitmore[3] presented convincing evidence, based on the stereochemistry of 1,2-shifts, for the configuration of (+)-hydratropic acid (I) relative to that of (+)-alanine (II).

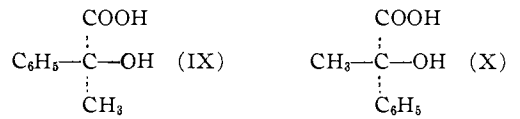


In order to establish the configuration of (+)-hydratropic acid relative to that of glyceraldehyde, it must also be supposed that (+)-alanine is configurationally related to L(+)-lactic acid (III). A number of independent investigations have given a high degree of probability to that assumption,[4] and strength is lent it by the fact that (+)-lactic acid and (+)-alanine have been related by chemical means not involving the asymmetric center to (−)-1-phenylethanol (IV)[5] and (−)-1-phenylethylamine (V),[6] respectively; the last two compounds have, presumably, the same configuration.[7]

The conclusion concerning the relative configuration of (+)-hydratropic acid has now been independently confirmed. The relative configuration of (+)-mandelic acid (VI) is established,[8] and the conversion of (+)-mandelamide to (+)-2-chloro-2-phenylacetamide (VII) with thionyl chloride alone undoubtedly proceeds with retention of configuration.[9] The remaining comparison, that between (+)-2-chloro-2-phenylacetamide and (+)-hydratropamide (VIII), was made by the use of melting point–composition diagrams. Since it is known that methyl and chloro groups are isomorphous,[10] it was not surprising that the configurationally related pair, (+)-VII and (+)-VIII, should form solid solutions (Fig. 1), whereas the quasi-enantiomorphous pair, (−)-VII and (+)-VIII, would show solid immiscibility (Fig. 2). According to the classification proposed in the introductory discussion, we are here dealing with type **2** phase behavior.

These results are in harmony with, and may be considered an independent substantiation of, the arguments regarding the stereochemistry of the reactions touched upon in the preceding discussion.

We had also hoped to throw some light on the vexing problem of the configuration of (−)-atrolactic acid by making use of the phase diagram method. (−)-Atrolactic acid may be regarded either as a phenylated D(−)-lactic acid (IX) or as a methylated D(−)-mandelic acid (X); optical comparisons permit, tentatively, a decision in favor of the



latter alternative.[11] However the claimed[12] correlation of the configurations of mandelic and atrolactic acids by chemical means is based on untenable assumptions regarding the configurations of (+)-"α"- and (+)-"β"-1,2-diphenyl-1,2-propanediols.

(2) *Cf.*, for instance, C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939); A. Campbell and J. Kenyon, *ibid.*, 25 (1946); C. L. Arcus, A. Campbell and J. Kenyon, *ibid.*, 1510 (1949).

(3) H. I. Bernstein and F. C. Whitmore, THIS JOURNAL, **61**, 1324 (1939).

(4) K. Freudenberg and M. Meister, *Ann.*, **518**, 86 (1935), and earlier papers; A. Fredga, *Svensk Kem. Tid.*, **54**, 26 (1942) [*C. A.*, **40**, 2797 (1946)]; P. Brewster, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature*, **166**, 178 (1950); M. L. Wolfrom, R. U. Lemieux and S. M. Olin, THIS JOURNAL, **71**, 2870 (1949); D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, *ibid.*, **72**, 2328 (1950); C. E. Meyer and W. C. Rose, *J. Biol. Chem.*, **115**, 721 (1936).

(5) P. A. Levene, *et al.*, *J. Biol. Chem.*, **89**, 471 (1930); *ibid.*, **113**, 55 (1936).

(6) W. Leithe, *Ber.*, **64**, 2827 (1931).

(7) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1252 (1937); P. A. Levene, A. Rothen and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937); P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature*, **166**, 179 (1950); H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 291 (1949).

(8) K. Mislow, *ibid.*, **73**, 3954 (1951).

(9) It seems certain that the reaction of thionyl chloride with carbinols of the type $C_6H_5(R_1)(R_2)COH$, as well as with mandelic acid and its esters, does not involve inversion.[7]

(10) H. Lettré, H. Barnbeck and co-workers, *Ber.*, **69**, 1151 (1936); **70**, 1410 (1937); **71**, 1225 (1938).

(11) (a) K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933); (b) K. Freudenberg and H. Biller, *ibid.*, **510**, 230 (1934); (c) W. Kuhn and H. Biller, *Z. physik. Chem.*, **29B**, 1 (1935). After the work described in this paper had been completed, we learned that V. Prelog had arrived at the same conclusion on the basis of his work on asymmetric syntheses (Abstract of papers presented at the 12th Int. Congress of Pure and Appl. Chem., New York, Sept. 11, 1951, p. 401).

(12) A. McKenzie and A. Ritchie, *Ber.*, **70**, 23 (1937).

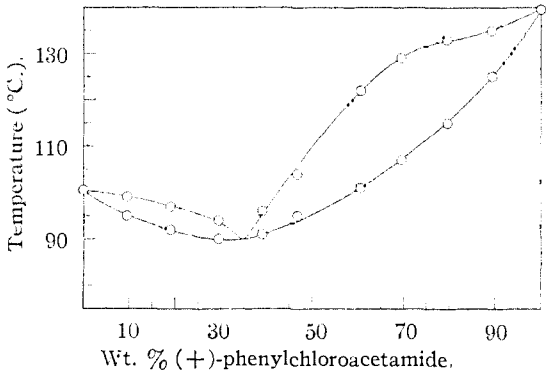


Fig. 1.—Melting point–composition diagram for the system (+)-hydratropamide–(+)-2-chloro-2-phenylacetamide.

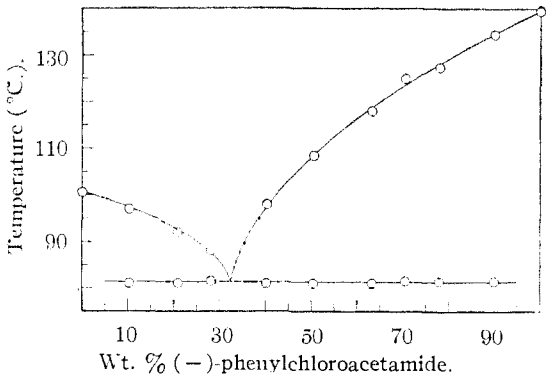


Fig. 2.—Melting point–composition diagram for the system (+)-hydratropamide–(−)-2-chloro-2-phenylacetamide.

The enantiomorphous mandelic acids form a racemate[13]; in this work it was found that the enantiomorphous atrolactic acids also form a racemic compound (Fig. 3). For this reason, and because of the similarities in their over-all structures, it seemed quite likely that the configurationally quasi-enantimorphous atrolactic and mandelic acids would form a quasi-racemate (type 3 phase behavior). This expectation was not fulfilled; no compound formation was observed in the systems comprised of (−)-atrolactic acid and the enantiomorphous mandelic acids (Fig. 4). The slight difference between the two systems is due, probably although not necessarily, to the fact that the (+)-mandelic acid which was employed in this work was not quite as optically pure as the (−)-mandelic acid.

Experimental[14]

(+)-Hydratropamide.—Hydratropic acid was prepared by the method of Campbell and Kenyon[15] and resolved through the strychnine salt.[16] The acid, $[\alpha]^{26}D$ +90.8° (*c* 3.48, benzene), was converted to the amide by the ammonolysis of the acid chloride.[16] After three recrystallizations from ethanol–water, the amide had a constant m.p. 100–101°, and $[\alpha]^{24}D$ +59.5° (*c* 1.07, chloroform) (reported[16] m.p. 103–104°, $[\alpha]D$ +58.3° (chloroform)).

D(−)- and L(+)-Mandelic Acids.—The acid was resolved through the cinchonine salt,[17] and the liberated acids recrystallized from benzene to constant melting point and rotation. The enantiomorphous acids had $[\alpha]^{22}D$ −156° (*c* 2.12, water), m.p. 133–134°, and $[\alpha]^{27}D$ +153° (*c* 2.17, water), m.p. 133–134°, respectively (reported[17] $[\alpha]D$ 158° (water), m.p. 133°).

(+)-, (−)-2-Chloro-2-phenylacetamides.—Resolved (+)-mandelic acid was converted to the (+)-amide, in 30–40% yields, by the ammonolysis of the methyl ester.[18] Treatment of the amide with thionyl chloride at room temperature[19] yielded (+,±)-phenylchloroacetamide (50–60%), m.p. 116–137°, which after five recrystallizations from chloroform gave needles of constant m.p. 139–140°, and $[\alpha]^{25}D$ +84.3° (*c* 1.21, acetone). In the same manner the enantiomorph was obtained, m.p. 139–140°, $[\alpha]^{25}D$ −84.2° (*c* 1.29, acetone), $[\alpha]^{26}D$ −88.1° (*c* 1.32, ethanol) (reported[19] m.p. 138–139°, $[\alpha]^{20}D$ −94.1° (acetone)).

(−)-Atrolactic Acid.—The acid, prepared by the hydrolysis of acetophenone cyanohydrin,[20,11a] was resolved through the morphine salt.[21] The liberated acid was recrystallized from benzene until melting point, 116–117°, and rotation, $[\alpha]^{27}D$ −37.8° (*c* 3.23, ethanol), remained constant (reported[21] $[\alpha]^{27}D$ −37.7° (ethanol), m.p. 116–117°).

Determination of Melting Ranges.—Weighed amounts of the components were thoroughly ground and mixed. Samples, packed into capillaries, were immersed in a standard melting point apparatus (oil type), and the temperature was raised at a constant rate of 1–2°/min. The initial thawing temperature and the final melting temperature were recorded as points, respectively, on the solidus and the liquidus of the corresponding phase diagram. Duplicate determinations, made in all cases, permitted a precision of ±0.5°.

In the case of the (+)-(−)atrolactic acid system, mixtures of (−)- and (±)-atrolactic acid were employed.

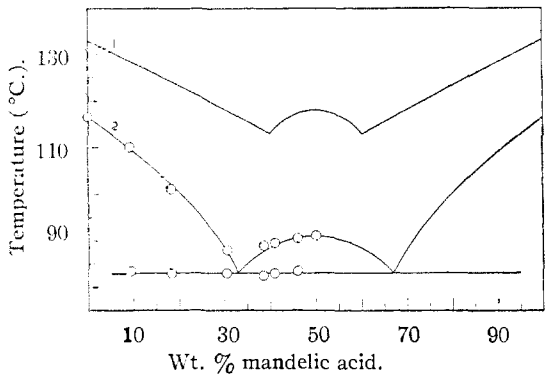


Fig. 3.—Melting point–composition diagrams for the systems (−)-mandelic acid–(+)-mandelic acid: (Curve 1, J. H. Adriani, ref. 13), and (−)-atrolactic acid–(+)-atrolactic acid (curve 2).

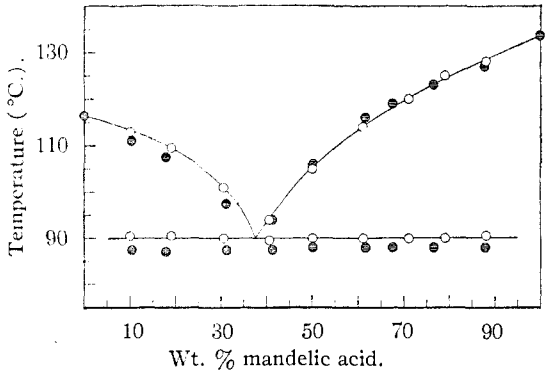


Fig. 4.—Melting point–composition diagrams for the systems (−)-atrolactic acid–(−)-mandelic acid (open circles) and (−)-atrolactic acid–(+)-mandelic acid (shaded circles).

NEW YORK, N. Y.

(13) J. H. Adriani, *Z. physik. Chem.*, **33**, 453 (1900).
(14) Melting points are corrected.
(15) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).
(16) C. L. Arcus and J. Kenyon, *ibid.*, 916 (1939).
(17) A. McKenzie, *ibid.*, 964 (1899).
(18) A. McKenzie and H. Wren, *ibid.*, 309 (1906).
(19) I. A. Smith, *Ber.*, **71**, 634 (1938).
(20) A. Spiegel, *ibid.*, **14**, 1352 (1881).
(21) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, 1016 (1910).