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RELATIVE DEVIATION FROM IDEALITY IN PHASE EQUILIBRIA AS A BASIS FOR THE CORRELATION OF STERIC CONFIGURATION IN RELATED ORGANIC COMPOUNDS

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Abstract—The principle underlying the so-called "quasi-racemate" method for the correlation of steric configuration is generalized. If the molecular interaction in a system of two substances of opposite configurations causes negative deviations from ideality as compared to the phase equilibrium in the corresponding system between related configurations the sign of the difference in relative deviation may be expected to persist for the derivatives of these substances. The comparison of freezing point lowerings, or solubilities, therefore, in various binary combinations of the active isomers of related substances is potentially a basis for the correlation of their configurations. An actual difference in types of solid phases formed, such as the formation or non-formation of a "quasi-racemic" compound, is not necessary for the general method. Examples of discarded data from the literature, are given, in which the deductions are exactly those confirmed by subsequent and independent procedures.

The use of phase diagrams in the study of the relative steric configurations of optically active organic substances is finding increasing application. The basis for the inferences drawn in this method of correlation, however, as it is currently used, seems to lack a generalizing principle, with the result that certain phase diagrams, which actually embody relations significant in the problems of correlation, are discarded as yielding no information. The purpose of this communication is to suggest as the underlying principle for the use of phase relations, that pairs of optically active substances having opposite configurations show some degree of (relative) negative deviation from ideality in their phase equilibria, when compared with the corresponding pairs having related configurations. On this basis it should be possible to extend the usefulness of the phase diagram method for correlation, and to make use of certain simple information which would otherwise, and so far has been, neglected.

The original suggestion for the use of phase diagrams in this field was made by Timmermans in 1929.[1] After confirming the observation of Centnerszwer,[2] that L-bromosuccinic acid and D-chlorosuccinic acid [or (−)I and (+)II] formed a solid compound while D-bromosuccinic acid and D-chlorosuccinic acid [or (+)I and (+)II] formed no compound but a continuous solid solution, Timmermans suggested that the first pair of substances were related to each other in the manner of antipodes, i.e., of opposite configurations, while the second pair represented corresponding or related configurations. The potentialities of this suggestion were effectively developed and exploited, with applications, by Fredga, who presented an important review in 1944.[3]

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[1] J. Timmermans, *Rec. Trav. Chim.* **48**, 890 (1929).
[2] M. Centnerszwer, *Z. physik. Chem.* **28**, 715 (1899).
[3] A. Fredga, *The Svedberg* (Memorial Vol) p. 261. Almqvist and Wiksells, Uppsala (1944).

Fredga suggested the term "quasi-racemic" for the type of compound involved. Another review, by Timmermans, appeared in 1952.[4]

The method is used for the correlation of the configurations of two substances, I and II, one being a derivative or modification of the other, through substitution, degradation, etc. All the applications of phase diagrams in these problems involve the comparison of the phase diagrams of what we may call the two *diastereo-systems* of the substances I and II. While the system (+)I-(−)I gives a symmetrical phase diagram, the phase diagram of the system (active)I-(active)II is unsymmetrical. Moreover, there will be two systems and two different phase diagrams: one for (+)I-(+)II (identical with (−)I-(−)II) and one for (+)I-(−)II (identical with (−)I-(+)II). We shall call these the two diastereo-systems I-II, distinguishing them as systems A and B, respectively.

The method is applied in the following situations.[3-7]

(1) If at least one of the substances I and II forms a (true) racemic compound, and if only one of the two diastereo-systems of I-II, say system A, forms a compound while the other, system B, does not, giving instead either a eutectic with pure solid components or a solid solution, continuous or discontinuous, then it is inferred that the substances of system A have opposite configurations while those of system B have related configurations.

(2) If diastereo-system A of I-II forms a compound while system B does not, and if the diastereo-system A of I-III also forms a compound while system B of I-III does not, again giving either pure components as solids or solid solution, then it is inferred that (+)II and (+)III have related configurations and that their configuration is opposite to that of (+)I. This is merely an extension of case (1), making possible the step-wise correlation of the configuration of a series of chemically related substances I-II-III-IV. . . .

(3) If the diastereo-system A of I-II gives a eutectic system with pure solid components while the B system gives solid solution, continuous or discontinuous, and if the diastereo-system A of I-III similarly gives a eutectic while the B system of I-III gives solid solution, then it is inferred, just as in case (2), that (+)II and (+)III are "related" in their configuration and that they are "opposite" to (+)I.

The conclusions thus drawn have always agreed with the correlations established by independent methods. Presumably no inferences are considered possible, directly from the phase diagrams, for the following cases:

(4) if both diastereo-systems give simple eutectic diagrams, (5) if both give solid solutions, and (6) if both give solid compounds.

Although case (3) does not involve compound formation, all the various applications made, namely cases (1), (2) and (3), are commonly referred to as the "quasi-racemate method".[7] Most of the applications made do involve the formation of a compound in one of the diastereo-systems, and hence various techniques have been called upon for the detection of such a compound. If it cannot be detected by means of the ordinary determination of the freezing point diagram, either because of difficulties in crystallization or because the compound is, possibly, stable only below the

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[4] J. Timmermans, *J. Chim. Phys.* **49**, 162 (1952).

[5] M. Matell, *Ark. Kemi* **5**, 17 (1952).

[6] K. Mislow and M. Heffler, *J. Amer. Chem. Soc.* **74**, 3668 (1952).

[7] A. Fredga, *Tetrahedron* **8**, 126 (1960).

liquidus temperatures of the system, it is looked for in equilibrated and quenched samples by X-ray and by infra-red examination.[8] Timmermans investigated several pairs of diastereo-systems by means of what may be called cryoscopy in aqueous solution.[9] The course of the freezing point curve for the equilibrium liquid + ice + solid I (or II, or compound, or solid solution, etc.) would reflect the phase relations of the binary system I–II at the temperatures of the experiment.[10] The procedure is essentially an application of Bruni's method for the study of optical isomers.[11] It is equivalent to the X-ray and infrared procedures in that it reveals the sub-solidus relations of I and II, i.e., their relations below the binary liquidus temperatures of the non-aqueous system I–II, if the solids other than ice are anhydrous.

Moreover, considerable attention is given to the question of the structure of the compound of I and II, to justify attributing opposite configurations to its components, or to determine, in other words, whether or not it is truly "quasi-racemic".[5,7,12] It is considered necessary to prove, in doubtful cases, that the compound is structurally similar (by formation of solid solutions or by X-ray and infra-red comparisons) to the "true racemate" either of I or of II. Such test would seem to be required, of course, if both of the diastereo-systems I–II formed solid compounds, diastereomers, one of which, the "quasi-racemate", would contain the components I and II in opposite configurations, the other not.

Another question given consideration[5,12,13] is the chance of success of the "quasi-racemate method" through actual compound formation, as depending on the "racemate-formation tendency" of either or both of the separate enantiomeric systems I and II. The "stronger" is this tendency and the more closely related are the substances I and II in their constituent groups, the higher is the expectation for the formation of a quasi-racemic compound in the diastereo-system involving opposite configurations. In the discussions of these "conditions for the formation of quasi-racemic compounds", the compound-formation "tendency" is even given a rough numerical value[13] on the basis of the phase diagram of the enantiomeric system (Fig. 1), either in terms of the composition spread between the eutectics t_2 and t_4 or in terms of temperature differences as the ratio $(t_3 - t_2)/(t_1 - t_2)$.

According to Fredga,[7] there is therefore only a "chance" that the "quasi-racemate method" will distinguish and correlate the configurations, and the use of the method is said to involve "an element of gambling."

This apparently has to be the case if we limit the possibility of drawing conclusions to the contrasting phase behaviors stated above as cases (1), (2) and (3), contrasts depending upon yes-no distinctions and ignoring any *degree* of difference between the diastereo-diagrams being compared. Whenever, for example, the two diagrams (A and B) turn out to be both simple eutectic in type, no conclusions are drawn. The information is simply discarded. The problem is then pursued either by modifying one or both of the substances by substitution or degradation until the similarity

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[8] N. Wright, *J. Biol. Chem.* **120,** 641 (1937); **127,** 137 (1939); E. L. Eliel and J. T. Kofron, *J. Amer. Chem. Soc.* **75,** 4585 (1953); A. Rosenberg and L. Schotta, *Ark. Kemi* **8,** 143 (1955); S. Gronowitz, *Ibid.* **11,** 361 (1957).

[9] J, Timmermans *et al., Bull. Soc. Chim. Belg.* **40,** 105, 689 (1931); **41,** 53, 399 (1932).

[10] J. E. Ricci, *The Phase Rule and Heterogeneous Equilibrium* p. 348. Van Nostrand, New York (1951).

[11] G. Bruni, *Att. R. Accad. Lincei* [5], **8–1,** 332 (1899); *Gazz. Chim. Ital.* **30–1,** 35 (1900).

[12] K. Pettersson, *Ark. Kemi* **10,** 283 (1956).

[13] K. Pettersson, *Ark. Kemi* **10,** 297 (1956).

between I and II is increased sufficiently to give the desired yes-no contrast, or by the application of entirely independent methods, such as concomitant variation of optical rotation in a series of solvents, study of optical rotatory dispersion curves, etc.

Fundamentally, however, there can be no "chance" in the kind of difference between the phase diagrams of the two diastereo-systems being compared. The system (+)I-(+)II differs from the system (+)I-(−)II in only one respect—the configuration of the component II. The corresponding melting points are identical and so are the corresponding heats of fusion. If the two systems were both to give eutectic diagrams, with the pure components as solid phases, the two diagrams would therefore be identical if the interaction of the species in the liquid phase were identical. Because of the configurational differences, however, the inter-molecular interaction must differ between the two systems. The degree of deviation from ideality, for the freezing-point or solubility curve of one of the components, must show a difference between the two diagrams. The deviation from ideality may be negative in both cases or positive in both cases, or of different signs, but one of the systems will appear to have relatively a negative deviation when compared with the other. Because of the identity, in all other respects, of the two systems, this relative negative deviation must be due to the configurational difference in the component II.

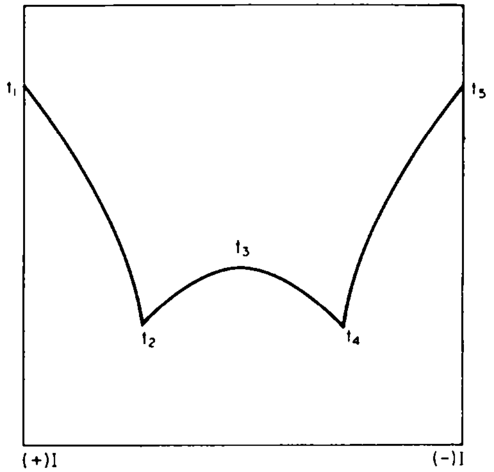

Fig. 1. Schematic diagram for enantiomers forming racemic compound.

Since the degree of negative deviation from ideality may be related to "compound-formation tendency" of the components, the formation of a "quasi-racemic" compound may be considered merely as one possible aspect of the difference in deviation between the diastereo-systems. If one of the two systems forms a compound and the other does not, it is found that the freezing point curve of at least one of the components is depressed, in the compound-forming system, relative to the corresponding curve in the other system, whether the latter is simple eutectic [Fig. 2[8] and Fig. 3[6]] or forms solid solutions [Fig. 4[3]]. This relation is entirely as expected, and is verifiable by the superposition of the many paired diagrams in the literature. A few examples appear to be irregular, such as the case of I = α-(naphthyl-1) propionic

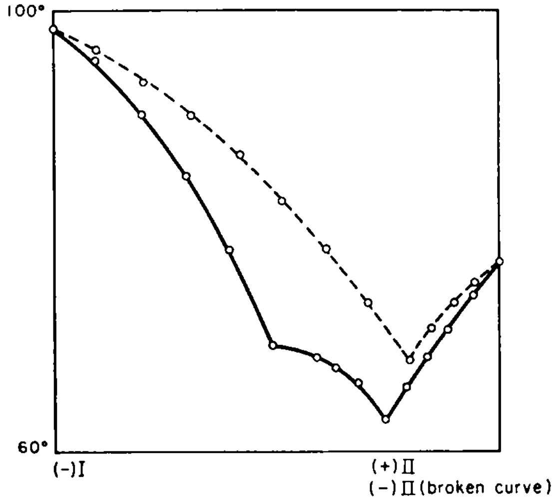

FIG. 2. Diastereo-systems: I = α-phenylvaleramide, II = α-phenylbutyramide.[12]

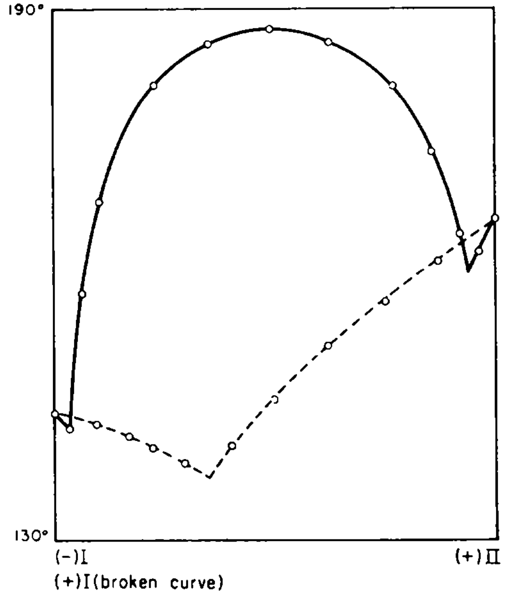

FIG. 3. Diastereo-systems: I = trichlorophenoxy-propionic acid, II = trichlanilioro-propionic acid.[7]

acid, II = α-(indole-3) propionic acid[14a] and that of I = methylglutaric acid, II = dimethylglutaric acid.[14b] The first of these involves an incongruently melting quasi-racemic compound, and it is possible that the small apparent inversion of the positions of the freezing point curve of a component may be due to the difficulties of crystallization of the proper solid phase during the determination of the liquidus. In the

[14a] B. Sjöberg, *Ark. Kemi* **13**, 1 (1958).
[14b] A. Fredga, *Ark. Kemi Min. Geol.* **24A**, No. 32 (1947).

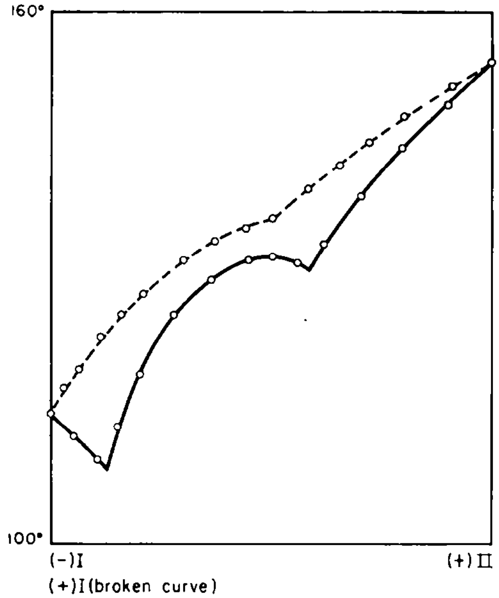

FIG. 4. Diastereo-systems: I = methylsuccinic acid, II = mercaptosuccinic acid.[3]

second case, the abnormal S-shape of the freezing point curve of methylglutaric acid suggests experimental difficulties.

The actual appearance in the equilibrium diagram of a solid compound depends of course both on the strength of the molecular interaction between the components and on the melting point of the potential solid compound relative to the liquidus curves of the components.[15] "Compound-formation tendency" thus has two aspects, the depression of the freezing point curves of the components, and the melting point and stability of the compound itself as a solid phase.

It turns out, then, that in some cases both diastereo-systems form solid compounds, known as diastereomers if they are of corresponding formulas. Since these are not enantiomers they must differ in melting point, and the difference in melting point must stem ultimately from the configurational difference in one of the components of the compounds. In the few cases for which the configurational relations are known and in which the two diastereo-systems both form or appear to form compounds, the compound containing the components in opposite configurations has the higher melting point, in line with what has already been pointed out for the higher compound-forming tendency or greater negative deviations for such configurations. Three examples[12] are the combinations of α-phenylbutyramide with hydratropamide, with α-phenylcaproamide and with α-phenyloenanthoamide.

The same distinction in the melting points of diastereomers is implied in the observation known as the rule of Winther:[16] that the antipodes of different acids have the same configuration if they are precipitated with the same alkaloid. Here "precipitation" refers to solubility not in an active solvent, however, but in an inactive one,

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[15] For discussion, see J. Kendall, A. W. Davidson and H. Adler, *J. Amer. Chem. Soc.* **43**, 1481 (1921); see also Ref. 10, p. 123.

[16] C. Winther, *Ber. Dtsch. Chem. Ges.* **28**, 3000 (1895).

such as water, ethanol, etc. The higher melting diastereomer should, in general, but not necessarily, be the less soluble one, at a given temperature, in the inactive solvent. Exceptions[17] to the "rule" therefore may be taken as indicating non-ideality in the relations of one or both of the two systems of inactive solvent + diastereomer; they do not necessarily mean that the difference in the melting points of the diastereomers is reversed. The fact that Winther's rule has but few exceptions means that the sign of the difference in the melting points of diastereomers is preserved according to the configurations involved, and that again the compound of the opposite configurations is the higher melting and for that reason almost always the less soluble in an ordinary solvent.

From this point of view, moreover, the question of the structure of the "quasi-racemate compound" would become of secondary interest only. The significant question is rather the difference between the two diastereo-systems in their phase relations and hence the difference between melting points of the two diastereomeric compounds if both systems form a compound; and this difference must immediately reflect the configurational difference, since this is the only variation between the two systems.

On the other hand, despite some degree of "compound-formation tendency", the potential compound may be too unstable or have too low a melting point to appear as a solid phase in the freezing point diagram.[15] But from the point of view here presented the actual formation of a solid compound is secondary. Its appearance may be taken as accompanying marked negative deviation, but the effect of configuration on the liquid state interaction should reveal itself nevertheless as a difference in the relative depression of the freezing point curves even in the absence of solid compound formation.

If both diastereo-systems give simple eutectic diagrams, then, one of them must show freezing point curves depressed relative to the other, a lower eutectic temperature, and higher solubilities (of solid components in the liquid) at any given temperature. Twelve examples of such pairs were found in the literature. In all but two of these cases the phase diagrams, although published, were not used as a basis for the correlation of configuration because they did not reveal phase distinctions in the sense of cases (1), (2) and (3); and the configurations were correlated by other methods. In each case, however, the difference, where detectable, between the phase diagrams of the two diastereo-systems is in accord with the principle that components with opposite configuration give a freezing point diagram showing negative deviation when compared with the diagram for the system involving related configurations.

A typical example is shown in Fig. 5.[18] Both diastereo-systems gave simple eutectic diagrams, and the author concluded that "information about the steric relations between the acids can not be obtained directly according to the quasi-racemate method." On the basis of the variation of optical activity in a series of different solvents it was subsequently inferred that (—)I and (+)II have opposite configurations. But this is seen directly from Fig. 5, in that these substances (full curve) give a phase diagram showing marked negative deviation relative to the diastereo-system (+)I–(+)II (dashed curve).

Three other equally clear examples of such eutectic pairs, which were discarded as

[17] An example is the case of α-phenylethylamine hydratropate; Ref. 12.

[18] K. Pettersson, *Ark. Kemi* 7, 279 (1954).

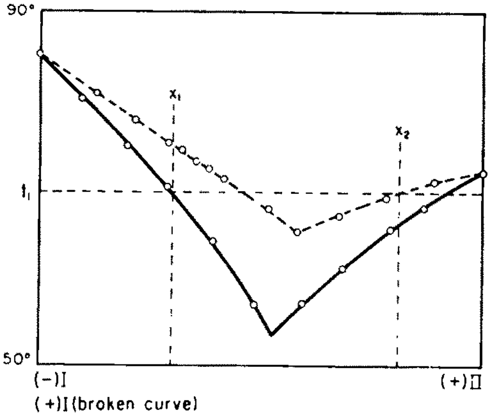

FIG. 5. Diastereo-systems: I = 2-thenylphenylacetic acid, II = 2-thienylhydrocinnamic acid.[18]

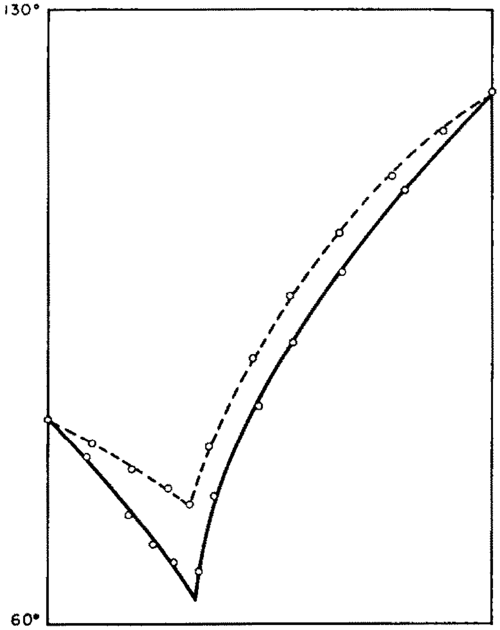

FIG. 6. Diastereo-systems: I = pentylsuccinic acid, II = butylsulfidesuccinic acid.[5]

phase-diagram information for configurational correlation, but actually embodying information agreeing with the correlations subsequently established by other methods, are shown in Figs. 6,[5] 7,[5] 8.[19]

Another example is that of Fig. 9.[6] Here the slightly (but distinctly) lower melting points (and eutectic) in the (−)(+) system as compared to the (−)(−) system were explained as "due, probable though not necessarily, to the fact that the (+) mandelic

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[19] H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *J. Amer. Chem. Soc.* **83**, 2517 (1961).

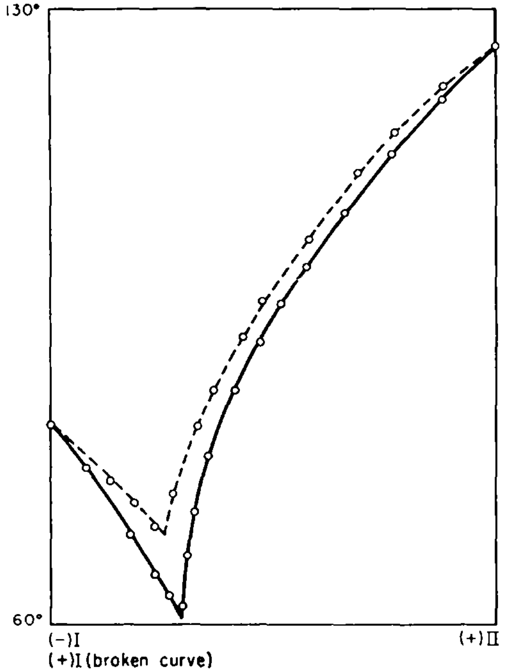

FIG. 7. Diastereo-systems: I = hexylsuccinic acid, II = pentylsulfidesuccinic acid.[5]

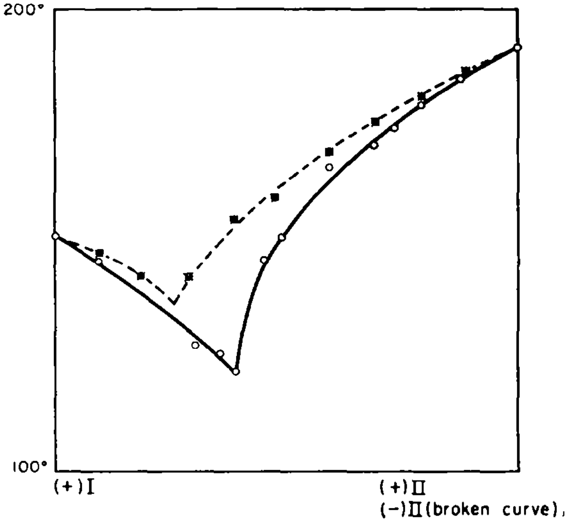

FIG. 8. Diastereo-systems: I = 1-methyl-2,2-diphenylcyclopropanecarboxylic acid, II = 2,2-diphenylcyclopropanecarboxylic acid.[19]

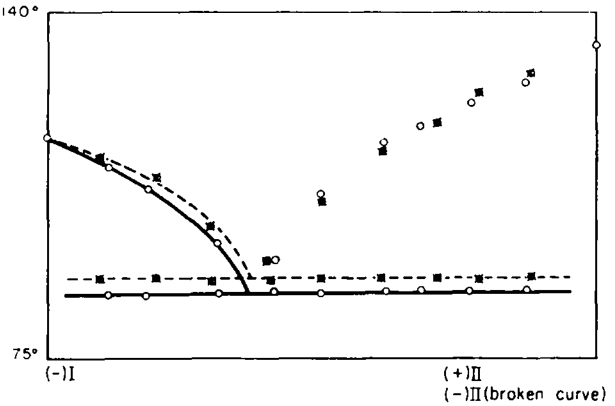

Fig. 9. Diastereo-systems: I = atrolactic acid, II = mandelic acid.[6]

acid . . . employed . . . was not quite as optically pure as the (—) mandelic acid." The diagrams suggest, however, that (—)I and (+)II have opposite configurations, as established later by other methods.[20]

In the case of dithiodilactic acid and 2 D-5L-dimethyladipic acid as components, which give two eutectic diagrams,[21] the lower eutectic temperature was shown to pertain to the pair known from chemical correlations to have opposite configurations. In the case of α-phenylglutaric acid and phenylthioglycolic acid as components and in that of α-phenyladipic acid and 2-phenyl-3-thiahexanedioic acid as components,[22] it was pointed out, on the basis of a suggestion by Fredga, that it would "seem possible" that the pairs showing the lower eutectic temperature might represent the pairs with opposite configurations. According to Fredga[7]: "It seems that if there is a difference, the eutectic temperature is always lower when the components have opposite configurations. The experimental material is, however, too small to permit any definite conclusions." The phenomenon was thus considered only as a possible empirical regularity, and its significance, as a manifestation of relative negative deviation fundamentally equivalent to actual compound formation, was not recognized.

Three cases in which the two eutectic diastereo-diagrams are practically identical in superposition are: hydratropamide with α-phenylvaleramide, with α-phenylcaproamide and with α-phenyloenanthoamide.[12] The diagrams were considered as "supplying no information about the steric relation between the compounds", and the correlations of their configurations were established by other methods. It is to be noted, however, that in the first and third of these cases, while the printed diagrams hardly show any difference the table of numerical values of the freezing points does show it, to the extent of ~1¼ degree along the curves; and the difference is in the right direction (lower for opposite configuration). In the second example, the average difference is only ¼ degree and in the wrong direction—but certainly insignificant, the freezing points having been reported to only ½ degree.

Another example of a pair of eutectic diagrams reported as "indistinguishable" is given by 2,2'-bis(hydroxymethyl)1,1'-binaphthyl and 6,6'-dimethyl-2,2'-bis (hydroxymethyl)-biphenyl.[23] Because of the scatter of the experimental points in this case,

[20] J. H. Brewster, *J. Amer. Chem. Soc.* **78**, 4061 (1956).

[21] I. Hedlund, *Ark. Kemi* **8**, 89 (1955).

[22] A. Westman, *Ark. Kemi* **14**, 115 (1959).

[23] M. Siegel and K. Mislow, *J. Amer. Chem. Soc.* **80**, 473 (1958).

however, we can not say whether there is any significant difference between the two diagrams, although the relative configurations are known.[24,25]

The difference, then, between the phase diagrams of the diastereo-systems is a potential one, a matter of sign and not of degree; and it will in some cases be too small for ordinary detection. Potentially, the sign of the difference between the two cases is distinguishable by the determination of two freezing points at a given composition, such as at x_1 or at x_2 in Fig. 5, for the crystallization of corresponding solid components. Alternatively it may be distinguished by the determination of the solubilities, at a given temperature, of corresponding components in the liquid phase. In Fig. 5, the solubility, at temperature t_1, of (+)I is greater in the liquid containing (+)II as solvent than that of (−)I, while the solubility of (+)II is greater in liquid (+)I as solvent than in liquid (−)I.

If the substances I and II are not closely related chemically, as would be the case in a phase diagram involving menthol + mandelic acid, the distinction between "opposite" and "related" configurations does not have the simple, direct meaning which it has in the case of the original example of chlorosuccinic acid and bromosuccinic acid. Nevertheless, regardless of the complexity of the substances I and II and of how far apart they may be in their chemical constitution, it remains that the system (+)I–(+)II differs from the system (+)I–(−)II in only one respect, the configurations of (+)II and (−)II, and that only this difference can be called upon to account for whatever difference exists between the systems in their phase behavior, in respect to: formation or non-formation of a solid compound, relative melting points of diastereomers, formation or non-formation of solid solutions of the components, and any relative difference in deviation from ideality between the two systems.

In all cases, then, which show a distinct difference between the two diastereo-diagrams, and for which the correlation of configuration seems to have significance, that diagram with relative negative deviation compared to the other seems to involve opposite configurations. Even if we hesitate to accept this as a correlation having any theoretical necessity, we may nevertheless use the observed regularities as a reasonable basis for the correlation of the configurations of a series of derivatives of a given substance II (i.e., II′, II″, II‴ . . .) through the study of their phase relations with a fixed reference active form of I, let us say (+)I. If the diastereo-system (+)I–(+)II′ shows negative deviations relative to the system (+)I–(−)II′, then that diastereo-system of the pair (+)I–II″ showing relative negative deviations may be expected to involve II″ in a form configurationally related to (+)II′. Such comparisons would take us step-wise through the successive derivatives of II.

If the sign of the difference, in the sense of deviation from ideality, can definitely be detected between the two diastereo-systems, the inference drawn on such a basis seems to be as valid as it is in the case of formation *vs* non-formation of a quasi-racemate compound, and there is no need to go further into the modification of the

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[24] K. Mislow, *Angew. Chem.* **70**, 683 (1958).

[25] Since the acceptance for publication of this manuscript, which had been communicated privately to Prof. A. Fredga, of Uppsala, the author has been informed by Prof. Fredga that one of his students (T. Raznikiewicz, *Acta Chem. Scand.*, in press) has now completed a study finding six more examples of eutectic pairs in which the components with opposite configurations give the lower eutectic temperature. This information further substantiates the generalization here proposed, namely the use of relative negative deviation as basis for the correlation of configuration.

substances to increase their chemical similarity until they do show the expected "yes-no" type of difference in phase behavior.

It may also be expected, moreover, that similar and corresponding differences, in respect to sign of relative deviations, between the diastereo-systems must exist—and be preserved through derivatives—in other phase transitions, such as the boiling point curve.[26] Theoretically, the two diastereo-systems must differ in some degree in all such phase equilibrium properties: freezing point, solubility, boiling point, vapor pressure, etc., and always in such a way as to correspond to negative deviations from ideality in one system relative to the other. It seems reasonable to expect that the sign of the difference should continue to correspond to the difference in configuration, through the derivatives of the substances. Whether even the sign of the difference between the diastereo-systems will be detectable in any particular case is an experimental question, but it seems to offer a reasonable potential basis for configurational correlation.

It is in this sense that the original and fruitful suggestion of Timmermans may take on a possible generality not limited to actual solid compound formation or to structural distinctions. The general extension possible through the comparison of simple solubilities was stated in the writer's book on phase rule[27] in 1951, but with hardly any expectation that it might be practically applicable, on the basis of data then available. Small differences in solubility, however, can now be expected to be detectable, at least in respect to the sign of the difference, by the cumulative fractionation processes of zone-melting technique in an active solvent, already demonstrated for the partial resolution of optical enantiomers,[28] or of chromatographic technique on an active solid surface. The information which may be gathered by such methods, then, if available for a series of chemically related substances, may, on the principle stated, be used to correlate their configurations.

At any rate, the current "quasi-racemate" method may be said to utilize only a part of the information which is at least potentially available in the phase diagrams of the systems to be compared. It seems possible to extend further the application of phase equilibria to the correlation of stereo-configurations on the basis of the proposition that the sign of the relative deviation between the two diastereo-systems being compared is preserved when the configurational relation is preserved.

Acknowledgement—The author is indebted to Dr. K. Mislow for his interest and co-operation.

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[26] For a case of measurable difference between "diastereoazeotropes" see C. J. McGinn, *J. Phys. Chem.* **65**, 1896 (1961).

[27] Ref. 10, p. 168.

[28] V. F. Doron and S. Kirschner, *Chem. Eng. News* p. 38. July 10 (1961).