211. *Mesohydric Tautomerism.*

By Louis Hunter.

Current work on the close connexion between tautomeric character and hydrogen-bond structure in a wide variety of compounds is reviewed, and provides the basis of a new classification of systems whose tautomerism depends upon " mobile hydrogen." Those systems in which the alternative sites of attachment of the mobile hydrogen atom are oxygen, nitrogen, or sulphur (but not carbon), are now regarded as exhibiting "mesohydric tautomerism"; compounds whose tautomeric character depends on the mobility of hydrogen attached to carbon, by virtue of its inability to form stable hydrogen bonds when thus combined, are excluded from this type of tautomerism.

Dual character, which in true prototropy is due to a mixture of tautomers (or at least to a mesomeric ion common to both tautomers), is shown in the case of mesohydric tautomerism to be due to a homogeneous substance. Separate tautomers in the latter type do not therefore exist, and further cases of alleged isomerism are examined and shown to be unfounded.

In a series of papers under the general title of " The Associating Effect of the Hydrogen Atom " * (Part I, J., **1937**, 1114; Part II, J., **1938**, 375; Part III, J., **1938**, 1034; Part IV, J., **1939**, 484; Part V, J., **1940**, 166; Part VI, J., **1940**, 332; Part VII, J., **1941**, 1; Part VIII, J., **1941**, 777; Part IX, J., **1941**, 820; Part X, J., **1942**, 420; Part XI, J., **1942**, 638; Part XII, this vol., p. 617), tautomeric substances of widely different classes have been shown to exhibit molecular association attributable to a hydrogen-bond structure. Hitherto, all examples of tautomerism dependent on the location of a hydrogen atom at alternative sites within a molecule have been classed together under the name " prototropy " (Lowry, J., **1923**, **123**, 828), in recognition of the essentially ionic character of the tautomeric change as it occurs in the best-known examples of this type, *e.g.*, keto-enols. The term prototropy implies the separate existence of " tautomers," which are structural isomers capable of interconversion by the transference of a proton from one position in the molecule to another.

During the progress of the current investigation (*locc. cit.*) it soon became apparent, not only that there is a close parallel between tautomeric character and molecular association, but also that this parallel does not extend to cases of tautomerism depending on the mobility of the hydrogen atom of a CH group. As a result of this, and at a time when only Parts I—VI had been published, the provisional suggestion was put forward (Hunter, *Chem. and Ind.*, **1941**, **60**, 32) that the tautomeric character and the molecular association of the substances investigated are due to one and the same cause, *viz.*, the intermolecular sharing of the hydrogen atom responsible for the tautomeric behaviour. If this is true, it follows that there is a fundamental distinction between the type of tautomerism exhibited in compounds where its operation involves the ionisation of a C–H link (true prototropy) and that exhibited in compounds where the tautomeric hydrogen atom is attached to some atom other than carbon. The name " mesohydric tautomerism " (*idem, ibid.*) was tentatively proposed for the latter type, which has now been augmented by such a wealth of new examples that it is desirable to review in detail the significance of this new aspect of tautomerism.

The Theory of Mesohydric Tautomerism.—Consider the general case of a tautomeric compound $\overbrace{A\sim\sim\sim B}^{H}$ in which the tautomeric hydrogen atom is attached to two alternative atoms A or B, which can themselves be united either directly (as in diad systems) or through a chain (as in triad, tetrad, pentad systems). The tautomeric behaviour of this compound has been conventionally represented as an equilibrium $[H]A\sim\sim\sim B \rightleftharpoons A\sim\sim\sim B[H]$, the shift of the hydrogen atom from A to B being accompanied by a redistribution of valencies along the chain $A\sim\sim\sim B$.

The current investigation has shown that, provided neither A nor B is carbon, the above compound exhibits molecular association by the operation of intermolecular B–H–A bonds. The hydrogen bond having its origin in resonance (Sidgwick, *Ann. Reports*, **1933**, **30**, 112; **1934**, **31**, 40), such a compound will therefore consist of aggregates of molecules arranged as in (I), in which (*a*) and (*b*) represent unperturbed states of which the true state of the molecular aggregate is a resonance hybrid. On rise of temperature, or by solution in a solvent, such an aggregate will tend to break up into smaller fragments, but these will retain a fundamentally similar (*i.e.*, hydrogen-bond) structure. Measurements of molecular weight indicate that these fragments are usually linear polymers, but there is evidence that in a few cases they exist predominantly as cyclic dimers, as in oximes, carboxylic acids, and pyrazoles (Part VII). Whether the fragments be linear or cyclic, however, their physical and chemical behaviour will be similar to that of the parent compound (I).

$$\cdots H{—}A\sim\sim\sim B\cdots H{—}A\sim\sim\sim B\cdots H{—}A\sim\sim\sim B\cdots H{—}A\sim\sim\sim B\cdots H{—}A\sim\sim\sim B\cdots H{—}A\sim\sim\sim B\cdots \quad . \; . \; . \quad (a)$$

$$—H\cdots A\sim\sim\sim B{—}H\cdots A\sim\sim\sim B{—}H\cdots A\sim\sim\sim B{—}H\cdots A\sim\sim\sim B{—}H\cdots A\sim\sim\sim B{—}H\cdots A\sim\sim\sim B— \quad . \; . \; . \quad (b)$$

(I.)

The tautomeric behaviour of the compound under consideration is now seen to be due to the fact that the chemical and especially the physical properties of the hybrid (I) are intermediate between those expected of (*a*) and (*b*), with the result that it possesses the properties of both $H{—}A\sim\sim\sim B$ and $A\sim\sim\sim B{—}H$, although neither of these tautomers has a real existence. *The compound* (I) *is therefore essentially homogeneous.*

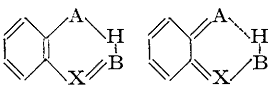
It is proposed to describe an arrangement of molecules as in (I) by the term " mesohydric structure," depending as it does on the intermolecular sharing of the tautomeric hydrogen atom, and the resulting tautom-

---

* Subsequently referred to by the number of the part in this series.

erism by the term " mesohydric tautomerism." These terms are used in recognition of the work of Oddo (*Gazzetta*, 1906, **36**, ii, 1) who first used the term " mesoidria " to describe the attachment of hydrogen simultaneously to two other atoms in accounting for the anomalous behaviour of certain *o*-hydroxyazo-compounds, and subsequently of other tautomeric systems. Oddo's work was, incidentally, the earliest recognition of what has since come to be called the hydrogen bond, although many of his examples (see, *inter alia*, Oddo's " Trattato di Chimica Organica," 1930, p. 41 *et seq.*) are not in harmony with modern concepts of stereochemistry.

Five- and six-membered chelate ring systems involving hydrogen as a member provide a special case of mesohydric structure in which, owing to the space disposition of the chain A〰〰B, the tautomeric hydrogen atom is shared between A and B *in the same molecule*, as in (II). Examples of this special type of mesohydric tautomerism are very numerous, and some are given under " tetrad and pentad systems " (below). Unlike (I), such compounds are non-associated by virtue of the *intra*-molecular co-ordination of the hydrogen atom.



(II.)

In conclusion, it must be pointed out that the mesohydric structure proposed for substances exhibiting hydrogen-bond association as illustrated in (I) is to be regarded as ideally simplified, for such a rectilinear arrangement takes no account of the exigencies of molecular and crystal architecture. Nevertheless, provided intermolecular bonding be through hydrogen, the precise arrangement of the molecules within the solid (or liquid) is immaterial to the functioning of mesohydric tautomerism.

Final proof of the correctness of the speculations given above must await determinations of structure by such unequivocal methods as *X*-ray diffraction. In this connexion it is noteworthy that Senti and Harker (*J. Amer. Chem. Soc.*, 1940, **62**, 2008), in a detailed *X*-ray examination of the crystal structure of acetamide, find the molecules to be arranged in a cellular structure consisting of interlocked rings each composed of six molecules linked by N–H–O bonds. This structure is closely similar to and completely in harmony with that already suggested for amides (Part I) on the grounds of their tautomerism and molecular association.

Examples of Mesohydric Tautomerism.—The following tautomeric systems, previously regarded as showing prototropy, are now attributed to mesohydric tautomerism. The evidence for their mesohydric structure is contained in the references given in parentheses. There are many other tautomeric systems for which a mesohydric structure may be predicted, but which lack proof of such structure at present; these are not included in the following list.

For convenience, examples are classified by Laar's method (*Ber.*, 1886, **19**, 730) according to the number of atoms in the chain separating successive hydrogen bonds.

Diad systems.

Pyrazoles, indazoles (:N·NH· cyclic) (Part VII).
Oximes (:NOH) (*e.g.*, Sidgwick, *Ann. Reports*, 1934, **31**, 41).

Triad systems.

Amides, anilides (–CO·NH–) (Parts I—IV).
Sulphonamides, sulphonanilides (–SO_2·NH–) (Part I).
Hydrazides (–CO·NH·NH–) (Part VI).
Diazoamino-compounds (–N:N·NH–) (Hunter, J., **1937**, 320).
Benztriazoles (–N:N·NH– cyclic) (Part X).
Amidines, glyoxalines, benziminazoles, guanidines (–N:CH·NH–) (Part VIII).
Thioamides, thioanilides, thiolbenzthiazoles (–CS·NH–) (Part XI).
Cyanamides (–NH·CN) (Part XII).
Carboxylic acids (–CO·OH) (*e.g.*, Sidgwick, *ibid.*, 1933, **30**, 115).

Tetrad systems.

Hydroxytriazens [–N:N·N(OH)–] (Elkins and Hunter, J., **1938**, 1346).

Pentad systems.

o-Hydroxyazo-compounds (*idem*, J., **1935**, 1598).
Arylazo-oximes (*idem*, J., **1941**, 823).
Formazyl compounds (–N:N·CR:N·NH–) (Part IX).
Thioacridone (Part XI).
Enolised β-diketones and β-keto-esters, etc.
Phenols and arylacylamido-compounds possessing *o*-substituent donor groups such as nitro-, aldehydo-, keto-, carboxy-, arylazo-, etc. (Parts II, III, and IV).

[*Note.*—The outstandingly high conductances of the hydrogen and the hydroxyl ions in aqueous and hydroxylic media are usually attributed to a mechanism (see, *e.g.*, Huggins, *J. Amer. Chem. Soc.*, 1931, **53**, 3190) involving the union of the ion to a chain of solvent molecules linked through hydrogen bonds. As a consequence of the mesomeric character of the resulting ion–solvent complex, an ion can become detached from either end of the chain, according to the direction of the electrical field; this results in a transmission of ionic charge at a rate far exceeding that at which an individual ion could travel. The mesohydric structure of such ion–solvent complexes bears a close resemblance to (I), and the whole process of ion transport by this mechanism can be regarded as a mesohydric tautomeric phenomenon.]

Relation of Mesohydric Tautomerism to Prototropy.—There is nothing in the theory of mesohydric tautomerism at variance with or excluding the possibility of prototropy. Indeed, the reactions of the hybrid (I), especially those carried out in basic or acidic media, must be largely the result of a process closely akin to prototropy; for there can be little doubt that by the action of bases or acids the hybrid (I) will be depolymerised with formation of mesomeric ions thus :

$$(\mathrm{I}) - n\overset{\oplus}{\mathrm{H}} \longrightarrow n(\overbrace{\mathrm{A}\sim\sim\sim\mathrm{B}}^{\ominus})$$

$$(\mathrm{I}) + n\overset{\oplus}{\mathrm{H}} \longrightarrow n(\mathrm{H}\text{–}\overbrace{\mathrm{A}\sim\sim\sim\mathrm{B}}^{\oplus}\text{–}\mathrm{H})$$

[n = number of unit molecules composing the polymer (I). If less than n protons are removed from or added to (I), only partial depolymerisation will ensue.]

Not only will the formation of these ions provide an adequate explanation of the formation of derivatives of (I) related in structure to the so-called tautomers H–A$\sim\sim\sim$B and A$\sim\sim\sim$B–H, but the reversal of the above reactions by restoration of a proton to the mesomeric anion $\overbrace{\mathrm{A}\sim\sim\sim\mathrm{B}}^{\ominus}$, or by withdrawal of a proton from the mesomeric cation $\mathrm{H}\text{–}\overbrace{\mathrm{A}\sim\sim\sim\mathrm{B}}^{\oplus}\text{–}\mathrm{H}$ will yield, not the separate tautomers themselves, but the homogeneous mesohydric structure (I).

An essential difference clearly exists, therefore, between tautomeric substances possessing a mesohydric structure (see list, p. 807) and all other types. In the former, attempts to separate tautomers, or to generate a tautomeric compound in circumstances which would be expected to lead to a single tautomer, will be frustrated by its assumption of a mesohydric structure; the result will inevitably be a single homogeneous substance such as the hybrid (I). On the other hand, where a mesohydric structure is impossible, as in tautomeric compounds $\overbrace{\mathrm{A}\sim\sim\sim\mathrm{B}}^{\mathrm{H}}$ where A and/or B are carbon (owing to the inability of hydrogen attached to carbon to form a stable hydrogen bond), and in all compounds showing anionotropy, the preparation of single tautomers or their separation from admixture can be confidently anticipated, depending only on sufficiently sensitive manipulative methods being available to overcome the more or less rapid interchange of the separate tautomers. The isolation of individual tautomers of this kind has, of course, been achieved in a great number of well-known instances, including the systems keto-enol, three-carbon, azomethine, nitro-paraffin, and numerous anionotropic systems. It is no accident that these are the very systems in which ionotropy has been demonstrated.

Alleged Isomerism in Compounds Exhibiting Mesohydric Tautomerism.—It has already been emphasised that, whereas true prototropy depends upon the existence of individual tautomers capable of interconversion, mesohydric tautomerism results in a manifestation of dual character by a compound essentially homogeneous. It is therefore vital to the theory of mesohydric tautomerism to investigate all cases of alleged isomerism in pairs of compounds within the types listed on p. 807. Many such pairs have been examined in the course of the current investigation (notably in Part IX) and their isomeric nature shown to be unfounded. Two further pairs are now considered.

(1) 2-*Phenyl*-β-*naphthiminazole.* (The interdependence of hydrogen-bond structure and tautomerism in derivatives of iminazole is fully discussed in Part VIII.)

This compound was first prepared by Hübner and Ebell (*Annalen*, 1881, **208**, 328) by reduction of 2-nitro-1-benznaphthalide (III), and subsequently by various alternative methods (Koll, *ibid.*, 1891, **263**, 314; Fischer, Reindl, and Fezer, *Ber.*, 1901, **34**, 935; Hinsberg and Koller, *ibid.*, 1896, **29**, 1500; Meldola and Forster, J., 1891, **59**, 703; Fischer, *J. pr. Chem.*, 1924, **107**, 46), all of which yield identical products (m. p.'s between 210° and 218°). In 1933 Galimberti (*Gazzetta*, **63**, 96) claimed to have isolated an isomer of widely different m. p. (296°), obtained by reduction of 1-*nitro*-2-*benznaphthalide* (VI), and on the basis of which he proposed structures (IV) and (V) for the alleged isomers. Galimberti's preparation has now been carefully repeated, revealing that the higher-melting substance is without doubt 2-*phenyl*-β-*naphthiminazole hydrochloride*, from which the free base (m. p. 218°) can be liberated by the action of alkali.

(III.) (IV; m. p. 218°.) (V; alleged m. p. 296°.) (VI.)

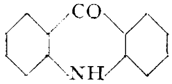
The identity of structures (IV) and (V) finally disposes of the objection raised by Green and Day (*J. Amer. Chem. Soc.*, 1942, **64**, 1170, footnote) to the mesohydric interpretation of the tautomerism of the iminazoles, and strongly suggests that their efforts to " immobilize " the iminazole ring will prove fruitless.*

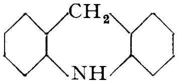
(2) *Acridone.* Acridone (VII) has all the characteristics of a highly associated substance. It is sparingly

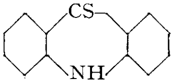
---

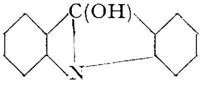
* *Note, added in proof.* In a recently available publication (*J. Amer. Chem. Soc.*, 1945, **67**, 1074), Kelly and Day confirm the non-existence of an isomeric 2-phenyl-β-naphthiminazole, though they do not identify Galimberti's product.

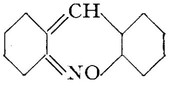
soluble in organic solvents, its m. p. is extremely high (354°), and it distils unchanged above this temperature. That its association is probably the result of a hydrogen-bond (N–H–O) structure is supported by the remarkably large reduction in m. p. brought about by replacing either its imino-hydrogen atom (*e.g.*, *N*-methylacridone,


(VII.)


(VIII.)


(IX.)


(X.)


(XI.)

m. p. 203°; *N*-ethylacridone, m. p. 159°; *N*-phenylacridone, m. p. 276°) or its oxygen atom as in acridane (VIII; m. p., 168°). The tautomeric behaviour of acridone would therefore appear to be adequately explained by assigning it a mesohydric structure, especially as its sulphur analogue, thioacridone (IX), has been shown to possess a similar structure (Part XI).

It is therefore with considerable reserve that the substance known as " acridol " should be accepted as a tautomeric form of acridone (X), the structure assigned to it in Heilbron's " Dictionary of Organic Compounds " (Vol. I, p. 20) and, as one possibility, in Beilstein's Handbuch (4th Edn., Vol. XXI, pp. 132, 335). That this formulation of acridol has raised doubts in the past is evident from the number of publications devoted to its structure (Beilstein, *op. cit.*); indeed, other equally plausible constitutions have been suggested for it (*e.g.*, Heller, *Ber.*, **1916**, **49**, 2758; Lehmstedt, *Ber.*, **1935**, **68**, 1455), the balance of evidence being strongly in favour of the amine-oxide structure (XI) (Tanasescu and Ramontianu, *Bull. Soc. chim.*, **1934**, **1**, 547). Finally, the usual ease of interconversion of true tautomers is not exhibited in the case of acridone and acridol; the latter is prepared indirectly (Freund, *Monatsh.*, **1896**, **17**, 396; Drechsler, *ibid.*, **1914**, **35**, 534; Kliegl and Fehrle, *Ber.*, **1914**, **47**, 1635), and is converted into the former only by processes which are well known to cause *isomeric* change, *e.g.*, by the action of nitrous acid (Drechsler, *loc. cit.*) or acetic anhydride (Kliegl and Fehrle, *loc. cit.*). Such evidence cannot be used in support of structure (X), for other substances (notably 3-phenylanthranil) behave similarly.

EXPERIMENTAL.

Reduction of 1-*Nitro*-2-*benznaphthalide* (*VI*).—This substance, though a new compound * and the starting point of Galimberti's preparation (*loc. cit.*), was neither analysed nor described by him. It has now been prepared by nitrating β-benznaphthalide in glacial acetic acid solution with somewhat more than the theoretical quantity of nitric acid (*d* 1·52). The *nitro-compound* separated after a short time, and crystallised from acetic acid in small straw-coloured needles, m. p. 170° (Found: N, 9·5. $C_{17}H_{12}O_3N_2$ requires N, 9·6%). Reduction to the naphthiminazole was effected by zinc dust and hydrochloric acid exactly according to Galimberti's procedure. The product crystallised from aqueous alcohol as a white microcrystalline powder, m. p. 310° (Galimberti, 296°), which proved to be 2-*phenyl*-β-*naphthiminazole hydrochloride* (Found: Cl, 12·4. $C_{17}H_{12}N_2$,HCl requires Cl, 12·65%). The free base was precipitated from an alcoholic suspension of the hydrochloride by addition of ammonium hydroxide, and crystallised from aqueous alcohol in the hydrated form, m. p. 122° (Fischer, *loc. cit.*, gives 120—122°), and from benzene in the anhydrous form as white needles, m. p. 218° (Found: N, 11·5. Calc. for $C_{17}H_{12}N_2$: N, 11·5%). No depression of m. p. was caused by admixture with an authentic specimen of 2-phenyl-β-naphthiminazole prepared by reduction of 2-nitro-1-benznaphthalide.

For contributing the evidence on which the theory of mesohydric tautomerism is based, the author desires to record his grateful thanks to the following co-workers: Drs. H. O. Chaplin, M. Elkins, J. A. Marriott, and Messrs. H. T. Hayes, T. G. Heafield, G. Hopkins, H. A. Rees, and C. B. Roberts. His thanks are also due to Mr. J. S. Whitehurst for repeating the work of Galimberti.

UNIVERSITY COLLEGE, LEICESTER.

[*Received*, *July* 10*th*, 1945.]