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Formation of Molecular Complexes by Diketobenzodiazines and their Methylated Derivatives with Phenol and Dihydroxybenzenes in Aqueous Solutions

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Introduction

In any attempt at molecular design for biological purposes, whether for producing a synthetic enzyme, a drug, or an antimetabolite, it is desirable to know how and to what extent organic groupings interact in aqueous media. The present contribution is concerned with results of an investigation attempting to evaluate such behaviour for very simple models. It is shown that formation of molecular complexes in both the solid state and in solution is significantly influenced by the 'lock and key' fit for the simple systems studied.

Diketobenzodiazines and their methylated derivatives were selected for these studies as they presented considerable variations in structure and orientation. These compounds, moreover, possessed structural features which were suggested from results of an earlier investigation of the same systems in nonaqueous media[1] to have rather strong complexing tendencies with respect to phenolic compounds. The present study is limited to interactions in aqueous solutions.

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Experimental

The solubility method described by Higuchi and Zuck[2] was used in this investigation to follow the extent of binding of a given weight of the individual benzodiazine as a function of the concentrations of several phenolic compounds added. The appropriate benzodiazine derivative (200 mg) was introduced into a series of reaction vessels. In the case of Compounds (II) and (IX), the amounts used were 100 and 375 mg respectively. These quantities are in excess of their individual solubilities in water. Varying volumes of a standard aqueous solution of the specific phenol were added to each vessel from a burette, and the volume made up to 10 ml with distilled water. The reaction vessels were 15-ml screw-capped vials fitted with Teflon liners. Occasionally supersaturation with respect to an insoluble complex was encountered. It was the general practice, therefore, to equilibrate a run at 30° for a minimum of 6 h, place it in an ice bath for 15 min and re-equilibrate at 30° for not less than 12 h. Equilibrations at 30° were effected by mechanically rotating the reaction vessels in a constant-temperature bath.

All analyses of the supernatant aqueous phase were made on a Cary Recording Spectrophotometer, Model 11MS at wavelengths between 320 and 324 mμ, depending upon the benzodiazine under investigation. The analytical procedure yielded the total concentration of the dissolved benzodiazine derived from both the complexed and uncomplexed forms.

Interpretation of the phase diagrams and the calculation of apparent equilibrium constants were made similarly to those made by Higuchi and Zuck.[2] The general 1 : 1 stoichiometric interaction:

$$\text{Benzodiazine} + \text{Phenolic Compound} \rightleftharpoons \text{Complex} \qquad (1)$$

would have an equilibrium constant given by

$$K = \frac{[\text{Complex}]}{[\text{Benzodiazine}]\,[\text{Phenolic Compound}]} \qquad (2)$$

Materials Used and Syntheses. Phenol, catechol, resorcinol, and hydroquinone were purified by distillation or by using appropriate solvents.

2,3-Diketo-1,2,3,4-tetrahydroquinoxaline (I) ('dihydroxyquinoxaline') was prepared according to the method of Phillips.[3]

1,4-Dimethyl-2,3-diketo-1,2,3,4-tetrahydroquinoxaline (II) was synthesized by the procedure given by Newbold and Spring.[4]

1-Methyl-2,3-diketo-1,2,3,4-tetrahydroquinoxaline (III) was isolated as the sodium salt which precipitated when 4 N NaOH was used in the preparation of (II) above, through the methylation of (I) using dimethyl sulphate. The sodium salt was washed with chloroform, dissolved in sufficient distilled water and acidified to congo red with 37 per cent HCl. The precipitate was collected, dried, and recrystallized from ethanol, m.p. 280–2° (281–3°[5]).

1-Methyl-2-keto-3-methoxy-1,2-dihydroquinoxaline (IV) and *2,3-dimethoxyquinoxaline* (V) were prepared simultaneously after the method of Cheeseman.[6]

2,4-Diketo-1,2,3,4-tetrahydroquinazoline (VI) ('benzoyleneurea') was synthesized by the base-catalyzed cyclization method described by Bogert and Scatchard.[7]

1,3-Dimethyl-2,4-diketo-1,2,3,4-tetrahydroquinazoline (VII) was prepared by the methylation of (VI) in sodium hydroxide solution using dimethyl sulphate; m.p. (from ethanol) 165–6° (163–5°[8]).

1,4-Diketo-1,2,3,4-tetrahydrophthalazine (VIII) ('dihydroxyphthalazine') was prepared by following the procedure of Radulescu and Georgescu.[9]

1,4-Diketo-2,3-dimethyl-1,2,3,4-tetrahydrophthalazine (IX) was prepared according to the directions given by Drew *et al.*[10] The product was recrystallized from water and the resulting dihydrate was dried *in vacuo* over magnesium perchlorate for 24 h. The anhydrous product was used.

1-Keto-2-methyl-4-methoxy-1,2-dihydrophthalazine (X) *and 1-keto-4-methoxy-2,3-dihydrophthalazine* (XI) were prepared as described by Rowe and Peters.[11]

All the melting points not reported above agreed well with literature values.

Results and Discussion

In Figs. 1, 2 and 3 are given, in tabular form, the phase diagrams constructed for the various benzodiazine derivatives. In each case, the apparent molar solubility of the benzodiazine (ordinate) has been plotted against the number of moles per litre

of the phenolic compound added (abscissa). Whenever an insoluble complex formed, its stoichiometry appears in the lower right hand corner of the diagram (based on moles of benzodiazine to moles of phenolic compound). The stoichiometric ratios of these insoluble complexes were analyzed graphically, spectrophotometrically, and in some cases elemental analyses were made. The apparent stability constant based on the assumed 1 : 1 stoichiometry is shown in the lower left hand corner of each plot. This was done, regardless of the stoichiometry of any insoluble complex that might form, to facilitate comparison of associative tendencies among the various structures.

The calculation of the apparent equilibrium constants involves judicious substitution for the appropriate molar concentration terms in equation (2), such that:

[Benzodiazine] = Water solubility of the benzodiazine, since the system is at constant activity with respect to that benzodiazine.

[Complex] = Apparent solubility of the benzodiazine when in the presence of a phenolic compound minus its water solubility when assuming first order dependency.

[Phenolic Compound] = The difference between the molar concentration of phenolic compound added initially and [Complex] when an assumed 1 : 1 complex interaction exists between reacting species.

As an illustration of a typical calculation, data from the interaction between *N*,*N*′-dimethyldiketoquinoxaline (II) and resorcinol will be used. The solubility of (II) in water at 30° is $1 \cdot 90 \times 10^{-2}$ mole/l. After equilibration of excess of the compound in $1 \cdot 59 \times 10^{-2}$ molar aqueous resorcinol solution, the apparent solubility of this benzodiazine is $2 \cdot 24 \times 10^{-2}$ mole/l. Substitution in equation (2) yields:

$$K = \frac{[(2 \cdot 24 - 1 \cdot 90) \times 10^{-2}]}{[1 \cdot 90 \times 10^{-2}] \times [(1 \cdot 59 - (2 \cdot 24 - 1 \cdot 90)) \times 10^{-2}]} = 14 \cdot 3$$

The general procedure employed in analyzing such diagrams and the fundamental limitations of such an approach have already been treated extensively.[12-16] It is assumed that any increase in solubility of a solid substance when a second substance is added is due to formation of one or more complex species between the

two. Such an assumption is fairly unambiguous for very dilute systems but for more concentrated solutions one may be faced with a semantic problem.[14] The systems under consideration in this communication, fortunately, rarely exceeded 0·2 M in concentration, generally being in the millimolar range.

As long as such a system contains an excess of the solid phase of the first substance, its activity, of course, is fixed, and no information concerning the dependency of the interaction on it can be obtained. Despite this limitation and the fact that some of the compounds under consideration may exist as dimers in aqueous solutions, we have found it convenient to express dependencies and other results on the basis that only monomeric species of the reactants are involved.

General behaviour. The phase diagrams obtained for the various benzodiazines with the several phenolic compounds can be readily classified into three general groups.

(1) Curves showing no discontinuity.

(2) Curves having initial increases followed by plateaus and subsequent drops.

(3) Curves showing no initial changes but rather precipitous drops after substantial concentrations of the phenolic compound have been added.

Proper analysis of these diagrams can yield pertinent information concerning the complexing behaviour of the systems.

The first group of curves (1) generally indicates formation of complexes only in the solution phase. The lack of sharp changes in the slope means that a second solid phase does not form in these systems. This suggests that intercomplex binding in these systems is relatively low. For the systems studied, interactions exhibited both positive and negative deviations from, as well as strict adherence to, first order dependency on the phenol concentrations (see phase diagrams for compounds (VI) and (VII), Fig. 2). Equilibrium constants for the assumed one-to-one interactions can be calculated exactly for these reactions only if the plots are linear. When deviations were encountered, these constants were calculated from the initial linear portion. Diagram VI-C, representing the results of the interaction between diketoquinazoline and catechol, formed a continuous curve which precluded any such calculation.

In the second group of curves (2), all showed an initial linear increase in solubility which was indicative of the behaviour described for the first group. At the point where the solubility of a particular complex was exceeded, an invariant plateau region appeared as a result of the precipitation of another solid phase, i.e. a molecular compound. When all excess solid benzodiazine was depleted from the system by the addition of the phenolic compound, the invariance no longer existed and the continued addition of the phenols removed the dissolved, free benzodiazine in the form of a molecular complex. The phase diagrams of compound (II), Fig. 1, illustrate this behaviour. Because of the initial linear rise, an equilibrium constant may be calculated for the particular interaction responsible for the increased solubility. Calculations can also be made from the descending parts of these plots.[15] If only one complex species formed, the two sets of data should yield the same constant. If two or more species were present in significant amounts this would not be true. It is evident that the precipitated complex may not necessarily have the same configuration as the species essentially responsible for any observed initial increase in solubility.

The third group of phase diagrams (3) showed an immediate invariant plateau region equal to the initial solubility of the benzodiazine. The interval of invariance was followed by a precipitous drop to virtually zero concentration of the benzodiazine (cf. phase diagram I-A). Such behaviour suggests that high affinities exist between the components of the adducts in the precipitated phase leading to extreme insolubility. It appeared in these cases that bonding between components of a single stoichiometric complex may often be indistinguishable from bonding between complexed molecules in the solid state. That is to say, the association between *D* (donor) and *A* (acceptor) to form *D–A* may not be significantly different from the intercomplex association of *D–A* to form *D–A–D–A–* . . . in the solid state. With this type of phase diagram an equilibrium constant cannot be readily calculated.

Quinoxaline derivatives. Results of interaction studies with these compounds are depicted in Figs. 1 and 2. With both compounds (I) and (II) in the quinoxaline series, solid molecular compounds were formed with all four phenols (Rows I and II, Fig. 1), whereas

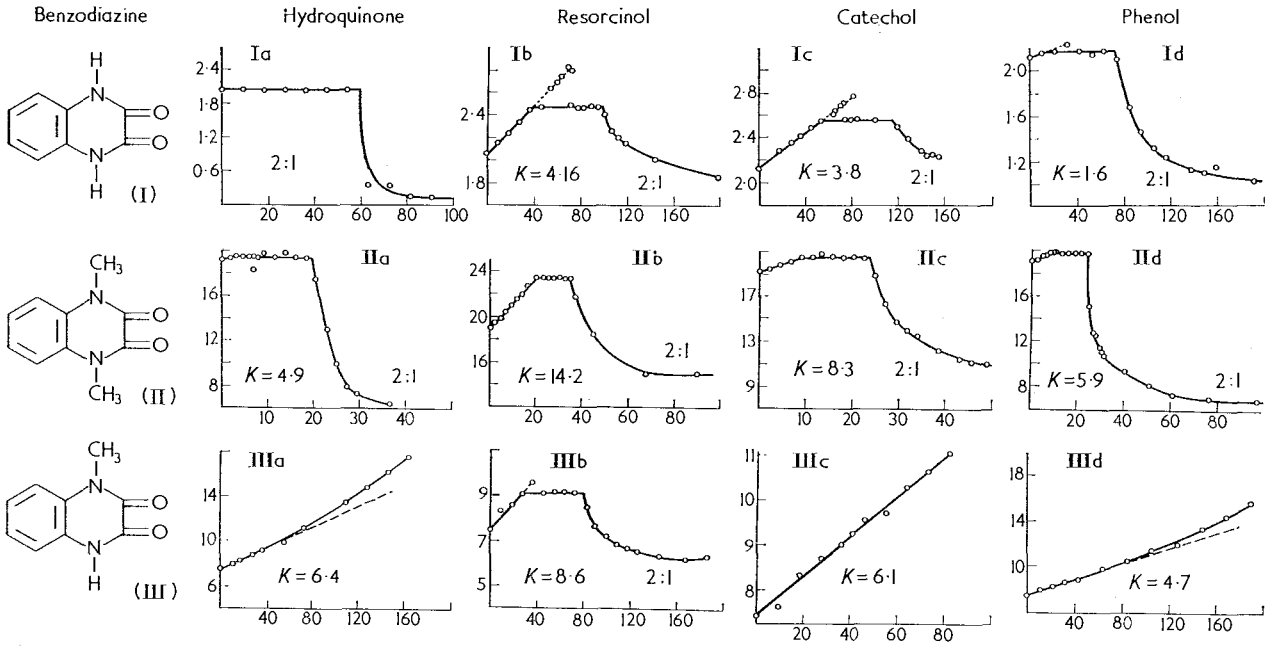


Fig. 1. Phase diagrams of interactions between benzodiazines and phenolic compounds in aqueous media at 30°. In each phase diagram, the apparent molar solubility ($\times 10^3$) of the benzodiazine (ordinate) is plotted against the total number of moles per litre ($\times 10^3$) of the phenolic compound added initially (abscissa). Column 1 shows the structure of the individual benzodiazine. In the lower left hand corner of the phase diagram is given the apparent equilibrium constant based upon an assumed 1 : 1 interaction between the benzodiazine and the phenolic compound. In the lower right hand corner appears the stoichiometric ratio of an isolable molecular compound (moles benzodiazine: moles phenolic compound).

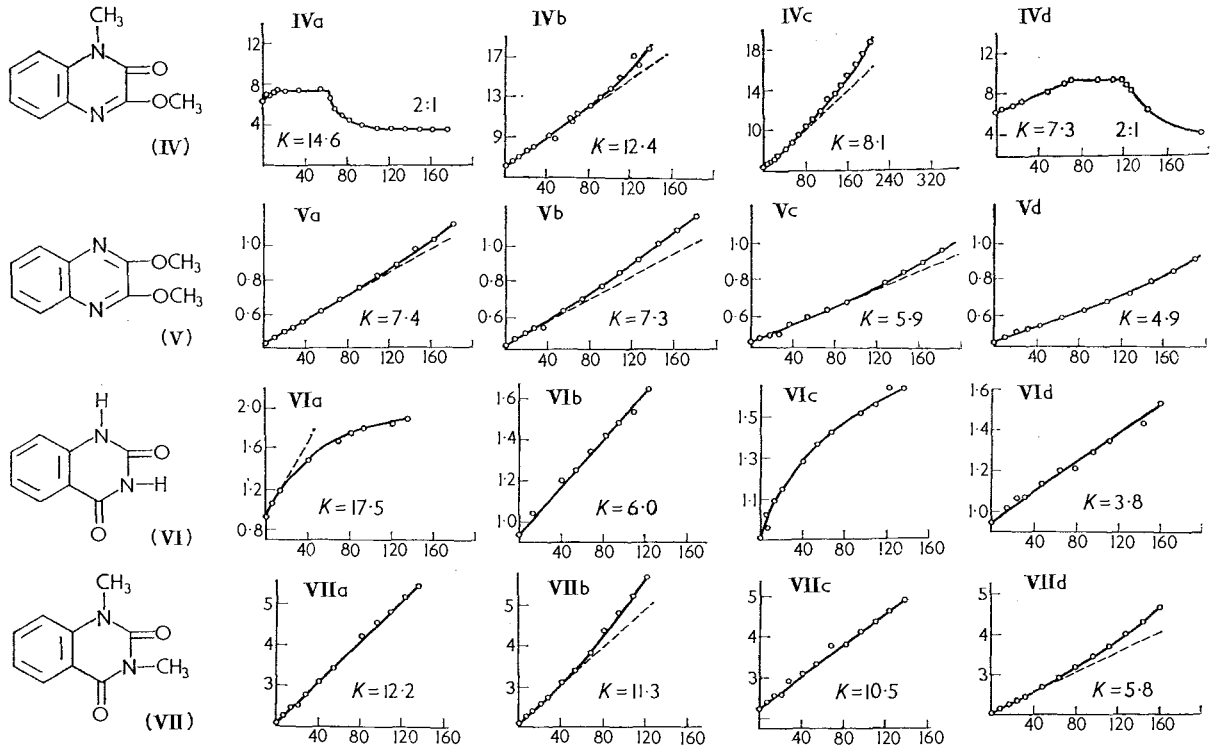
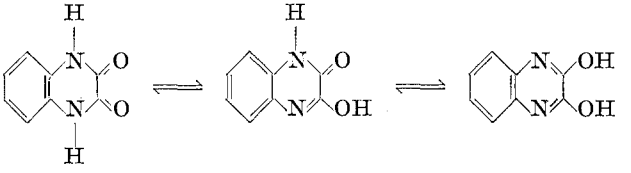


Fig. 2. Phase diagrams of interactions between benzodiazines and phenolic compounds in aqueous media at 30°.

compound (III) yielded a solid complex only with resorcinol (III-B, Fig. 1). Likewise, only the interactions of compound (IV) with hydroquinone and phenol (IV-A and IV-D, Fig. 2) resulted in formation of insoluble molecular compounds. In each case, however, the stoichiometric ratios were two moles of the quinoxaline derivative to one mole of the appropriate phenolic compound. Table I lists the experimental data on these molecular compounds. All other phase diagrams in the quinoxaline series indicate formation of complexes in the solution phases only.

In the quinoxaline series, only the interaction between compound (I) and hydroquinone (I-A, Fig. 1) was of the type that showed an immediate invariance in water solubility [type (3)]. This is significant in light of the fact that diketoquinoxaline is known to be strongly self-complexed by hydrogen bonding both in the solid state and in solution. Its high melting point (greater than 350°)[3] and lack of solubility in ordinary solvents (water solubility = $2 \cdot 3 \times 10^{-3}$ mole/l) attest to this. Yet any hydroquinone added to an aqueous system containing solid diketoquinoxaline is capable of breaking the hydrogen bonded self-complex to give essentially quantitative amounts of a molecular compound in the proportions 2 moles diketoquinoxaline to 1 mole of hydroquinone. As suggested above, this behaviour is probably due mainly to extremely low solubility of the formed complex species. The formation constants of such complexes may or may not be very high. In the present instance the latter may be the case since hydroquinone appears to sublime from the solid complex when heated well above 200°.

Compound (I) has been labelled 'diketoquinoxaline', whereas it is commonly designated as 'dihydroxyquinoxaline'. Both these structures and the monoketomonohydroxy form are tautomeric isomers.



Compounds (II), (III), (IV), and (V) prevent either partial or total tautomerism through methylation of (I) so that one of the

three forms is largely fixed. Compound (I) behaves much like compounds (II) and (III) in its complexing tendencies which suggests that the diketo form may predominate. If compound (I) were in the form of the dihydroxy isomer, for example, one might expect it to complex well with *o*-phenylenediamine. Yet the apparent equilibrium constant calculated on a 1 : 1 interaction with this diamine is only 2·5 (the linear increase in solubility of compound (I) as a function of the concentration of *o*-phenylenediamine is not given graphically here). Böeseken *et al.*[17] arrive at the same conclusion from their investigations of the conductance of boric acid solutions in the presence of this quinoxaline derivative.

Comparison of the equilibrium constants in Rows I and II, Fig. 1, shows that, in general, the stabilities of the *N*,*N*′-dimethyldiketoquinoxaline complexes are apparently roughly three times greater than those of the corresponding unsubstituted diketoquinoxaline complexes. This may be attributed in part to the greater nucleophilicity of the methylated compounds, and in part to hydrophobic interaction, discussed in earlier papers.[13-16] It might also be due to a dependence of these reactions on the benzodiazine concentration higher than the assumed first order.

The behaviour of the *N*,*N*′-dimethyldiketoquinoxaline complexes at their melting point is of interest. The complex with hydroquinone melts at 213–215°, but complexes of the other phenolic compounds exhibit incongruent melting; mild sintering is followed by an abrupt collapse of the crystalline material with an immediate separation of a liquid and a solid. The remaining solid then disappears slowly over a wide temperature range (Table I). The behaviour is probably due to reversal of the complexing reaction at higher temperatures.

In an attempt to find a quinoxaline derivative whose water solubility was intermediate between that of compound (I) (water solubility = $2 \cdot 3 \times 10^{-3}$ mole/l.) and compound (II) (water solubility = 19×10^{-3} mole/l.), 1-methyldiketoquinoxaline (compound (III), water solubility = $7 \cdot 5 \times 10^{-3}$ mole/l.), was synthesized and studied. The results appear in Row III, Fig. 1. Only with resorcinol was an insoluble complex formed (III-B). The solid complex had a 2 : 1 stoichiometry and incongruent melting point (Table I). The numerical values for the equilibrium constants

for the interactions between compound (III) and the several phenols are, in general, intermediate between those for the corresponding complexing interactions of diketoquinoxaline and dimethyldiketoquinoxaline.

The benzodiazine, 1-methyl-2-keto-3-methoxy-1,2-dihydroquinoxaline, compound (IV), has available two possible polar complexing sites, i.e. the keto group and the heterocyclic nitrogen

Table. I. Experimental data on molecular compounds formed in the quinoxaline series

Experimental stoichiometries[a] (determined from phase analysis), moles	Form	m.p., °C[b]
2·02 compound (I) : 1 Hydroquinone	matted flakes	>200 (incongr.)
2·02 compound (I) : 1 Resorcinol	matted flakes	>200 (incongr.)
2·01 compound (I) : 1 Catechol	matted flakes	>200 (incongr.)
2·02 compound (I) : 1 Phenol	matted flakes	>200 (incongr.)
2·04 compound (II) : 1 Hydroquinone	plates	213–215
2·01 compound (II) : 1 Resorcinol	plates	182 (incongr.)
2·11 compound (II) : 1 Catechol	needles	184 (incongr.)
1·99 compound (II) : 1 Phenol	needles	165 (incongr.)
2·01 compound (III) : 1 Resorcinol	matted needles	232 (incongr.)
1·98 compound (IV) : 1 Hydroquinone	fine needles	162–163
1·96 compound (IV) : 1 Phenol	matted needles	85–86

[a] See ref. 12. Stoichiometries determined by spectrophotometric analysis of the solid complex were essentially the same.
[b] m.p. uncorrected.

atom. Both sites are electronegative and capable of accepting a proton for hydrogen bonding. The results of its interactions with the four phenolic compounds appear in Row IV, Fig. 2. Solid complexes were formed with hydroquinone (IV-A) and phenol (IV-D), both with stoichiometries of 2 : 1. The experimental data are given in Table I. Soluble complex formation was encountered when resorcinol (IV-B) and catechol (IV-C) were studied. As seen in the phase diagrams of the latter two cases, positive deviation from first order dependence was observed. The direction of the deviation from linearity suggests that the major reaction or reactions involved were at least bimolecular with respect to the phenols. The same type of behaviour is

exhibited in all the four phase diagrams (V-A, V-B, V-C, and V-D, Fig. 2) dealing with dimethoxyquinoxaline solubility characteristics. In the dimethoxyquinoxaline structure (V) only the basic, heterocyclic nitrogens would be expected to be involved in associations with proton donors.

Quinazoline Derivatives. The results of the interactions between the four phenolic compounds and diketoquinazoline (VI) appear in Row VI, Fig. 2. Although diketoquinazoline is a position isomer of diketoquinoxaline, their complexing tendencies are not similar. Whereas diketoquinoxaline yielded slightly soluble, solid complexes with all four phenols, diketoquinazoline associated with these phenols to form complexes in solution only. The shapes of the plots suggest that the benzodiazine may exist in solution in a dimerized form and that the complexing reaction may involve the monomeric species.

As with its position isomer, compound (I), diketoquinazoline is capable of existing in any of its possible tautomeric structures. The structures that this benzodiazine may assume are: the diketo-, the dihydroxy-, or one of two possible forms of the monoketo-monohydroxy- structures. The latter two possibilities arise from the lack of symmetry of the pyrimidine nucleus. Which of these structures predominates either in the solid state or in solution is not well established. Elderfield[18] considers this compound to be a true enol–keto tautomer based upon its chemical reactions, high melting point and water insolubility. It is fairly well established, however, that with amides the keto form is favoured in protodotic solvents while the enol form is preferred in nucleophilic or aprotic solvents. Regardless of the structure of this benzodiazine in solution, two nucleophilic, polar sites would be available for association with proton donors.

The phase diagrams depicting the solubility behaviour of *N,N'*-dimethyldiketoquinazoline are shown in Row VII, Fig. 2. This benzodiazine is isomeric with compound (II), but exhibits entirely different physical and complexing properties. Like its unmethylated parent compound, it formed only soluble complexes. Comparison of the behaviour of (VII) with (II) is difficult in view of the large difference in their solubilities. It should be pointed out that these systems gave well defined solid complexes in nonaqueous solvents.[1]

Phthalazine derivatives. Phthalylhydrazide (VIII) is a position isomer of compounds (I) and (VI) and as such should show a lesser tendency to complex with phenols than any of its methylated derivatives, in keeping with the behaviour of its isomers. The phase diagrams of its solubility as a function of the concentration of the four phenols are given in Row VIII, Fig. 3. In each case, a linear rise in apparent solubility was noted.

N,N'-Dimethylphthalylhydrazide (IX), which is isomeric with compounds (II) and (VII), complexes with each of the phenols and the results appear in Row IX, Fig. III. A slightly soluble, solid complex was observed to form with each of the dihydroxybenzenes (IX-A, IX-B, and IX-C), while the solubility of the phthalazine was linear when phenol itself was added to the aqueous system (IX-D). It is interesting to note that the stoichiometric ratios for each of the insoluble complexes differed. The interaction with hydroquinone produced a 2 : 1 complex, while with resorcinol a 5 : 2 complex formed, and with catechol a 1 : 1 stoichiometry resulted. The experimental data for these solid complexes appear in Table II.

Table II. Experimental data on molecular compounds formed in the phthalazine series

Experimental stoichiometries[a] (determined from phase analysis), moles	Form	m.p. °C[b]
1·93 compound (IX) : 1 Hydroquinone	needles	175–177
2·44 compound (IX) : 1 Resorcinol	needles	151–152
1·10 compound (IX) : 1 Catechol	needles	144–146
3·08 compound (X) : 1 Hydroquinone	amorph.	128–130
2·20 compound (X) : 1 Resorcinol	amorph.	110–114
1·93 compound (X) : 1 Phenol	amorph.	66–68
2·95 compound (X) : 2 Catechol	amorph.	74–76

[a] See ref. 12. Stoichiometries determined by spectrophotometric analysis of the solid complex were essentially the same.
[b] m.p. uncorrected.

A change in stoichiometric ratios among the different solid adducts with the several phenols and 1-keto-2-methyl-4-methoxyphthalazine (X) was also encountered. The phase diagrams for

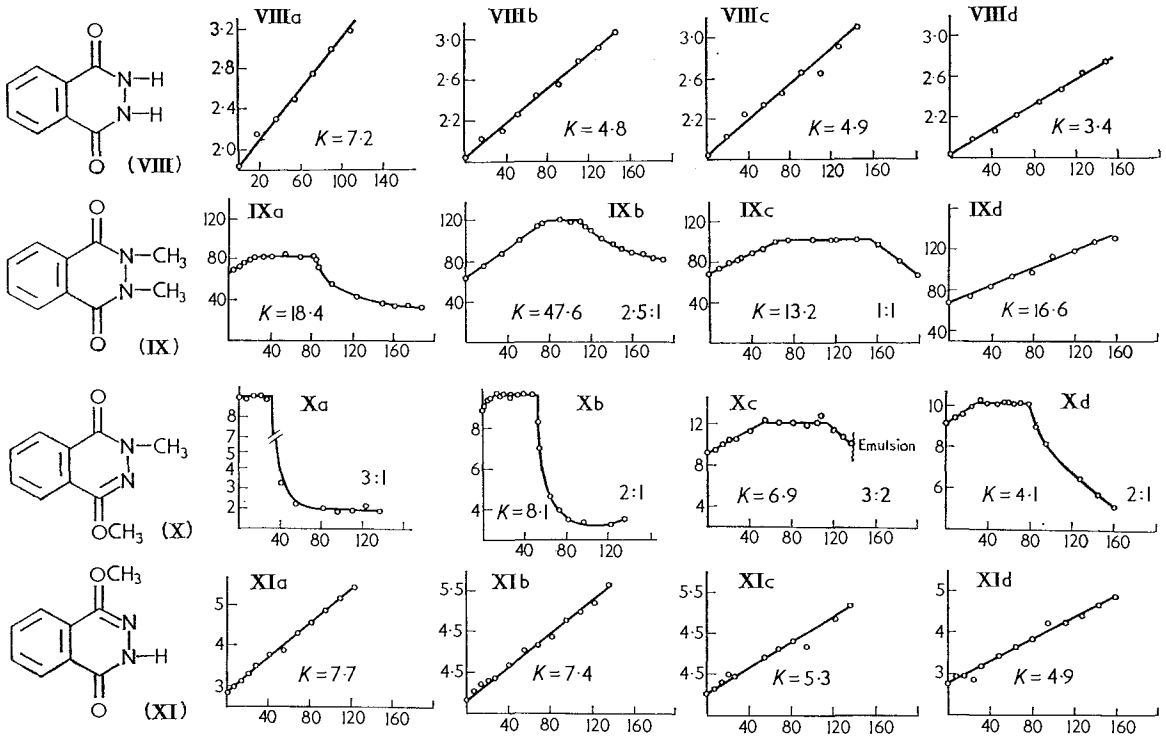


Fig. 3. Phase diagrams of interactions between benzodiazines and phenolic compounds in aqueous media at 30°.

these interactions appear in Row X, Fig. 3. With hydroquinone, compound (X) yielded a very insoluble complex (X-A), [type (3)], whose stoichiometry was 3 : 1. The phase diagrams for the interaction with both resorcinol (X-B) and phenol (X-D) show precipitation of 2 : 1 complexes, while with catechol a 3 : 2 complex resulted (X-C). The experimental data for these solid molecular compounds appear in Table II.

The effects of the aqueous system upon the complexing behaviour of compounds (IX) and (X) are not readily understood but they may have a bearing upon the changing stoichiometries of the various complexes formed in the phthalazine series. In the first place, compound (IX) forms a dihydrate when recrystallized from water. The two moles of water are easily lost when stored over anhydrous magnesium perchlorate at room temperature for approximately 24 h. Whether insoluble hydrated complexes are formed is difficult to say since they can not be recrystallized without dissociation into their respective components, nor can an accurate analysis be made easily on the solid without pre-drying it over dehydrating agents.

Secondly, the insoluble complexes formed between compound (X) and resorcinol, catechol, and phenol were oils while they remained in contact with water. While in this state, distribution of the compounds of the system undoubtedly occurred between the oil and water phases, which accounts for the poor analytical results obtained. Only after decantation of the aqueous phase was it ever possible to obtain a solid, apparently amorphous mass.

It is fairly well established that compounds (I) and (VI) exist primarily in the diketo form both in the solid state and in aqueous solution. Sheĭnker and Pomerantsev[19] have indicated this, as well as showing that compound (VIII) tautomerizes half way to the monoketomonohydroxy form in solution and in the solid. By formation of a monomethoxy derivative of compound (VIII) to yield compound (XI), this configuration should be retained; yet water solubility (compound (XI) $= 2 \cdot 9 \times 10^{-3}$ mole/l.) would be greater than for compound (VIII) ($1 \cdot 8 \times 10^{-3}$ mole/l.) but less than for compound (X) ($9 \cdot 1 \times 10^{-3}$) and (IX) ($6 \cdot 9 \times 10^{-2}$ mole/l.). The results of the studies with the monomethoxyphthalazine (XI) appear in Row XI, Fig. 3. In all cases the interactions remained first order with respect to the concentrations of the four phenolic

compounds, and their separate equilibrium constants indicate a trend toward proportionality to water solubility of the particular benzodiazine.

Conclusions

Although a more thorough investigation is required for a clear-cut elucidation of the structures of these complexes, there is little doubt that at least dipolar and electron sharing forces are involved in the association of the benzodiazine and hydroxybenzenes in these adducts. On the basis of the 2 : 1 stoichiometric ratios in the quinoxaline series, for example, it appears that competitive hydrogen bonding is not the only form of interaction of consequence. Higuchi and Lach[13] attributed this behaviour in part to the interactions of the aromatic, hydrophobic portions of the reactants which are 'squeezed out' by the high internal pressure of water resulting in a relatively high degree of interaction. The aromatic portions of the reactants not only enhance the possibility of polarization of the amido carbonyls in the benzodiazines but also provide a planar 'surface' upon which other planar 'surfaces' may stack themselves aided by π-electron interactions.

Although the relative complexing tendencies of these systems as manifested by solubility behaviour shown on the 44 phase diagrams, are relatively weak as compared to caffeine systems, it would appear that these interactions are still significant. Binding tendencies are sufficiently strong in roughly 40 per cent of the cases to precipitate the complex species as separate solid phases. In the remaining instances, interactions occur to a comparable extent but apparently the species formed are too soluble to yield a second phase. It is evident that interactions involving molecules much larger than these, or macromolecular surfaces, may utilize several points of contact which may greatly magnify the over-all binding tendencies, despite the fact that individual site interactions may be of the same order of magnitude as those illustrated in these plots.

In general, the relative magnitudes of the various apparent stability constants seem to follow the degree of water solubility of the benzodiazines, i.e. the greater the water solubility of the benzodiazine, the greater the magnitude of the apparent stability

constant with all the phenolic compounds studied. This may be partly due to the fact that the constants were calculated arbitrarily on a 1 : 1 basis. Since the experimental method employed, as pointed out earlier, permitted determination at only a single activity of the heterocyclic compounds, it was not possible to establish their concentration dependency. These results seem to suggest that the dependency may be greater than one.

Some 'lock and key' dependency seems to exist in these systems when the interaction constants at low phenolic concentrations are compared. In this concentration range, probably only one molecule of phenol is involved in complex formation. On this basis the stability constants indicate that two-point attachment between polar groups in the benzodiazines and hydroxy protons of the diphenols exists. The best indication of this occurs in the dimethylated benzodiazine interactions; e.g. the decreasing order of stabilities of complexes of compound (II) is resorcinol > catechol > phenol > hydroquinone. Construction of molecular models of reactants shows an easy two-point attachment between the two phenolic protons of resorcinol and catechol to the two carbonyl oxygens on adjacent carbon atoms of compound (II). The stability constant for the interaction with catechol is less than that with resorcinol, possibly because there is some intramolecular interaction in catechol molecules. Two-point attachment between compound (II) and hydroquinone is difficult to realize with models.

With compound (VII), the decreasing order of stability in solution is hydroquinone > resorcinol > catechol > phenol. Models of compound (VII) and the phenolic compounds indicate that all three dihydroxybenzenes fit well through a two-point attachment to the two carbonyls of compound (VII). The magnitudes of the stability constants for the three dihydroxybenzenes illustrate this ease of fit by being numerically close to each other.

The decreasing order of stability constants for compound (IX) is resorcinol > hydroquinone > phenol > catechol. Once again models of the reactants show a facile possibility of a two-point attachment between resorcinol or hydroquinone with the two carbonyls of compound (IX), but not with catechol.

Both compounds (IV) and (X) have essentially the same two