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The azinyl–azinylidene tautomerism of azinylmethanes and general problems of the tautomerism of azines

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ABSTRACT. The results of studies on the tautomerism of azinylmethanes are surveyed. The terminology, the structure of the tautomeric forms, the thermodynamics and mechanisms of their interconversion, the dependence of the equilibrium on structure factors and the character of the medium, and certain general characteristic features of tautomeric equilibria of the azinyl–azinylidene type are discussed.

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I. Introduction

The tautomerism of organic compounds is an important branch of organic chemistry with an interesting history and tradition, the interest in which has been sustained also in recent years.[1–3] It is possible to differentiate three main problems which have stimulated the interest in tautomerism.

1. The dependence of the structure and physical properties of the compounds on their tautomeric composition
2. The inter-relation between tautomerism and reactivity.
3. The search for and construction of tautomeric molecules with properties of practical importance (photochromic systems, models of enzyme active centres, rearranging molecules).

Since prototropism is as a rule associated with the heteroatomic groups OH, NH, SH, etc., it is not surprising that tautomeric equilibria are encountered particularly frequently in heterocyclic compounds. The structure and physical and chemical properties of the latter are frequently difficult to understand if their tautomeric characteristics have not been elucidated. It is not fortuitous that virtually every chapter in modern monographs on the chemistry of heterocyclic compounds (see, for example, Barton and Ollis[4]), devoted to a particular class of heterocyclic compounds, includes also a section on tautomerism. The tautomerism of azine derivatives† (Scheme 1), whose fundamental character has been emphasised in an extensive monograph[3] in connection with the study of the structure of DNA, is especially important. The tautomerism of azines has also been discussed in connection with the problem of enzyme catalysis,[6] in the study of the reactivity on internal factors and medium effects,[7] etc.

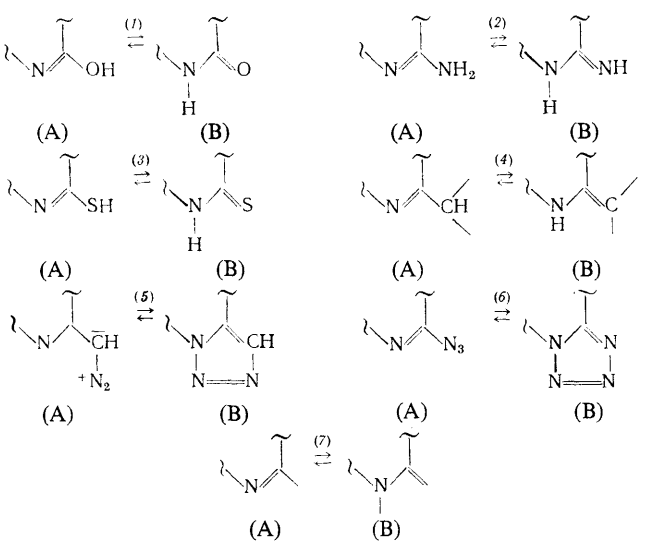
Scheme 1 presents the principal types of tautomeric equilibria observed in the series of azine derivatives as a function of the character of the exocyclic fragment undergoing tautomerism. Among equilibria of types (*1*)–(*6*), the tautomerisms of hydroxyazines [equilibrium (*1*)] and aminoazines [equilibrium (*2*)] have been most completely studied, which is to a significant extent due to their biochemical importance. An important difference of the tautomeric equilibria of azinylmethanes consists in the fact that the rate of dissociation of the CH bond is significantly lower than those of the OH, NH, or SH bonds. This increases the lifetime of the tautomers and makes it possible to use the NMR method effectively. Its application to equilibria (*1*)–(*3*) is hindered by the proton exchange, which is rapid on the NMR time scale. Thus, apart from their independent interest, azinylmethane derivatives can also serve as key models for the search for and formulation of general characteristics of the tautomerism of the azinyl–azinylidene type: (A) ⇄ (B).

The tautomerism of substituted methylazines[4] has not so far been the subject of a special review. Admittedly there exists a monograph[3] in which the literature up to 1975 is presented, but the very character of the monograph precluded a detailed treatment of the analysis of such tautomeric molecules. Furthermore, during the

† There is some uncertainty as to which compounds should be classified as azines. If a formal standpoint and nomenclature are adopted as a basis, then the group of azines will include, together with diazines, triazines, and tetrazines, also, for example, thiazines but not pyridine (see, for example, the Chemical Encyclopaedic Dictionary).[5] On the other hand, from a non-formal point of view, pyridine is in many respects closer to diazines and triazines than are oxazines or thiazines. Bearing in mind the chemical similarity, there is a genuine need for differentiating the group of six-membered heteroatomic compounds—benzene analogues where one of several –CH= groups have been replaced by a nitrogen atom –N=. It would be useful to adopt firmly the term "azines" for this particular group of compounds. We may note that in a recent fundamental publication[4] the section on azines included pyridine and its analogues but did not deal with nitrogen-containing cyclic compounds with oxygen, sulphur, etc.

last ten years numerous important data on the tautomerism of substituted methylazines have been published. The present review deals with studies on the prototropic tautomerism of azinylmethanes (up to 1988) as well as certain general features characteristic of both the tautomerism of azinylmethanes and and azinyl-azinylidene tautomerism as a whole. We endeavoured to restrict the treatment to derivatives based on the aromatic ring of azines or their condensed benzo-analogues. We shall not discuss in detail in this review the relation between tautomerism and reactivity, although important studies in this field have been published recently.[7,8] Nevertheless, it is essential to emphasise the methodological relation between the study of tautomeric and chemical properties in relation to a class of potentially tautomeric compounds such as azinylmethanes, hydroxyazines, etc. A series of studies have been published[9] on tautomerism and dual reactivity, where it was shown that the phenomenon of dual reactivity is extremely general and is by no means always caused by tautomerism. This conclusion concerning the dual reactivity of tautomeric molecules is frequently treated too broadly and is applied to their reactivity as a whole. Nevertheless, if the class of compounds considered from the standpoint of chemical behaviour exhibits also a tautomeric property, its far-reaching characterisation is impossible without considering such properties. Just as the study of the structure of a chemical compound precedes a complete understanding of its chemical properties, so does the study of the tautomeric structure constitute a necessary basis (stage) for the understanding of the reactivity of compounds exhibiting tautomeric properties.[1]

Scheme 1



For tautomers whose stabilities are close, the relation between the composition of the reaction products in the tautomeric equilibrium is determined by the familiar Curtin–Hammett principle.[2,10] For slow (relative to the reaction rates) tautomeric interconversions, the composition of the product is predetermined by the tautomeric equilibrium constant K_T. For "fast" reactions, no direct relation between the structure of the tautomers and the composition of the reaction products may be observed. Nevertheless, in these cases too it is necessary to understand the tautomeric characteristics if only to be able to elucidate which of the tautomeric forms is responsible for the formation of the products.

It is likewise noteworthy that the range of energies corresponding to the contents of the tautomers being compared is very narrow ($\Delta G \simeq 0-5$ kcal mol^{-1}) and the chemist frequently deals with potentially tautomeric compounds existing almost wholly in one form or another. Although in this case one may speak of the absence of tautomerism, nevertheless the study of such systems is undoubtedly essential in the investigation of tautomerism from general standpoints. The specific properties of individual tautomers whose reactivities, generally speaking, differ radically can be most fully manifested under these conditions. In the case of a marked difference between the chemical properties of the tautomers, the specific fixation or displacement of the equilibrium to one side or another (for example with the aid of methylation, by means of structural factors, medium effects, complex formation, and irradiation) can be one of the ways of regulating the reactivity of compounds.

Thus the knowledge of the tautomeric properties of compounds not only helps to explain and predict their chemical properties but also provides a possibility for regulating them.

The main types of tautomeric interconversions (*1*)–(*6*) in series of azines (Scheme 1) can be combined on the basis of the characteristic rearrangement of bonds [equilibrium (*7*)]. The two principal features of this rearrangement are the change in the hybridisation of the nitrogen atom from the "pyridine" type to the "pyrrole" type ("amide" type) and the change in the multiplicity of the exocyclic bond involved in the tautomeric transformation.

In the classification of equilibria of types (*1*)–(*6*), one usually adopts as a basis the structure of the exocyclic group, for example, the "hydroxy–oxo" tautomerism of hydroxyazines (1), the thiol–tautomerism of mercaptoazines (2), etc. In those cases where it is necessary to differentiate the general features of a family of equilibria, it is also logical to base the treatment on the structural characteristics of the azine component of the molecule, treating it as a substituent in relation to the exocyclic fragment. Using the IUPAC nomenclature for naming the azine groups, we shall if necessary refer henceforth to equilibria of type (A) ⇄ (B) as pyridyl–pyridylidene and pyrimidyl–pyrimidylidene tautomerisms or in the general case the azinyl–azinylidene tautomerism (which can be shortened to azinyl–ylidene or azaheteroaryl–ylidene tautomerism). The names proposed above can be applied not only to the sigmatropic tautomerism[11] of type (*1*)–(*4*), associated with the migration of a proton, but also to the tautomerism of the electrocyclic type [equilibria (*5*) and (*6*)], where the topology of the change in the bonds also satisfies the conditions mentioned above. Within this family, it is useful to employ the general classification of tautomeric processes.[11] Almost all the processes examined below are [1,*j*]sigmatropic rearrangements where it is possible to identify an atom or group whose position is altered ("migrant") and the remainder of the molecule ("skeleton").[12]

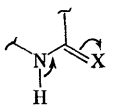
For heterocyclic molecules, synchronous or multistage processes with participation of two (or more) migrating groups are common.[2,3,13] The term "diotropic transformations" proposed previously[14] appears inadequate in this instance, because it is firmly related to the type of mechanism of the interconversion. Potentially tautomeric molecular systems with two and more migrating groups can be more conveniently classified as di-(tri-, etc.)sigmatropic systems, while the corresponding type of equilibria, where the different forms differ by the positions of two migrating groups, can be referred to as disigmatropic equilibria.[15]

In view of the lack of firm boundaries between the phenomena of tautomerism and isomerism, there should exist some consistency in

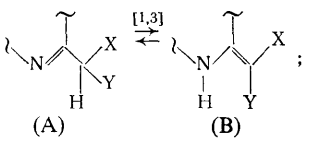
the terminology employed. Thus, taking into account the analogy of the pairs of terms "isomerism"—"isomerisation" and "tautomerism"—"tautomerisation" (the latter expression will be used to designate the tautomeric rearrangement (A) ⇄ (B) (but not the equilibrium).

II. The [1,3]sigmatropic tautomerism of azinylmethanes

The tautomeric equilibrium of unsubstituted azinylmethanes (A) ⇄ (B) is fully displaced to form (A). Judging from experimental data, the relative capacity of substituted azines for transition to form (B) increases in the series of exocyclic groups CH < NH < OH, which apparently reflects the stabilisation which arises when the endocyclic NH group is conjugated with the C=C, C=N, and C=O fragments respectively:[16]



As in the case of aminoazines,[17,18] the appearance of the ylidene tautomer in the series of azinylmethanes is promoted by electron-accepting substituents in the exocyclic fragment:[16,19]

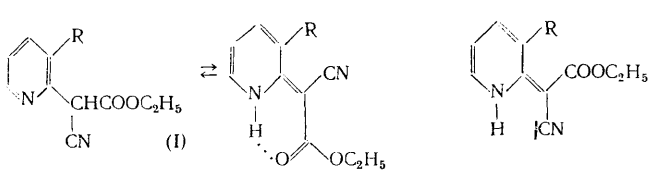


(A) (B)

X = Y = CN, NO_2, COOR, SO_2R, $C_6H_4NO_2$.

Type (4) tautomerism was apparently first mentioned by Chichibabin in 1918.[20] A little later he succeeded in observing tautomeric forms of types (A) and (B) for dinitrobenzylpyridine.[21] During the same years, tautomerism was observed in the series of pyridylmethanes[22] and quinolinylmethanes,[23,24] whose study was subsequently continued.[25]

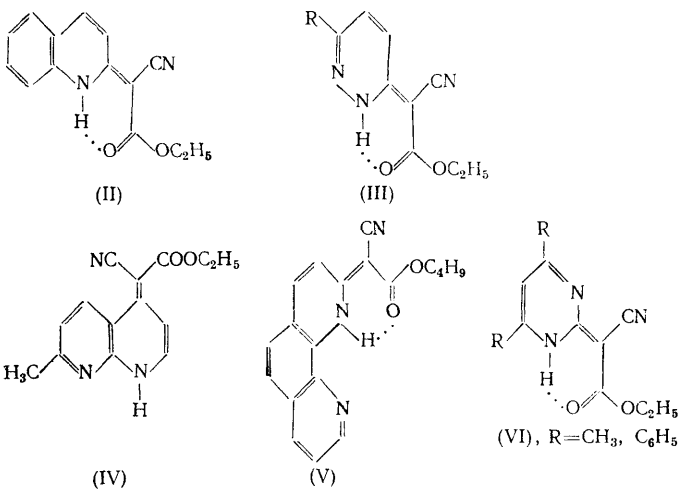
In the series of substituted CH-azines, the tautomerism of azinylcyanoacetic esters has been studied in fair detail. Thus, according to ^{1}H NMR spectroscopic data obtained in $CDCl_3$,[26] pyridyl-2-cyanoacetic ester (I, RH) is in the ylidene form (B) (δ_{NH} = 14.1 p.p.m.). For the analogous 3-methyl derivative, it has been suggested[27] on the basis of ^{1}H NMR spectra that the non-chelate ylidene tautomer (B′) (R = CH_3) is formed. It may be that, in view of the low rate of the tautomeric interconversion, form (B′) was observed by the authors[27] under non-equilibrium conditions. The formation of thermodynamically stable non-chelate tautomers requires special conditions, for example, basic solvents, which stabilise the form of type (B′) as a result of the formation of an intermolecular hydrogen bond (HB).



(A) (I) (B) (B′)

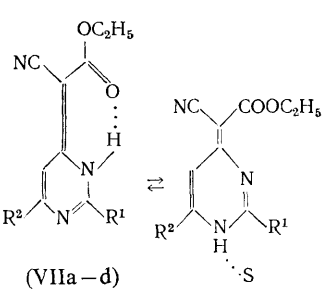
Thus the use of dimethyl sulphoxide (DMSO) as the solvent led to the formation of significant amounts of non-chelate ylidene forms in the case of substituted pyrimidinyl-2-cyanoacetic esters.[28]

Quinolinylcyanoacetic ester (II) [29,30] and the analogous pyridazine (III),[30] pyrazine,[31] naphthyridine (IV),[32] and phenanthroline (V) [29] derivatives, obtained by the reaction of the corresponding *N*-oxides or halogeno-derivatives with cyanoacetic ester, exist in the ylidene tautomeric form. The latter predominates also for pyrimidinyl-cyanoacetic ester (VI), whose structure was examined by Zagulyaeva and Mamaev[33] and was later proved by UV spectroscopy.[34]



(II) (III) (IV) (V) (VI), R=CH_3, C_6H_5

In the case of cyanoacetic derivatives of di- or tri-azines, several types of ylidene tautomers can be produced. Thus, 4-pyrimidinyl-cyanoacetic esters (VII) can form ylidene tautomers with the *ortho*- and *para*-quinonoid disposition of the double bonds in the heterocycle. Both tautomers of 2-methylpyrimidinyl-4-cyanoacetic ester (VIIb) were isolated in a pure state (solid phase).[35] It was shown that in solvents of low polarity the *ortho*-quinonoid tautomer is more stable; the formation of the *para*-quinonoid tautomer is promoted by polar media and solvents forming hydrogen bonds.[36,37]



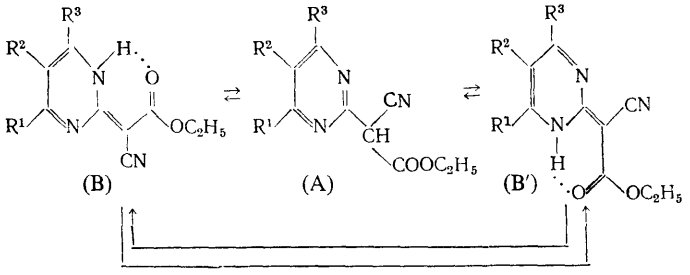
(VIIa–d)

(VIIa): $R^1 = R^2 = H$;
(VIIb): $R^1 = CH_3$, $R^2 = H$;
(VIIc): $R^1 = CF_3$, $R^2 = H$;
(VIId): $R^1 = H$, $R^2 = C_6H_5$.

The stabilisation of the *para*-quinonoid tautomer by polar solvents was also observed for the unsubstituted 4-pyrimidinyl-cyanoacetic ester (VIIa) and its trifluoromethyl analogue (VIIc). The steric hindrance in 6-phenyl-4-cyanoacetic ester (VIId) prevents the formation of the *para*-quinonoid tautomer either in DMSO, or in hexamethylphosphoramide (HMPA), or in the crystalline state.[35]

Two types of ylidene tautomers (B) and (B′) have been detected for pyrimidinyl-2-cyanoacetic esters (VIII) substituted asymmetrically in the pyrimidine ring. Analysis of the spin–spin coupling of the ring protons in the ^{1}H NMR spectrum made it possible to distinguish reliably these forms and to determine the ratios of the forms (A), (B), and (B′).[28] For example, 2% of the tautomer (A),

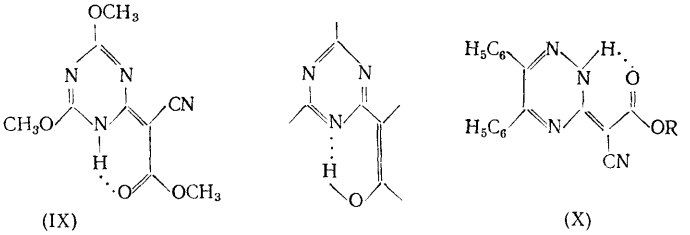
70% of the tautomer (B), and 28% of the tautomer (B′) were detected for the pyrimidinylcyanoacetic ester (VIIId) in $CDCl_3$.[28] The occurrence of the degenerate tautomeric transformations of the type (B) ⇄ (B′) ($R^1 = R^3 = H$) was established by a pulse mode double resonance ^1H NMR study using transfer of a saturation label.[28,38]



(B) (A) (B′)

(VIIIa): $R^1 = R^2 = R^3 = H$; (VIIIb): $R^1 = R^3 = H$, $R^2 = OCH_3$; (VIIIc): $R^1 = R^3 = H$, $R^2 = N(CH_3)_2$; (VIIId): $R^1 = C_6H_5$, $R^2 = R^3 = H$.

Among 1,3,5-triazine derivatives, the tautomerism of the dimethoxy-derivative (IX) was studied in greatest detail.[39] It exists in $CDCl_3$ predominantly in the ylidene tautomeric form. Traces of the aromatic form (A) of this compound were detected by IR spectroscopy (the change to a hexane solution entails an increase in the content of this tautomer[38]). It has been assumed[39] that the enolic tautomer of compound (IX), involving an enolised ester group, exists. However, from ^{14}N NMR data, it has been shown[28,40] that an appreciable amount of the enolic tautomer is not formed in cases of this kind. The signal of the NH group observed in the ^{14}N NMR spectrum (−260 p.p.m. relative to CH_3NO_2) is typical for nitrogen of the amide type;[41] on the other hand, in the case of enolisation, a downfield shift of the signal should have been observed (−100 p.p.m.). 1,2,4-Triazinylcyanoacetic ester (X) also exists in the ylidene tautomeric form.[42]

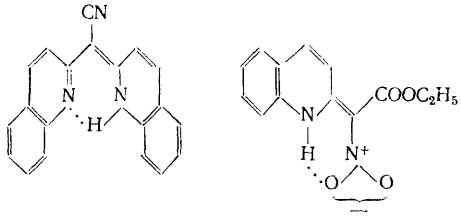


(IX) (X)

^{14}N NMR	−260 p.p.m. (exp.)	−100 p.p.m. (expected value)

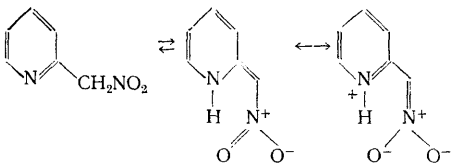
Thus, the ylidene tautomer of cyanoacetic acid derivatives of unsubstituted azines is as a rule more stable than the aromatic tautomer. The aromatic tautomers have been detected in trace amounts only for pyrimidinyl-2-cyanoacetic and pyrazinyl-2-cyanoacetic esters.[28,31] The presence of a cyclic substituent affects appreciably the position of the tautomeric equlibrium and in many cases the content of forms (A) and (B) may prove to be comparable, as happens, for example, for 5-methoxy- or 5-dimethylamino-pyrimidinyl-2-cyanoacetic esters (VIIIb, c).[28]

In the series of azines, the structure of malonodinitrile derivatives has also been studied. Regardless of the nature of the heterocycle, malonodinitrile derivatives exist in the ylidene tautomeric form.[19,27,29–31,33,34,43–46] The lower electron-accepting capacity of the COOR group compared with the nitrile group is responsible for the lower tendency of azinylmalonic ester to be converted into the ylidene form. The aromatic tautomer of azinylmalonic esters is usually more stable.[34,47–49] However, in certain cases, for example for pyridinyl-4-malonic and pyridazinyl-3-malonic esters, the contents of the tautomers (A) and (B) were comparable.[50] The azinyl−azinylidene tautomeric equilibrium occurs for bisquinolinylmethanes of type (XI)[51,52] and derivatives of nitroacetic ester (XII).[30]



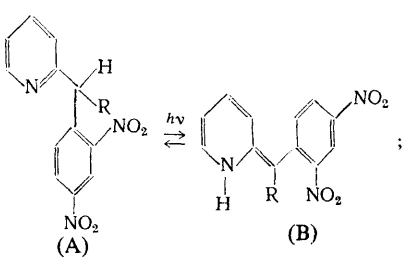
(XI) (XII)

The substituted azinylmethanes examined above contain two electron-accepting substituents at the CH fragment, but the presence of only one acceptor is sometimes sufficient for the occurrence of an equilibrium of type (A) ⇄ (B). Thus, in the nitration of a large series of methylazines, it has been observed that the nitromethylazines (XIII) obtained in this process are capable of the (A) ⇄ (B) tautomerism.[53] (It is noteworthy that the representation of the ylidene tautomer in the above study by another resonance formula does not alter the essential features of the situation. It is essential not to confuse resonance representations of the same ylidene tautomer with the tautomeric equilibrium itself.)



(A) (B) (XIII)

The ylidene tautomers of certain azinylmethanes are kinetically stable and can be formed, in particular, under the influence of UV irradiation. Among such compounds, derivatives of *o*-nitrobenzyl type are best known.[54] After the irradiation of compound (XIV), the appearance of a coloured ylidene form is observed. It undergoes thermal tautomerisation to the starting material.[55] With increase in the electron-accepting capacity of the substituent at the CH fragment, the equilibrium (A) ⇄ (B) occurs even in the ground state. Thus for compound (XV) in $CDCl_3$ such equilibrium was established by ^1H NMR and UV spectroscopic methods.[56]



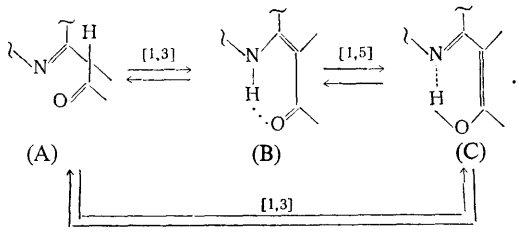
(A) (B)

(XIV): R = H; (XV): R = $COOCH_3$.

In this case too, irradiation increases the fraction of the tautomer (B), i. e. one may speak of an example of a photosensitive equilibrium of the azinyl–azinylidene type.[56] (A detailed discussion of the photoinduced tautomerisation of the azinyl–azinylidene type is outside the framework of the present review.)

III. Intrachelate [1,5]sigmatropic tautomerism of substituted methylazines

The compounds examined above are characterised by a low tendency towards a tautomeric rearrangement of the substituents in the exocyclic group. More favourable possibilities for tautomerism in the side chain are provided by acyl groups, which constitute the basis of the most frequently encountered tautomeric equilibria of the keto–enol type. The structure and tautomerism of acylmethylazines (including the simplest representative 2-acetonylpyridine) have been the subject of a prolonged controversy.[57]

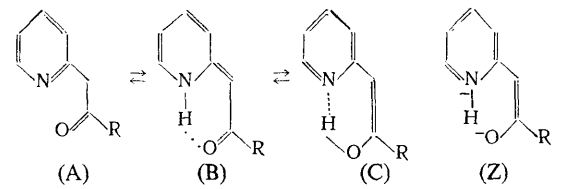


The tautomeric transitions (A) ⇄ (B) and (A) ⇄ (C) are instances of [1,3]sigmatropic tautomerism.[11] Intermolecular proton transfer is characteristic of such processes, while an intramolecular mechanism is unlikely because of symmetry requirements.[58] Since the rate of proton migration between the heteroatom and the carbon atom is usually low,[59] the study of such equilibria by NMR does not present appreciable difficulties in most cases. The intrachelate tautomeric (B) ⇄ (C) transition, an example of the [1,5]sigmatropic tautomerism, occurs, on the other hand, by an intramolecular mechanism characterised by a high rate and the NMR spectra show average signals due to both forms—(B) and (C).[60]

Vigorous investigation of the character of the potential energy surface (PES) for the [1,5]transfer of a proton, carried out in relation to the enolic form of malonodialdehyde (XVI) by both experimental and theoretical methods,[61] showed that the two-well PES profile corresponds to this type of equilibrium (Fig. 1). Since even in this favourable case the one-well potential does not occur, its existence for asymmetric chelates of types (B) and (C) appears unlikely.[62]

A reliable demonstration of the occurrence of the tautomers (B) and (C) (two-well potential) is provided by the spectroscopic identification of both tautomers with the aid of some kind of "rapid" method (IR, UV, and photoelectron spectroscopy, etc.). It is essential to note that formulae with equalised bonds are used not so much to designate a one-well potential surface for this compound but to state the uncertainty in the position of the proton (OH or NH form) (Fig. 1).[63]

Another uncertainty arising when the intrachelate tautomerism is discussed is frequently associated with the fact that in some studies the possibility of the formation of a "zwitter-ionic" tautomer is discussed. Thus, for the pyridine derivatives (XVII), the authors[64] consider also the tautomeric form (Z) together with forms (A), (B), and (C). However, it is easy to see that the formulae (B) and (Z) are merely different resonance designations of the same tautomer.



(XVII): R = CH_3 (a), C_2H_5 (b), C_3H_7 (c), iso-C_3H_7 (d), CF_3 (e), C_6H_5 (f), t-C_4H_9 (g).

In many early studies, the authors considered only two tautomeric forms for compounds of the pyridine series (XVII): the keto-form (A) and the enolic form (C). The possibility of the formation of the ylidene tautomer (B) in the equilibrium mixture was not then discussed.[65,66] For example, the picolinylketones (XVIIa–e)[65] and derivatives of phenylacylpyridine (XVIIf),[66] whose structures had been determined by IR, UV, and ^1H NMR spectroscopic methods, were examined from these standpoints. It was found that the tautomeric composition of the picolinylketones (XVIIa–e) is not correlated with the polarity constants of the substituent R, but there is a satisfactory correlation with the constants E_s reflecting the steric requirements of the substituents.[65] Evidently the neglect of the possibility of the formation of the ylidene tautomer (B) lowers the reliability of the conclusions reached. The tautomerism of the simplest representative of acylmethylazines—2-acetonylpyridine (XVIIa)—has been investigated[67] and the authors took into account all three possible tautomers. Information about the positions of both the "slow" tautomeric equilibria (A) ⇄ (B) and (A) ⇄ (C) and of the "fast" tautomeric equilibrium (B) ⇄ (C) has been obtained with the aid of ^1H NMR. Mondelli and Merlini[67] based their treatment on the fact that allylic interaction of the protons of the methylidyne and methyl groups (J_{CH/CH_3} = 1–2 Hz) should occur in the enolic tautomer (C) of acetonylazines. In the ylidene tautomer, the interaction of these protons takes place across a single bond and is significantly weaker; the corresponding spin–spin coupling constant is assumed to be zero. J_{CH/CH_3} = 0.65–0.75 Hz for acetonylpyridine, which indicates, according to the authors,[67] the predominance of the enolic form in the equilibrium (B) ⇄ (C). It is thought that, as a consequence of the weakness of the spin–spin

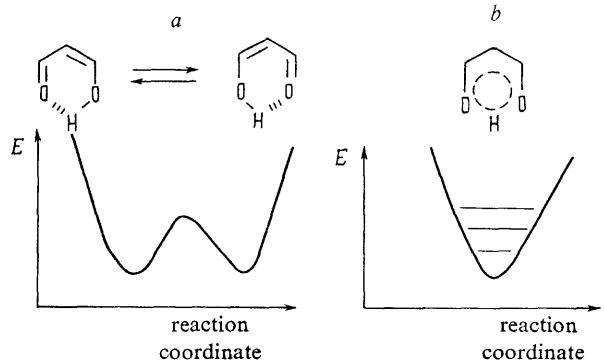


Figure 1. The character of the potential energy surface for two-well (*a*) and one-well (*b*) profiles.

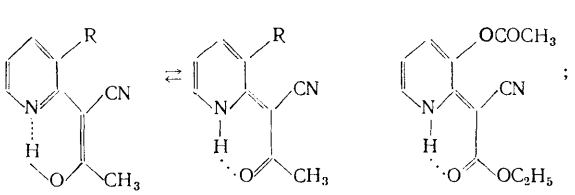
coupling and also because of the lack of rigour of the zeroth approximation for J_{CH/CH_3} in the case of the ylidene form, it is in many cases difficult to use the above criterion, especially for quantitative estimates.

Using ^1H NMR spectroscopy, Klose and Uhlemann[64] examined the tautomerism of ^{15}N-labelled picolinylketone derivatives (XVIId, g). Since $^{15}N-H$ spin–spin coupling was not observed, the ylidene form was rejected. In reality, a small amount of this form is produced,[68] but the observation of the corresponding small splitting apparently requires a more sensitive apparatus. Nevertheless, the possibilities of the above method are very great because, by virtue of the weak dependence of $J_{^{15}N-H}$ on the structure, in most cases there is no need to synthesis model compounds. The magnitude of the splitting for the tautomer (B) is close to 90 Hz, while for the enolic form it is apparently zero,[69] which ensures the quantitative estimation of K_T.

New possibilities arise in connection with the use of high-field instruments and special pulse trains (INEPT) for increasing the sensitivity and the measurement of ^{15}N NMR spectra on the basis of the natural abundance of the isotope. The possibilities of the broad-band version of the INEPT procedure for the measurement of $J_{^{15}N-H}$ have been demonstrated recently in the study of the tautomeric acylmethylazines of the pyridine, pyrimidine, and quinoline series.[70]

In contrast to earlier data,[64,72] Cassity et al.[71] state that the equilibrium (A) ⇄ (B) occurs for a series of picolinylketones (XVIIa, d, f, g). It may be that[57] this claim is a result of the careless reading of the communication[67] to which the authors refer in order to confirm their conclusions. The contradictory nature of the data on the structures of simple acylmethylazines was pointed out as early as 1982 in a study[57] of the tautomeric equilibrium of t-butyl 2-picolinyl ketone (XVIIg) and its quinoline analogue in 25 solvents. The value of the above study[57] is somewhat reduced because the position of the "fast" equilibrium (B) ⇄ (C) was not investigated and it was assumed (referring to the study of Mondelli and Merlini[67]) that only the (A) ⇄ (C) equilibrium obtains for the pyridine analogue and only the (A) ⇄ (B) equilibrium obtains for the quinoline analogue. This approach can lead to inaccurate conclusions. Thus the examination of the spectral characteristics of acylmethylazines in various solvents has shown[73] that the third tautomer occurs also for the above ketones.

The tautomerism of 2-cyanoacetonylpyridine (XVIII) has been discussed.[74] On the basis of ^1H NMR, IR, and UV spectroscopic data, the authors[74] postulate that the enolic tautomer (C) predominates in chloroform, cyclohexane, and basic aqueous media, while the tautomer (B) predominates in methanol and in acid media.

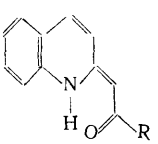


(C) ⇄ (B); (XX)

(XVIII): R = H; (XIX): R = $OCOCH_3$.

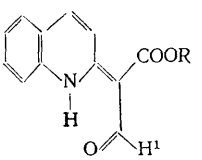
More reliable data, obtained by the joint application of the ^{17}O and ^{14}N NMR methods[75] showed that the equilibrium (B) ⇄ (C) occurs in $CHCl_3$ with the ylidene form predominating. A shift of the equilibrium towards the ylidene tautomer may be expected also for substituted cyanoacetonylpyridine (XIX), although the authors[76] give preference to the other chelate form (C). The ylidene structure of compound (XIX) is supported by the identity of the UV spectrum of compound (XIX) with that of its close analogue (XX), for which the formation of an enolic form of type (C) is uncharacteristic owing to the low tendency of the ester group to enolise. The significant difference between the chemical shifts of the chelate proton for compounds (XIX) and (XX) (δ = 17 and 14 p.p.m.), observed by Stein et al.,[76] may be caused by the difference between the strengths of the hydrogen bonds in the ylidene forms of these compounds.

Contradictory data on the structures of condensed acylmethylazines have been quoted in the literature. Thus the enolic structure has been attributed[77] to phenacylquinoline (XXI) and to acetonylquinoline (XXII). However, other workers[67] have adduced evidence in support of the ylidene form, in agreement with the data of Yamazaki et al.[78] Nevertheless, in the assignment of the signals in the ^1H NMR spectra of 2-phenacylquinoline (XXI), Hay and Wolfe[79] used the enolic form as a basis.



(XXI): R = C_6H_5;
(XXII): R = CH_3.

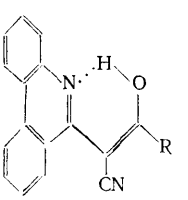
(XXI), (XXII)



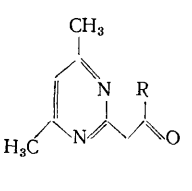
(XXIII)

In view of the absence of the characteristic splitting of the signals due to the protons of the methyl and methylene groups and also as a result of comparing the UV spectra of acetonylcholines and model compounds, it has been concluded[67] that the two forms (A) and (B) of 2-acetonylquinoline (XXII) are in equilibrium. The study of a series of acylmethylquinolines and of the formyl derivative (XXIII)[78,80] led to the preference being given to form (B) among the chelate tautomers. The conclusion that the formyl(quinolinyl)acetic ester (XXIII) has the ylidene structure can be reached in view of the absence of spin–spin coupling of $H^{(1)}$ and the proton of the hydroxy-group, which would have occurred in the case of the enolic tautomer.[80]

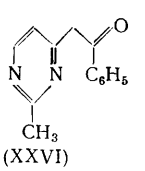
The structure of the phenanthridine derivatives (XXIV, R = CH_3, C_6H_5) has been examined in a study[81] where preference was given to the enolic form on the basis of the proton chemical shift (16.8 p.p.m.). This conclusion is inconsistent with the usually observed effect of the electron-accepting substituent and of annelation (in both cases the ylidene tautomer is stabilised) and requires additional confirmation.



(XXIV)



(XXV)

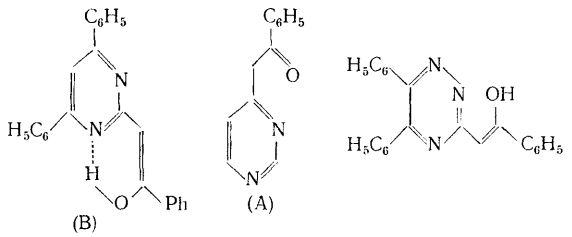


(XXVI)

In the series of diazines, studies have been made of the tautomerism of substituted acetonylpyrimidines (XXV) and phenacylpyrimidines (XXVI)[82–84] and also of 2- and 4-trichloro- and 2- and 4-trifluoro-acetonylpyrimidines.[85]

On the basis of ^1H NMR spectroscopic data for compounds (XXV) and (XXVI), it has been stated[82,84] that the tautomers (A) and (B) or (C) are present in the mixture, but the choice between the enolic and ylidene tautomer was not made. The tautomerism of

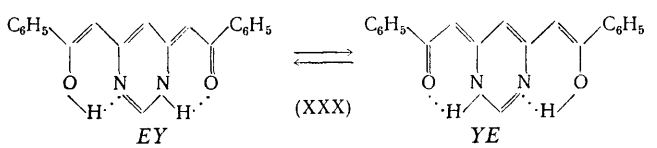
2-phenacyl-4,6-diphenylpyrimidine (XXVII) has been investigated by ^{1}H NMR and UV spectroscopy.[83] The absorption in the UV spectrum of the tautomeric forms (A), (B), and (C) was modelled by the absorption of the corresponding *C*, *O*-, and *N*-methyl derivatives. The absence of the ylidene tautomer (B) from the equilibrium was demonstrated; the ratio of the forms (A) and (C) is 1:2 (in $CHCl_3$) according to ^{1}H NMR data.[83]



(B) (XXVII) (A) (XXVIII) (XXIX)

Judging from the ^{14}N and ^{17}O NMR data, 4-phenacylpyrimidine (XXVIII) contains comparable amounts of the tautomers (B) and (C) [from ^{1}H NMR data, the fraction of form (A) in $CHCl_3$ is 20%].[86] The synthesis of a series of substituted acylmethylated pyrimidines, quinazolines, and pyrazines has been described,[87] but the tautomerism of these compounds has not been studied. The occurrence of the keto–enol equilibrium has been noted for phenacyl-1,3,5-triazine (XXIX) (with reference to ^{1}H NMR data).[42] However, these results do not permit a reliable exclusion of the presence of the ylidene tautomer.

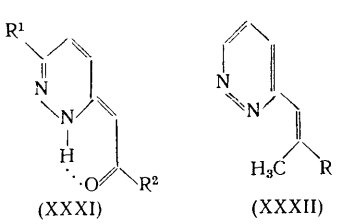
The tautomerism of 4,6-diphenacylpyrimidine (XXX) is more complex.[15] Using ^{17}O NMR and by observing the tautomerisation dynamics using ^{1}H NMR in $CHCl_3$, it has been possible to establish the presence of five tautomers (*KK*, *KE*, *KY*, *EE*, and *EY*, where *K*, *E*, and *Y* are indices denoting the keto-, enol-, and ylidene fragments in the 4- and 6-positions).



EY (XXX) *YE*

It is of interest to note that the [1,5]–[1,5]disigmatropic EY ⇄ YE equilibrium is an example of tautomerism of the cyclodismutation type, previously deduced within the framework of the formal classification of tautomeric systems.[11]

Among the chelate forms of acylmethylpyridazines (XXXI), preference has been given[88] to the NH form. The main evidence in support of this was obtained by comparing the ^{1}H NMR spectra in $CDCl_3$ with the spectra of model compounds (XXXII) (relative to the enolic form).

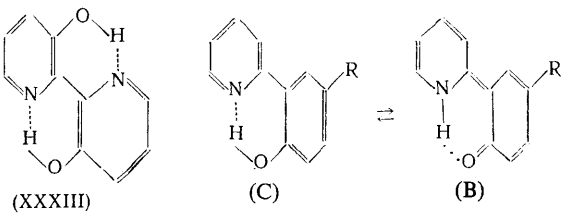


(XXXI) (XXXII)

However, the OH group in compound (XXXI) would be a stronger donor than the CH_3 group in compound (XXXII) as a result of which models of the type (XXXII) may prove to be relatively unsuitable. In particular, reliable ^{14}N and ^{17}O NMR data for phenacylpyridazine, which was considered by Ohsawa et al.,[88] have shown that the contents of the two chelate tautomers in $CHCl_3$ are comparable.[86]

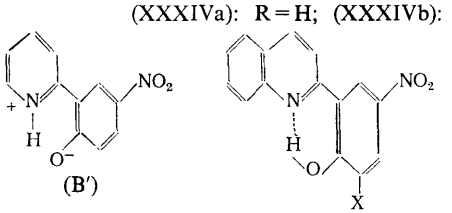
o-Hydroxyphenylazines and their condensed analogues are an interesting group of compounds capable of undergoing intrachelate tautomerism of the [1,5]sigmatropic type. The photoinduced tautomerisation of these compounds has been studied in detail in the series of *o*-hydroxyphenyl- and hydroxynaphthyl-azines,[89] including the procedure using laser flash photolysis with picosecond resolution.[90–92] Disigmatropic [1,5]–[1,5]tautomerisation has been observed for the bipyridyl analogue (XXXIII).[93] *o*-Hydroxyphenylazines are effective photostabilisers of polymers[94,95] and the characteristic features of their tautomerisation can have a significant effect on their properties. The tautomerism of these compounds in the ground state is therefore of special interest. In particular, it is of interest to discover the structural limits of the stability of the aromatic tautomeric form (to which total stabilising properties are attributed) as well as factors favouring the formation of the ylidene tautomeric form.

The first hypotheses concerning the occurrence of the ylidene form (B) were put forward as early as 1918 in a study of *o*-hydroxyphenylpyridine (XXXIVa).[20] Later it was suggested,[96] from IR spectra, that the *p*-nitrophenyl derivative (XXXIVb) has the zwitterionic structure (which is easily seen to constitute another resonance representation of the ylidene tautomer).



(XXXIII) (C) (B)

(XXXIVa): R = H; (XXXIVb): R = NO_2.



(B′) (XXXIVb)

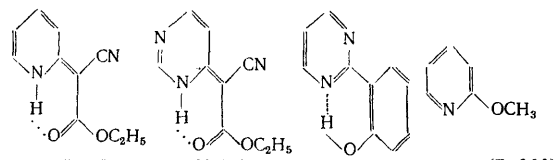
(XXXVa): X = H
(XXXVb): X = NO_2.

It has been shown with the aid of ^{17}O NMR and UV spectroscopic methods[97] that the ylidene tautomers of hydroxyphenylpyridine (XXXIVa) and of its nitro-analogue (XXXIVb) are not observed in $CHCl_3$. However, the ylidene tautomer of the nitrophenylquinoline (XXXVa) is present in small amounts while the content of this tautomer of the dinitro-derivative (XXXVb) becomes dominant.

The studies of the tautomerism of acylmethylazines examines above contain a large number of contradictory examples, sometimes involving mutually exclusive conclusions about the structures of the same compounds. This is caused primarily by the difficulties arising in the study of fast intrachelate equilibria by traditional methods. Reliable information about an intrachelate equilibrium of the type (B) ⇄ (C) can be obtained by observing the NMR spectra of the nitrogen and oxygen atoms which are involved directly in the tautomeric transformation. In contrast to the H and C atoms, the

hybridisation of the N and O atoms in the tautomeric transition changes, as a result of which the differences between the chemical shifts of the indicator nuclei should be extremely large (hundreds of p.p.m.).

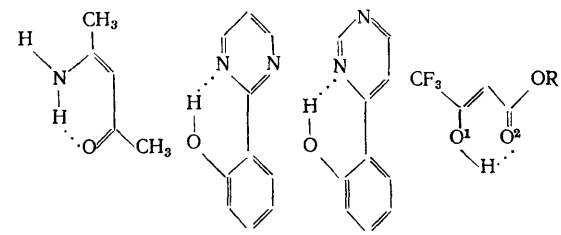
It has been suggested[68,86] that a combination of the ^{14}N and ^{17}O NMR methods be used to establish the position of the intrachelate tautomeric equilibrium of the type (B) ⇄ (C). The ratio of the (B) and (C) tautomers is estimated from the positions of the nitrogen and/or oxygen signals relative to the signals of model compounds. The corresponding azinylidenecyanoacetic esters were used to estimate the chemical shifts of the nitrogen atom in the ylidene form. The position of the ^{14}N NMR signal for the enolic forms was modelled with the aid of *o*-hydroxyphenylazines, for which the enolic structure of the chelate tautomer has been established reliably.[98]

Compound 

$\delta(^{14}N)$, p.p.m. -215 ± 5 -230 ± 3 -130 ± 5 -110 (Ref.99)

The ^{14}N NMR signal of the NH form (B) is fairly narrow ($\Delta_{1/2} \simeq 200$ Hz) in contrast to the signal of form (A) ($\Delta_{1/2}$ up to 800 Hz).[99] The ^{14}N NMR spectroscopy is therefore effective when the ylidene form predominates in the equilibrium (B) ⇄ (C).

2-Aminopent-2-enone, in which the carbonyl group is incorporated in the enaminocarbonyl fragment involved in the hydrogen bond, as in the ylidene form, was used to model the ^{17}O NMR shifts of the ylidene tautomer (B). In selecting a model for the ^{17}O NMR of the enolic tautomer (C), it was important to take into account the conjugation of the OH group with the heteroaromatic ring through the double bond and also the intramolecular hydrogen bonds. These requirements are satisfied in many respects by *o*-hydroxyphenylazines [$\delta(^{17}O) \simeq 94-97$ p.p.m.] and the enolic forms of β-ketoesters.[98] Comparison of the chemical shifts of hydroxyphenylazines and β-ketoester enols showed[98] the position of the OH signal of the unmodified enolic fragment depends comparatively little on the form of the proton-accepting component of the chelate ring (the carbonyl group in β-ketoazines and the azine fragments in *o*-hydroxyphenylzines).

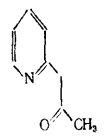
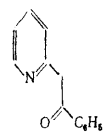
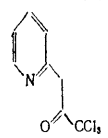
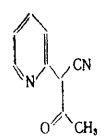
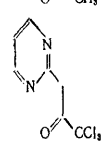
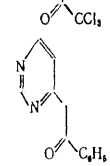
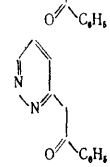
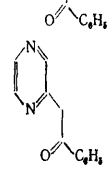
Compound 

$\delta(^{17}O)$, p.p.m. 419 96 94 O^1 96, O^2 315

The accuracy of the determination of the contents of the (B) and (C) tautomers by the ^{14}N and ^{17}O NMR methods has been analysed.[68]

The ^{14}N and ^{17}O NMR spectroscopic data in Table 1 agree fairly satisfactorily, which makes it possible to establish reliably the structure of acylmethylazines and to resolve the contradictions existing in the literature. Thus the chemical shifts found for acetonylpyridine and phenacylpyridine indicate the virtually complete displacement of the equilibrium (B) ⇄ (C) to the enolic tautomer (C). The ^{17}O NMR data, which are more accurate when the enolic tautomer predominates, show that, together with forms (A) and (C), the ylidene tautomer is also present albeit in small amounts. The accumulation of electron-accepting substituents in the exocyclic group favours the ylidene tautomer to a greater extent. Isotypical derivatives of azines exhibit different tendencies towards conversion into the ylidene tautomeric form (B), whose fraction in the intrachelate equilibrium (B) ⇄ (C) is a maximum for 4-pyrimidine and 3-pyridazine derivatives. The high sensitivity of the intrachelate tautomeric equilibrium to the effect of the

Table 1. The chemical shifts in the ^{14}N and ^{17}O NMR spectra of acylmethylazines and the ratios of the tautomers (B) and (C).[86]

Compound	$\delta(^{14}N)$, p.p.m.	Tautomer ratio (C)/(B)	$\delta(^{17}O)$, p.p.m.	Tautomer ratio (C)/(B)
	−130±5	>90/10	143±3	>90/10
	−131±5	>90/10	125±3	>90/10
	−194±3	25/75		
	−199±1	20/80	356±1	10/90
	−140±5	90/10	162±3	80/20
	−142±5	90/10	162	80/20
	−131±5	50/50		
			109 [100]	100/0

substituent at the carbonyl group is striking. Thus transition from acetonylpyridine (XVIIa) to its trichloromethyl analogue reverses the ratio of forms (B) and (C).

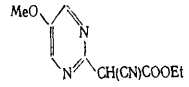
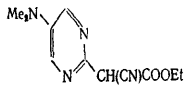
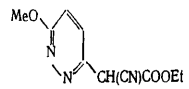
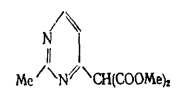
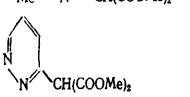
^{14}N and ^{17}O NMR methods have been used to investigate the tautomerism of acylmethylpyrazines and their annelated analogues.[100] Compared with pyridine derivatives, acylmethylpyrazines exhibit a smaller tendency towards transition to the ylidene form, which remains unstable even in the case of trifluoroacetonylpyrazine. As for other acylmethylazines, annelation greatly stabilises the NH tautomer

The above data demonstrate the great potential possibilities for the joint employment of the $^{15,14}N$ and ^{17}O NMR methods in the study of the tautomerism of heterocyclic compounds.

IV. Thermodynamics, kinetics, and mechanism of the tautomeric interconversions of azinylmethanes

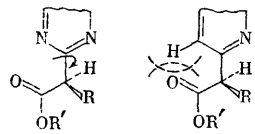
The temperature dependence of the equilibrium and the thermodynamic parameters ΔH and ΔS for pyrimidine and pyridazine derivatives[101] are listed in Table 2. The tautomeric equilibrium (A) ⇄ (B) proved extremely sensitive to changes in temperature. An extremely high ΔS has been observed for compounds (VIIIb, c), which is uncharacteristic of prototropic equilibria as a whole. For example, ΔS for the keto–enol equilibria involving benzoylacetic esters or for the tautomerism of 2-hydroxypyridine varies in the range from 8 to 16 J mol^{-1} K^{-1}.[102,103] The values of 60–70 J mol^{-1} K^{-1} found by Petrenko et al.[101] agree with the entropies in the azido-tetrazole tautomeric equilibrium,[101,104] which, however, is not of the prototropic type.

Table 2. Thermodynamic parameters of the tautomeric equilibrium.[101]

Compound	Structural formula	ΔH, kJ mol^{-1}	$-\Delta S$, J mol^{-1} K^{-1}
(VIIIb)		21.1±0.2	62±1
(VIIIc)		23.2±0.2	71±1
(XXXVI)		7.9±0.6	47±2
(XXXVII)		12.2±0.6	38±2
(XXXVIII)		4.7±0.8	24±2.5

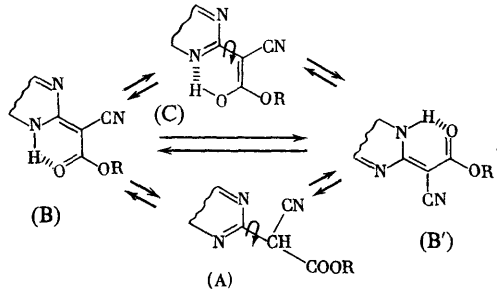
The unfavourable entropy change on transition to the ylidene tautomer in the case of pyrimidinylcyanoacetic esters (VIIIb, c) is evidently associated with the loss of freedom of rotation about the exocyclic C–C bond in the ylidene tautomer.

Scheme 2



When the C–H fragment, which is more bulky than the N atom, is present in the β-position [compound (XXXVI), Table 2], the rotation in the tautomer (A) becomes hindered (Scheme 2), which reduces the difference between the entropies of the tautomers (A) and (B).[105] The further decrease in ΔS for the malonic esters (XXXVII) and (XXXVIII) (Table 2) is associated with still greater hindrance to the rotation of the more bulky exocyclic group.[101]

The kinetic characteristics of the tautomeric transformations of azinylmethanes were obtained in a study of the tautomerism of pyrimidinyl- and pyridazinyl-malonic esters[50] as well as phenylacylquinolines.[106] In both studies, it was concluded that the tautomerisation mechanism is of the ionic-dissociative type and is close to that which is well known for keto–enol tautomeric systems. This mechanism is supported by the following experimental data: the occurrence of acid–base catalysis, the dependence of the rate of tautomerisation on the concentration of the tautomeric compound (autocatalysis), and the ready deuterium exchange of the acid protons of the NH and CH groups.[106,107] In the ionic-dissociative mechanism, the dissociation (or formation) of a C–H bond is the rate-limiting stage; this has been confirmed in a study[107] of the tautomeric equilibrium involving pyrimidinylcyanoacetic ester (VIIIb) by the kinetic isotope effect (k_H/k_D = 3.5).

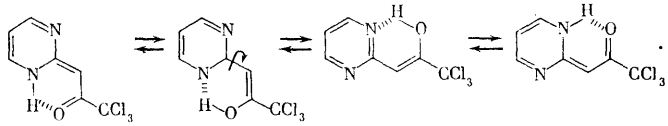


The mechanism of the annular tautomerism of the type (B) ⇄ (B′) has been studied.[38,39] The merging of the signals of the methoxy-groups in the ^1H NMR spectrum of 4,6-dimethoxy-1,3,5-triazinyl-2-cyanoacetic ester (IX) was observed on passing from $CDCl_3$ to DMSO and dimethylformamide (DMF)[39] and the authors suggest that this merging is caused by a rapid intramolecular reaction proceeding via the intermediate enolic form. However, later UV spectroscopic data[38] obtained in various solvents indicate a pronounced (if not complete) ionisation of compound (IX) in DMSO and DMF. Thus the changes observed in the ^1H NMR spectrum[39] can be altogether unrelated to tautomerism. The mechanism of the annular tautomerism has been investigated[38] in relation to the pyrimidinyl-2-cyanoacetic ester (VIIIa), which is less acid and is scarcely ionised in DMSO or DMF.

Evidently the [1,3]sigmatropic tautomerisation examined above can involve with equal probability both the N(1)H and the N(3)H group. Hence it follows that, in the presence of even traces of form

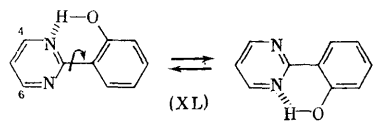
(A), the interconversion of forms (B) and (B′) via the tautomer (A) is one of the routes of [1,5]tautomerisation. The mechanism with participation of the aromatic tautomer (A) should differ from the other possible mechanisms of the (B) ⇄ (B′) process (for example, via the formation of the enolic form of the anion) by the presence of a kinetic isotope effect, which has in fact been detected[38] in the study of the kinetics of the degenerate tautomeric transformation of compound (VIIIa) with the aid of the pulse version of the method involving the transfer of a magnetic saturation label.[108] It is believed that the mechanism with participation of form (A) is not ruled out also in the case of the triazinylcyanoacetic ester (IX) mentioned above, particularly bearing in mind that appreciable amounts of the aromatic tautomer of this compound in hexane have been detected.[38]

Evidently the probability of an intramolecular mechanism of the tautomeric type (B) ⇄ (B′) transformation via the enolic tautomer increases if the side group contains the readily enolisable carbonyl group. Such a mechanism apparently actually operates for 2-trichloroacetonylpyrimidine (XXXIX):[86]



(B) (C) (C′) (B′)

Although comparable amounts of the ylidene form are present in the equilibrium with the enolic form of compound (XXXIX),[86] the C(4) and C(6) signals in the ^{13}C NMR spectrum have been averaged as a consequence of the rapid (B) ⇄ (B′) exchange even at room temperature. Since the (B) ⇄ (C) stage is extremely fast,[60,61] the following question arises: can the barrier to the rotation in the enolic form, associated with the rupture of a fairly strong hydrogen bond, be so low that averaging at this temperature is ensured? The study of the temperature spectra of the model compound (XL) showed that this type of rotation does indeed have a low barrier. Thus the separation of the C(4) and C(6) signals in the ^{13}C NMR spectrum arises only when the solution of compound (XL) in $CHCl_3$ is cooled to −50 to −60 °C.[86]



(XL)

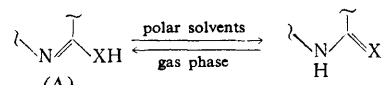
Thus the mechanism of the degenerate tautomeric transformation (B) ⇄ (B′) for substituted azinylmethanes can change depending on the nature of the substituents in the side group.

V. The influence of the solvent and structural factors on the tautomerism of azinylmethanes and general characteristics of tautomeric equilibria of the azinyl–azinylidene type

1. The influence of the solvent

Vigorous studies in recent years have shown that the solvent can have a decisive effect on tautomeric equilibria of the azinyl–azinylidene type. The change to solvents of low polarity and the gas phase greatly destabilises the ylidene form, which has been repeatedly demonstrated for hydroxyazines.[109–110] The existence of reliable experimental data made compounds of this series a favourite model for testing the most modern computational schemes for medium effects based on quantum-chemical calculations and the Monte Carlo method.[111,112]

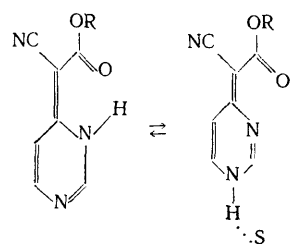
Theoretical estimation of the effect of solvent polarity for azinylmethane derivatives[113] within the framework of the method of solvatons[114] permitted the elucidation of the principal trend: a non-polar solvent and the gas phase favour the aromatic form (A), while a polar solvent shifts the equilibrium towards the ylidene tautomer (B):



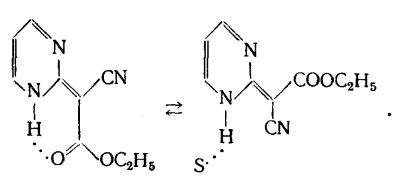
(A) (B)

X = O, NR, CR^1R^2.

Numerous experimental data obtained in the study of the tautomeric equilibria of azinylmethanes in various solvents agree well with this prediction.[113] This behaviour is apparently associated with the specific rearrangement of the electronic structure of the heterocycle on passing to the ylidene form. Judging from quantum-chemical calculations,[113] a marked alternation of the electron density in the ring is characteristic of this form, which, on the basis of the Born approximation,[115] favours solvation by polar solvents. It has been suggested[113] that bulky substituents at a CH fragment, which do not undergo changes in structure on tautomerisation, can abolish the tendency mentioned above. It may be that the low sensitivity of the tautomerism of derivatives of malonic and dinitrophenylacetic esters to the character of the solvent is in fact associated with this factor.[113]



In many cases the change of solvent induces the appearance of a new tautomeric form. This situation is characteristic of derivatives of 4-pyrimidinylmethane, for which the use of polar or specifically solvating solvents leads to the appearance of the ylidene tautomer with the *para*-quinonoid disposition of the double bonds.[35–37] Judging from quantum-chemical calculations[36] and experimental data,[116] this feature is characteristic also of other 4-substituted pyrimidines, for example 4-hydroxypyrimidines.[116] On the other hand, in the case of 2-pyrimidinylcyanoacetic ester (VIIIa), the addition of a highly basic solvent (DMSO, HMPA) apparently leads to the dissociation of the intramolecular hydrogen bond and the appearance of non-chelate tautomers of the ylidene type:[117]

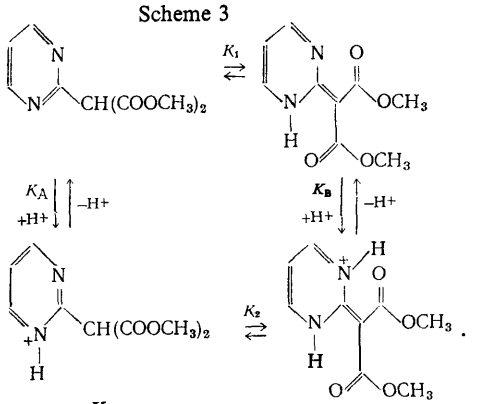


(VIII a)

For highly acidic compounds [for example, 2-trifluoromethyl-4-pyrimidinylcyanoacetic ester (VIIc)], dissolution in DMSO (or HMPA) is accompanied by appreciable and sometimes even complete ionisation.[37] This can be readily established by comparing the UV spectrum of this compound in DMSO with the spectrum of the corresponding sodium salt. Nevertheless, the possibility of ionisation in solutions is frequently not taken into account, which can lead to erroneous conclusions.[38,39] Hydroxylated solvents (alcohols, acetic acid) stabilise the ylidene tautomer both as a result of solvent polarity and as a result of specific solvation.[113]

The effect of protonated solvents (CF_3COOH), which has been investigated in relation to azinylmalonic and azinylcyanoacetic esters,[117,118] is very strong. It has been suggested[117] that, by virtue of the conjugation of the C=N fragment with the electron-donating NH group, form (B) is apparently more basic ($K_B > K_A$). According to Eqn. (1), this means that protonation shifts the tautomeric equilibrium towards the ylidene form. The most striking example is provided by the equilibrium of derivatives of 2-pyrimidinylmalonic esters,[117] which exist in form (A) and do not exhibit tautomeric properties in neutral solvents of the type of $CHCl_3$. On the other hand, in the presence of trifluoroacetic acid, whose acidity ensures the monoprotonation of pyrimidine derivatives, the equilibrium shifts towards the ylidene tautomeric form (B).[117]

Scheme 3



$$K_2 = K_1 \frac{K_B}{K_A} \qquad (1)$$

The reverse shift—towards the protonated form (A)—is observed under these conditions for pyridyl- and quinolinyl-cyanoacetic esters, which has been confirmed by UV and NMR spectroscopic data.[30,118]

The high sensitivity of the tautomeric equilibrium to solvation effects is characteristic also of the intrachelate tautomerism of the [1,5]sigmatropic type. It has been found for *o*-hydroxyphenylazines[97] and acylmethylazines[73,100] that, as in the case of tautomeric equilibria of the [1,3]sigmatropic type, polar solvents stabilise the ylidene form.

Comparison of the results presented above the effect of the solvent on the tautomerism of azinylmethanes with data on the tautomerism of hydroxy- and amino-azines[3] suggests that prototropic equilibria of the azinyl-azinylidene type as a rule obey a universal rule: a decrease in solvent polarity or transition to the gas phase destabilises the tautomer of the ylidene type. On the other hand, if account is taken also of data for the effect of the solvent on non-prototropic equilibria of the azinyl—azinylidene type (for example, the tautomerism of azidoazines where polar solvents favour the tautomer of the ylidene type—the tetrazole form[119]), then the above tendency is seen to be very general for the entire family of tautomeric equilibria of the azinyl—azinyldene type. There is no doubt that such generality is caused by the similarity of the topologies of the bonds of the corresponding tautomers (see Scheme 1) [Scheme 3?], which is independent of the type of substituent.

2. The influence of structural factors on the tautomeric equilibrium

The combination of a large number of different tautomeric systems into the family of tautomeric equilibria of the azinyl—azinylidene type[86] is not purely formal. Although the type of exocyclic fragment introduces its characteristic features, nevertheless it is clear that the topological similarity in the (A) ⇄ (B) bond rearrangement predetermines the existence of certain general features of the tautomerism of the azaheteroaryl—azaheteroarylidene type. This follows from the profound relation between the topology of the molecules and their electronic structure, which has been discovered in recent years.[120] Bearing in mind the importance of tautomerism of the azinyl—azinylidene type and the existence of extensive experimental data, the search for such features is of very great current interest. Evidently the dynamic characteristics of the tautomerism (mechanism, kinetics) will vary markedly as a function of the type of the azine component and the nature of the exocyclic fragment. On the other hand, general features may be expected primarily as regards the thermodynamic characteristics and their dependence on various factors. The medium effects, the characteristics of the influence of which were examined above, and the effects of structural changes must be regarded as the most important factors. Among the latter, one can differentiate the influence of the type of heterocyclic nucleus and of the substituents in the heterocycle and in the side fragment as well as the influence of annelation.

Despite the extensive experimental data on the tautomerism of substituted azines, the number of systematic data concerning the effect of structural factors is small. Since such studies are extremely laborious, the following approach to the study of the effect of structural factors is useful:[86,121–124] for a topologically similar group of tautomeric systems, the electronic structures of the tautomers (the redistribution of charges and bond orders in the tautomeric transition and the change in frontal orbitals) are analysed. Using the formalism of the molecular orbital perturbation method (MOP), the principal trends and the characteristic features of the effect of structural factors on the position of the tautomeric equilibrium can be discovered. Taking into account the resulting prediction, a specific experimental test is carried out in order to formulate finally the manifested features or trends.

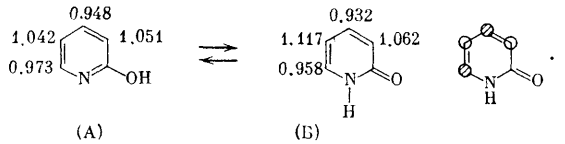
Examination of the frontal MO of the tautomers in the series of hydroxy-, amino-, and methyl-azines[122] made it possible to note the isolobal analogy[125] for isotypical tautomers: the forms and energies of the corresponding frontal MO are similar. Since the interaction of substituents with isolobal fragments is qualitatively similar, one may expect similar trends in the "response" of various equilibria of the type (A) ⇄ (B) to identical structural perturbations.

The effects of the heteroatom and the substituent can be estimated conveniently qualitatively with the aid of "difference charts", which reflect the relative changes in key electronic, energy, or orbital characteristics in the transition (A) ⇄ (B). Employing the usual approximations of the MOP method, it has been found that,[86,121–124] in order to estimate the effect of the heteroatom and the inductive and mesomeric effects of the substituents, it is

necessary to use the charts of the differences between the charges, energies, and the squares of the coefficients of the frontal MO. Although the calculations which have been performed correspond to the gas phase, allowance for the polarity of the medium within the framework of the Germer model[114] demonstrated the low sensitivity of the difference charts to the solvent.[122–124]

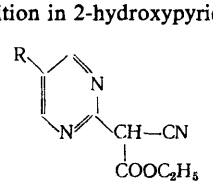
In the analysis of the inductive effect of the substituent within the framework of the MOP method, one considers the change in the π-electron density on the atom at which the substituent is introduced.[126] According to non-empirical calculations (using the STO-3G basis set),[123] the transition from form (A) to form (B) in the case of 2-hydroxypyridine leads to an increase of the π-electron density in the 3- and 5-positions and to its decrease in the 4- and 6-positions in the heterocycle. These changes are presented in Scheme 4 as graphical difference charts on which the shaded positions correspond to a positive sign of Δq and the open positions correspond to a negative sign.

Scheme 4

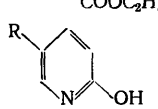


Accordingly, the fraction of the tautomer (A) should increase following the introduction of an electron-accepting substituent in the shaded positions in the heterocycle or of an electron-donating substituent in the unshaded positions. This prediction has been largely confirmed experimentally for substitution in the α-position (relative to the heteroatom), where electron-accepting inductive substituents stabilise form (A), while electron-donating substituents destabilise it.[3,122] The trifluoromethyl group has precisely this effect on the equilibrium in the series of substituted hydroxy- and methyl-azines.[3,123] Nevertheless, the effect of substituents does not reduce to electron-donating substituents favouring the pyridine form and electron-accepting substituents favouring the aromatic form. For example, the introduction of the methyl group in the 5-position in 2-pyrimidinylcyanoacetic ester (VIIIa) leads to a shift of the tautomeric equilibrium towards the aromatic tautomer, as predicted by the charge difference charts.[123]

Comparison of the charge difference charts[123] shows that their topology for mono- and di-azines remains constant regardless of the type of exocyclic tautomerising fragment and the nature of the heterocycle. One may therefore expect that the character of the *I* effect of substituents in the series of tautomeric equilibria of the azinyl–azinylidene type is to a significant extent universal. Indeed, according to the available experimental data,[123] the effect of the methyl group on the tautomerism of 2-hydroxypyridine is similar to its effect on the position of the tautomeric equilibrium involving pyrimidinylmethanes: the introduction of the methyl group in the 5-position in 2-hydroxypyridine stabilises the aromatic tautomer.



R	K_T (hexane)
H	0.67
CH_3	3.6



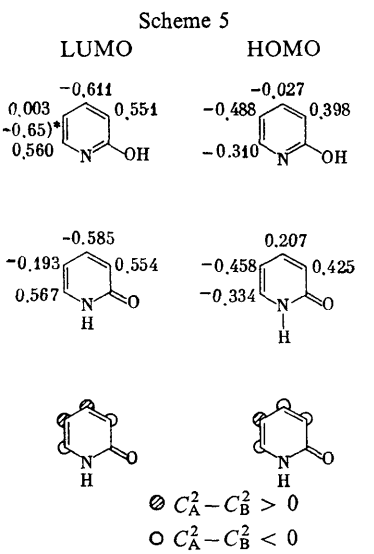
R	pK_T (water)
H	3.0
CH_3	2.6

$K_T = [A]/[B]$

Ultimately, comparison of the charge difference charts with the experimental data made it possible[123] to formulate the main trend in the inductive effect of substituents — the introduction of electron-donating substituents in the *meta*-position relative to the exocyclic tautomerising fragment shifts the equilibrium towards the ylidene form, while its introduction in the *ortho*- and *para*-positions shifts the equilibrium towards the aromatic tautomer. Electron-accepting substituents have the opposite inductive effect.[123]

It is of interest that, for substituents of the mesomeric type, such reversal of the effect on transition from electron-donating to electron-accepting substituents may not in fact be observed, which can be seen from a comparison of the charts for the difference between the squares of the coefficients of the frontier MO (Scheme 5). Thus the introduction of mesomeric substituents of both electron-donating and electron-accepting types in the *para*-position relative to the tautomerising fragment should shift the equilibrium towards the aromatic tautomer because for this position the difference between the squares of the coefficients of both frontier MO is greater in form (A) than in form (B).

Scheme 5



*Coefficient of a neighbouring unoccupied MO

Experimental data agree with this conclusion. For example, the introduction of the electron-donating $N(CH_3)_2$ group, the electron-accepting *p*-$NO_2C_6H_4$ group, and the "neutral" C_6H_5 group in the 5-position of 2-pyrimidinylcyanoacetic ester (VIIIa) increases the fraction of the aromatic tautomer (Table 3). A similar behaviour

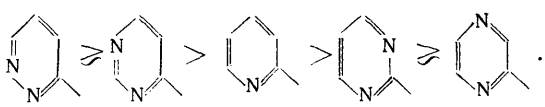
Table 3. Tautomeric equilibrium constants for 5-substituted 2-pyrimidinylcyanoacetic esters (VIII).[122]

R	K_T(A/B)	
	$CDCl_3$	hexane + 2% $CHCl_3$
H	0.01	0.67±0.02
OCH_3	0.54	3.0±0.05
$N(CH_3)_2$	0.66	
C_6H_5	0.01	1.0±0.05
$O_2NC_6H_4$	0.25	

has been observed also for cyanoacetic esters of the pyridazine series[127] and also for hydroxy-azines, which has been noted by Petrenko and Lapachev.[122] The latter implies that, in the case of mesomeric substituents, the character of the effect of the substituent in azines with different exocyclic tautomerising fragments is the same.[122]

It follows from the charts of the differences between the squares of the coefficients[122] and the π-electron densities[123] that identical effects of the substituent (as a result of the mesomeric and inductive contributions) on the position of the tautomeric equilibrium should be encountered fairly rarely. Bearing in mind the character of the approximations of the simple MOP method, direct comparison of the contributions of the inductive and mesomeric effects on the basis of difference charts is scarcely possible. At the same time, joint examination of the experimental data and difference charts frequently makes it possible to discover which effect predominates.[122]

In order to understand and predict the tautomeric properties in the series of different azines, it is important to estimate the tendency of each type of azine to rearrange to the ylidene form. Analysis using difference charts and experimental tests have shown[124] that isotypical azine derivatives are fairly clearly differentiated as regards their tendency to undergo a transition to the ylidene tautomeric form. Thus it has been shown that the transition from the pyridine tautomeric compound to the analogous 2-pyrimidine or 2-pyrazine derivative promotes a shift of tautomeric equilibrium towards the aromatic tautomer, while transitions to 4-pyrimidine and 3-pyridazine derivatives promote the transition to the ylidene tautomer.[124] Thus the series of relative tendencies by isotypical azine compounds to undergo a transition to the ylidene tautomeric form is as follows:



Analysis of the distribution of electron density on the nitrogen atoms and in the bonds, the search for isolobal analogy, and inspection of difference charts for tautomeric pairs have made it possible to discover the basis of this similarity, which is observed among tautomeric equilibria of the azinyl–azinylidene type. Despite the multiplicity of approximations, which make it necessary to treat with caution the predictions obtained, the simplicity and clarity of the method make it promising for the construction of a general approach to the study of equilibria of the azinyl–azinylidene type and also of other types of tautomeric equilibria differentiated on the grounds of their topological relationship.

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The data examined show that tautomeric interconversions occur very widely in the series of substituted azinylmethanes. Apart from their independent importance, tautomeric azinylmethanes are very convenient models for the determination of the general characteristics of the tautomerism of the azinyl–azinylidene type, which is the most important type of tautomerism in the series of azines.

The MOP method proved to be effective for the discovery and prediction of features of this kind. Its use makes it possible to examine from a general standpoint the dependence of the tautomeric equilibrium of the azinyl–azinylidene type on structural factors. A similar methodology (the differentiation of a family of tautomeric equilibria on the basis of topological criteria, analysis of the similarity of the electronic structures of the tautomers, the use of the MOP method for the interpretation of experimental data, and the prediction and determination of the characteristic features) can be applied also to other classes of tautomeric equilibria.

Tautomeric azinylmethanes constitute one of the examples of molecules with a similar behaviour, which exist in different forms depending on the structure, medium, temperature, or irradiation. There is no doubt that interest in "flexible" molecules of this kind with extensive structural possibilities will continue to grow in the future, especially in connection with the construction of biochemically important molecules and their analogues, as well as compounds with more complex functions for applied purposes. The experience gained in the study of the tautomerism of heterocycles will then also prove essential.

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