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Investigation of Keto-Enol Tautomerism by Nuclear Magnetic Resonance Spectroscopy

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The review considers methods for the determination of tautomeric composition from NMR spectra and gives a systematic account of the results of studies on keto-enol tautomerism. The bibliography includes 160 references.

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I. INTRODUCTION

The introduction of physical (primarily spectroscopic) methods into organic chemistry made it possible to achieve in a short period considerable advances in the study of the phenomenon of tautomerism. The most recent of these methods (nuclear magnetic resonance) is the most promising and offers universal procedures for such investigations. High-resolution NMR spectra yield a wide variety of information about a tautomeric system: the chemical and steric structures of the tautomers, the positions and strengths of hydrogen bonds, the amounts of different tautomers, and the rate and mechanism of their interconversion. The advantages of the NMR method and the interest in tautomeric problems—a field which allows a wide scope for the application and verification of the fundamental concepts of organic chemistry[1-2]—resulted in a rapid growth of the number of relevant publications (from a few in 1960† to hundreds at the present time). Despite the evident interest of the investigators of tautomerism in NMR spectroscopy, there are no reviews in either Soviet or foreign literature giving a systematic account of the results from the large-scale application of NMR in the study of tautomerism in the last few years.

The available review literature comprises short illustrative chapters in certain monographs[4-9] and papers[10-15]. In the present review an attempt has been made to fill this gap and to describe the advances in the field of tautomerism made using NMR. Within the limits of a single review, it is not possible to examine in sufficient depth the NMR studies on tautomerism of all types. The authors restricted themselves to prototropic‡ tautomerism as a result of the migration of a proton between carbon atoms and a heteroatom (N, O, S) or between two heteroatoms.

† The first study in which NMR was employed to investigate tautomerism was published in 1953[3].

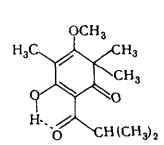
‡ NMR has been successfully employed to investigate the prototropic tautomerism associated with the migration of a proton between carbon atoms and also various types of non-protrotopic tautomerism[15].

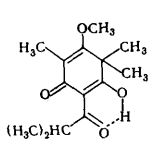
In the discussion of the tautomerism of various classes of organic compounds attention has been concentrated on the equilibrium tautomeric composition and the factors which determine it. The chemical shifts are quoted on the τ-scale.

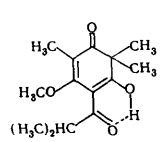
II. METHODS OF ANALYSIS OF TAUTOMERIC SYSTEMS BY NMR SPECTROSCOPY

In slow tautomeric transformations, which satisfy the inequality $1/t_A + 1/t_B \ll |\nu_A - \nu_B|$ (ν_A and ν_B are the NMR signal frequencies and t_A and t_B are the average lifetimes of the tautomers A and B), the NMR spectra of forms A and B can be observed separately and the tautomeric composition can be readily determined from the intensities of the corresponding spectral lines (to within 1%) [4-8].

Thus in the NMR spectrum of the natural dye tasmanone dissolved in $CDCl_3$ [16] the signals of all the methyl groups consist of two very close components with an intensity ratio of 1 : 1.9 and in addition there are two signals due to the chelate enolic protons (−9.4 and −8.7 p.p.m.). The lines merge when the solution is made alkaline but the splitting reappears on neutralisation of the added alkali. This leads to the conclusion that the system consists of a mixture of two enolic tautomeric forms (1A and 1B)§, the rate of the interconversion of which is greatly accelerated in the presence of a base, which increases the concentration of the anion.

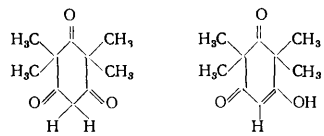

(IA)


(IB)


(II)

§ This rules out the alternative structure of tasmanone, in which there is only the enolic form (II).

The next stage of the analysis, involving the assignments of the spectral lines to specific tautomeric forms, is based on the ^{1}H NMR data for tetramethylphloroglucinol (III)—a model compound. These data show that the enolisation of the carbonyl group leads to the descreening of the adjacent geminal methyl groups. Therefore the low-field (less intense) signal of the corresponding groups of tasmanone was assigned to form (IB). Clearly the other less intense signals are also due to the form (IB), the content of which is 35%.



(IIIA) (IIIB)

If the interconversions of tautomers A and B take place at a frequency exceeding $|\nu_A - \nu_B|$, their NMR signals merge and are characterised by an average chemical shift $\tau = p_A\tau_A + p_B\tau_B$, where τ_A and τ_B are the chemical shifts¶ and p_A and p_B the fractions of forms A and B ($p_A + p_B = 1$). A similar expression is valid also for the spin–spin coupling constants (SSCC):† $J = p_AJ_A + p_BJ_B$.[4-8] In this case the fraction of any form (for example A) is found from the following formulae:

$$p_A = (\tau - \tau_B)/(\tau_A - \tau_B), \quad (1)$$

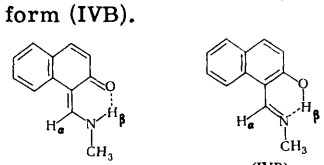
$$p_A = (J - J_B)/(J_A - J_B). \quad (2)$$

The case where appreciable spin–spin coupling obtains between the given nuclei in only one tautomer is frequently encountered (for example, $J_B = 0$). Then

$$p_A = J/J_A. \quad (3)$$

The accuracy of the determination of the proportions of tautomers in fast tautomeric interconversions is much lower than in slow interconversions. The absolute error for p_A and p_B amounts at best to several per cent. The principal sources of error are the inaccuracies in the values of τ_A, τ_B, J_A, and J_B, which are usually assumed equal to the corresponding values for model non-tautomeric compounds. In certain studies[17,18] corrections have been applied for the change in the chemical shifts in ^{1}H NMR on methylation of aromatic and heteroaromatic compounds at the oxygen and nitrogen atoms, which permits a more accurate prediction of the values of τ for the tautomeric forms modelled.

As an example, we shall determine the tautomeric composition of the Schiff base (IV). The $H_\alpha - H_\beta$ spin–spin coupling constant is close to 13 Hz‡ for form (IVA) and is zero for form (IVB).



(IVA) (IVB)

¶ In this review the proton chemical shifts are expressed on the τ-scale (p.p.m.)[5].

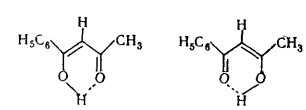
† The interaction of nuclei not involved in rapid intermolecular exchange is considered here. Otherwise the splitting of the NMR signals due to spin–spin coupling is not observed.

‡ This value is characteristic of the *trans*-form of the fragment =CH–XH, where X = O [19] or NR.[20]

Measurement of $J_{\alpha\beta}$ (9.8 Hz at 0°C in $CDCl_3$) makes it possible to estimate by Eqn. (3) the content of form A (75%). A similar value (83% of A) was obtained by comparing the $H_\beta - NCH_3$ spin–spin coupling constant (4.6 Hz) with the corresponding values for forms A (5.5 Hz) and B (0 Hz). Finally, more accurate data can be obtained from the ^{15}N–H spin–spin coupling constant. For the aminoketone forms, J_{NH} is close to 95 Hz and is zero for the iminoenol forms. The observed value of J_{NH} for (IV) is 72.3 Hz, which corresponds to 76% of form A [20,21].

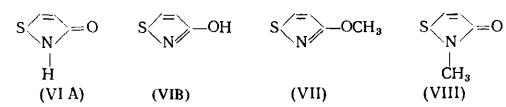
The problem of the short-lived internal tautomers A and B of benzoylacetone and other β-diketones cannot be readily solved with the aid of ^{1}H NMR spectroscopy, since the chemical shifts of the stable protons differ only slightly for the two forms and the values of τ_{OH} for these forms are unknown. The ^{17}O NMR spectra are more informative[22,23]. The ^{17}O nuclei of the carbonyl groups absorb near 495 p.p.m. and those of the enol groups near 35 p.p.m. relative to the signal for water (data from the spectra of model compounds).

In acetylacetone, where the enolisation of a given carbonyl group is equally probable, the average ^{17}O chemical shift is 265 p.p.m. However, the ^{17}O signal of the benzoyl group of benzoylacetone (V) is displaced towards higher fields (230 p.p.m.), which indicates the presence of an excess of tautomer A. Using Eqn. (3), it is possible to estimate the tautomeric composition (56% of A and 44% of B). The acetyl oxygen signal is displaced towards low fields (300 p.p.m.) in accordance with the lower probability of the enolisation of this group:



(VA) (VB)

In conclusion we shall quote an example of the determination of tautomeric compositions from the chemical shifts and spin–spin coupling constants of stable protons. 3-Hydroxyisothiazole in dimethyl sulphoxide exists as a mixture of forms (VIA) and (VIB), which are rapidly interconverted. The average chemical shifts and spin–spin coupling constant of the protons in the 4- and 5-positions (3.41 and 1.22 p.p.m.; 5.1 Hz) are closer to those for the fixed-configuration compound (VII) modelling form (VIB) (3.25 and 1.12 p.p.m.; 4.7 Hz) than to the values for the model compound (VIII) (3.81 and 1.55 p.p.m.; 6.3 Hz). Calculations by formulae (1) and (2) agree and show that the fraction of form (VIB) is 75%: [24]



(VI A) (VIB) (VII) (VIII)

In many cases the presence of a small amount of one of the tautomeric forms, the NMR signals of which cannot be observed, can be detected indirectly, namely from the deuterium exchange involving this form. Thus measurements by ^{1}H NMR spectroscopy of the rate of deuteration of the alkyl groups of ketones, which like bromination proceed via the enol form, not only makes it possible to confirm the presence of the enol but also allows the determination of the predominant enolisation pathway in asymmetric ketones.

For example, 4,4-dimethyl-2-pentanone (IX) can exist in two enolic forms.

$H_3C-CO-CH_2-C(CH_3)_3$ (IX A) $H_2C=C(OH)-CH_2-C(CH_3)_3$ (IXB) $H_3C-C(OH)=CH-C(CH_3)_3$ (IXC)

The rate constants for the deuterium exchange involving the methyl (8.1×10^{-6} s^{-1}) and methylene (2.4×10^{-6} s^{-1}) groups were determined from the decrease of the methyl and methylene group signal intensities in the ^1H NMR spectrum as a result of the deuteration of forms (IXB) and (IXC). These data show that the preferred enolic form is (IXB) [25]. An analogous procedure may be employed in more complex cases [26].

The NMR method permits a quantitative estimation of the rates of both rapid and slow chemical reactions [4,5,27-31], in particular tautomeric transformations [27,32-34]. The methods used in such estimations differ, depending on the rate of interconversion of the tautomeric forms.

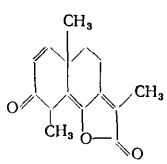
III. KETO-ENOL TAUTOMERISM

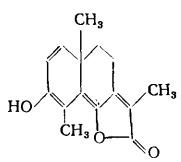
1. MONOCARBONYL COMPOUNDS

In the simplest ketones enolisation is slight [35] and cannot be detected directly by spectroscopic methods. Nevertheless, the presence of the enolic form can be deduced indirectly from the deuteration of α-carbon atoms, which proceeds via the enolate anion or the enolic form.

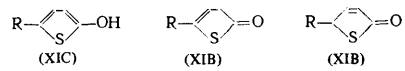
Rappe and Sachs [25,36-40] and other workers [41-45] measured the rate constants for deuterium exchange from ^1H NMR spectra, determined the predominant enolisation pathway for a number of asymmetric ketones, and investigated the effect of the solvent on the rate of deuterium exchange. In particular, it was shown that enolisation takes place most readily in the direction of the methyl group and least so in the direction of the methylidyne group of ketones.

In more complex systems where enolisation leads to the formation of conjugated bonds, the content of the enolic form may prove to be significant and susceptible to direct measurement. Thus the contents of the keto-form (XA) and enol form (XB) of santonin (X) and dihydrosantonin were determined from the intensities of the corresponding ^1H NMR lines in various solvents [46]. Santonin (100% of the keto-form in the crystalline material) is enolised very weakly in chloroform (less than 5%) and considerably in methanol (39%) and pyridine (70%). Dihydrosantonin (100% enol in the solid state) is almost completely enolised in pyridine and less so in methanol (84%) and chloroform (43%). The shift of the equilibrium towards the enol in proton-accepting solvents is probably associated with the formation of an intermolecular hydrogen bond stabilising the enolic form. The keto-enol interconversion in santonin takes place at low rates, which is indicated by the slow substitution of the proton at C-4 by deuterium in the presence of D_2O even at high temperatures.


(X A)


(X B)

Hörnfeldt investigated the tautomerism of various hydroxythiophens [47-49]. ^1H NMR spectra revealed 25-30% of the hydroxy-form (XIA) of 5-aryl- and 5-thiono-2-hydroxythiophens (XI) in methanol, whereas in carbon tetrachloride this form was absent.

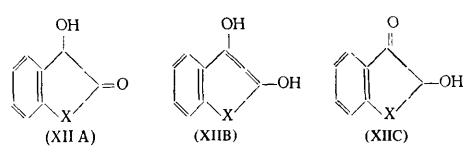

(XIC) (XIB) (XIB)

Form (XIA) was not detected in 5-alkyl-substituted 2-hydroxy-thiophens. In the presence of catalytic amounts of acids or bases, there is a rearrangement to an equilibrium mixture of the keto-forms (XIB) and (XIC), the composition of which depends on the hyperconjugation effect of the substituent and on the polarity of the solvent. The kinetics of the rearrangement (XIB) $\rightleftharpoons$ (XIC) have been investigated [47,48].

In alkyl-substituted 3-hydroxythiophens, the hydroxy-form (enol) is present in considerable amounts even in a non-polar solvent (carbon disulphide) (80, 55, and 30% for 5-methyl-, 5-t-butyl-, and 2,5-dimethyl-derivatives respectively). The chemical shifts of the signal due to the enolic proton are in the range between 3.3 and 3.8 p.p.m. [47]; 2- and 3-mercaptothiophens exist in the thiol form [50].

3-Hydroxythionaphthene was investigated by two groups of workers [51-53]. Their results show that the freshly sublimed substance exists entirely in the keto-form.

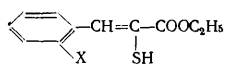
Sterk et al. [54] showed that in polar solvents the lactone of *o*-hydroxymandelic acid exists in the 3-oxo-form (XIIC, X = O). The 2-oxo-form (XIIA, X = O) predominates in non-polar media at high temperatures. The dienol form (XIIB, X = O) form was not detected.


(XII A) (XIIB) (XIIC)

In dihydroxyindole solutions in bromoform there is an equilibrium between forms (XIIA, X = NH) and (XIIB, X = NH), which on raising the temperature is displaced towards the dienol form (XIIB, X = NH).

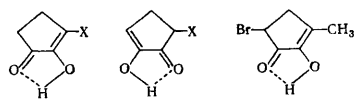
2. α-DICARBONYL COMPOUNDS

Acyclic 1,2-dicarbonyl compounds are as a rule weakly enolised. However, some of their aryl-substituted derivatives may contain significant amounts of the enolic form in a slow equilibrium with the diketo-form [55]. The ^1H NMR spectra show that, in contrast to pyruvic acid and its esters which do not contain an enolic form [56], aryl-substituted derivatives of thiopyruvic acid (XIII, X = H, CH_3, or Cl) exist largely in the thiol form [57]:


(XIII)

The degree of enolisation of cyclic α-diketones depends on ring size. The smaller the ring the more pronounced is the electrostatic repulsion between the adjacent dipoles of the carbonyl groups, which reduces the stability of the diketo-form [58].

Five-membered α-diketones are as a rule completely enolised in non-polar solvents as well as in aqueous solutions[58,59]. The ^{1}H NMR spectrum of 3-methylcyclopentane-1,2-dione in chloroform[60,62] not only fully confirms complete enolisation but also gives information about its direction. The absence from the spectrum of the vinyl proton signal and the chemical shift of the unsplit methyl group signal (8.07 p.p.m.)[61] support the structure (XIVA, X = CH_3). The structure (XIVA, X = Br) was also proved for 3-bromocyclopentane-1,2-dione, which is completely enolised in acetone[62]. 5-Bromo-3-methylcyclopentane-1,2-dione exists in acetone in the enolic form (XV)[58].



(XIVA) (XIVB) (XV)

3-Bromo-3-methylcyclopentane-1,2-dione, which exists in the diketo-form in a freshly prepared acetone solution, is gradually converted into the enolic form[15], the enolisation being accompanied by the migration of the halogen from the 3-position to the 5-position[62].

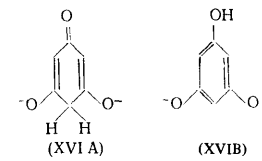
Six-membered cyclic α-diketones contain the diketo-form in addition to the enolic form[9,63]. Judging from the ^{1}H NMR spectra, in dilute aqueous solutions cyclohexane-1,2-dione is enolised approximately to the extent of 50%[64]. The rate of the keto–enol transformation is low but increases in the presence of acids and alkalis. At the same time there is a marked shift in the tautomeric equilibrium. Bakule and Long[64] determined the enthalpy and entropy of the keto–enol transformation in an aqueous medium (6 kcal mole^{-1} and −21 e.u. respectively). According to ^{1}H NMR and ^{17}O NMR data, in benzene cyclohexane-1,2-dione is completely enolised and the rate of exchange between the two equivalent enolic forms is low[22]. In the first case a distinct triplet due to the vinyl protons is observed and in the second case the individual signals of equal intensity due to the carbonyl and hydroxyl oxygen atoms. Freshly prepared cyclohexane-1,2-dione is fully enolised, but after two days 14% of the diketo-form appears[61].

Seven-membered cyclic α-diketones exist predominantly in the diketo-form[55]. In contrast to β-diketones (see below), α-diketones cannot form a mesomeric monoanion common to the two enolic forms; the interconversion of these enolic forms can therefore only occur via the diketo-form. The rates of these transitions are determined by the rates of their keto–enol interconversions, which are slow under the usual conditions. Chemical shifts of the enolic protons of α-diketones are in the range of positive values of τ. For example, τ_{OH} = 3.38 p.p.m. for 3-methylcyclopentanedione in chloroform[61]. This shows that the intramolecular hydrogen bond of the five-membered chelate ring is weak[5].

3. PHENOLS AND SIMILAR COMPOUNDS

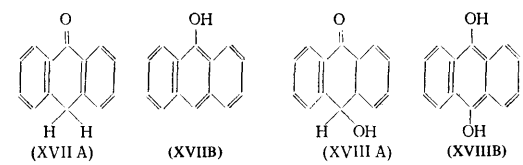
Phenols may be regarded as specific keto–enol systems[9,65]. However, the amount of the keto-form of simple phenols, if it exists at all, is too small to be measured. The keto-enol interconversion is considered as one of the pathways of the exchange of aromatic protons for deuterons in pyrogallol and β-naphthol in an alkaline medium[66].

Forms other than enolic have not been detected for phloroglucinol (a pyrogallol isomer) and its monoanion. However, the dianion exists in the keto-form (XVIA)[65]. This conclusion was arrived at using data obtained by a number of methods, but the ^{1}H NMR spectra are the most convincing[67]. The aromatic form of the dianion (XVIB) has not been detected in appreciable amounts.



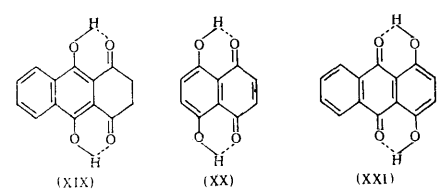
(XVI A) (XVIB)

Sterk investigated the effects of temperature on the anthrone (XVIIA)–anthrol (XVIIB) and oxanthrone (XVIIIA)–9,10-dihydroxyanthracene (XVIIIB) keto–enol equilibria in various solvents[68].



(XVII A) (XVIIB) (XVIII A) (XVIIIB)

The content of anthrone increases from 5% in bromoform to 50% in pyridine and 73% in dimethyl sulphoxide (at 40°C). The (XVIIIA) ⇌ (XVIIIB) equilibrium depends only slightly on the solvent (5–30% of the enol at 40°C) but is strongly displaced towards the enol (XVIIIC) when the temperature is raised. Dihydroquinizarin exists entirely in the diketo-form (XIX) regardless of the medium and temperature[68,69].

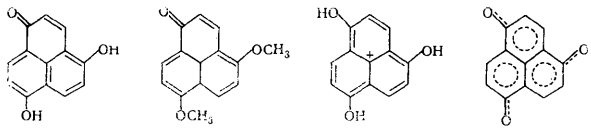


(XIX) (XX) (XXI)

Tautomerism associated with rapid migration of the proton involved in the intramolecular hydrogen bond between the oxygen atoms has been observed in 1,4-dihydroxynaphthoquinone (XX), in contrast to quinizarin, which exists in form (XXI)[69].

An unusual tautomerism was observed by the ^{1}H NMR method in 4,7-dihydroxyphenalenone (XXII)[70]. The spectrum of (XXII) should contain three quartets of type AB due to the three pairs of interacting aromatic protons in the three non-equivalent rings. Precisely this type of spectrum has been observed for 4,7-dimethoxyphenalenone (XXIII). The non-equivalence of the rings of (XXIII) is shown not only in different screening of the protons but also in different spin–spin coupling constants (J_{23} = 8.4 Hz, J_{56} = 9.2 Hz, and J_{89} = 10.1 Hz). However, the spectrum of (XXII) contains only one quartet, common to the three pairs of protons, which can be explained by the effective equivalence of all the rings achieved as a

result of the rapid interconversion of three equivalent structures of type (XXII).

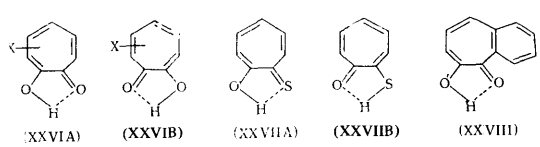


(XXII) (XXIII) (XXIV) (XXV)

This conclusion is confirmed by the value of J_{AB} for (XXII) (9.2 Hz), which is equal to the mean of the three J_{AB} constants for (XXIII). The first stage in these tautomeric transformations may be the formation of the cation (XXIV) or the dianion (XXV).

Tropolones (XXVI) (non-benzenoid aromatic α-diketones) are completely enclosed[71]. The ^{1}H NMR [71,72] and ^{17}O NMR [22] spectra confirm both their complete enolisation and the averaging of the electronic environments of the protons and oxygen nuclei in the left-hand and right-hand parts of the molecules of tropolone and its 5-substituted derivatives as a result of the rapid exchange between the equivalent enolic forms. The merging of the ^{17}O NMR signals of the hydroxy- and carbonyl groups indicates that the lifetimes of these forms are not more than 10^{-5} s. The rapid interconversion of the enolic forms of tropolones, in contrast to saturated α-diketones, is due to the presence of a mesomeric anion common to both enolic forms and reduces to the migration of a proton from one oxygen atom to the other with a corresponding π-electron shift.

In the case of asymmetrically substituted tropolones, the question arises of the preferential direction of enolisation, i.e. the proportions of forms (XXVIA) and (XXVIB). It has been shown[73] that the equilibrium in 3-bromotropolone is somewhat displaced towards the form (XXVIA, X = Br).



(XXVIA) (XXVIB) (XXVIIA) (XXVIIB) (XXVIII)

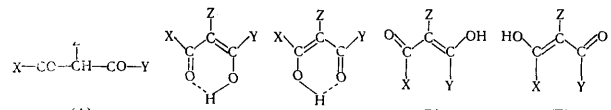
The enolic protons of tropolones in $CDCl_3$ and CCl_4 absorb in the range 0–3 p.p.m., i.e. they are more descreened than the enolic protons of saturated α-diketones. One cannot rule out the possibility that this effect is due not only to the descreening effect of the aromatic rings but also to the stronger intramolecular hydrogen bonds[71] in tropolones, the existence of which is indicated by infrared spectra[74].

Evidence of the predominance of the thiono-form (XXVIIA) of 2-mercaptotropolone (XVII) and its 4- and 6-alkyl-substituted derivatives has been obtained by ^{1}H NMR (in carbon tetrachloride) and other spectroscopic methods[75]. The chemical shift of the enolic proton[56] is 0.12 p.p.m.

In contrast to tropolone, 6,7-benzotropolone exists in form (XXVIII), in which the aromaticity of the benzene ring is unaffected[76].

4. OPEN-CHAIN β-DICARBONYL COMPOUNDS

In general β-dicarbonyl compounds, which include diketones, ketoaldehydes, ketoacids, and their esters and amides, may exist in five tautomeric forms: the diketo-form (A), two *cis*-enolic forms (B) and (C), and two *trans*-enolic forms (D) and (E). The reported presence of appreciable amounts of the dienolic form[77] has not been confirmed[78]. In water and alcohols the keto-form (A) can exist as hydrates and hemiacetals, readily revealed by the NMR method§.



(A) (B) (C) (D) (E)

The interconversion of structures (B) and (C) does not require the dissociation of the intramolecular hydrogen bond and reduces to the migration of a proton between two oxygen atoms. Therefore it is very rapid. The lifetime of the tautomer is less than 10^{-4} s.[33] All other tautomeric transformations in this system are as a rule slow. The half-life associated with the attainment of the keto–enol equilibrium at room temperature after separation of the tautomers amounts to minutes for acetylacetone[82], hours for α-phenylformylacetic acid esters[32], and days for β-carbonyldithioacid acid esters[83]. Thus in the general case the NMR spectra of the above tautomeric compounds should contain the individual signals of forms (A), (D), and (E) and the common signal of forms (B) and (C).

(a) Keto–enol Equilibrium

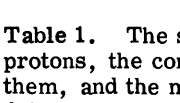
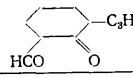
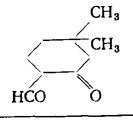
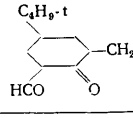
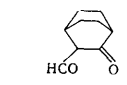
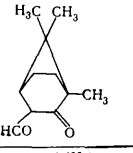
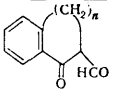
Here we shall consider the effect of molecular structure, temperature, and medium on the position of the keto–enol equilibrium, i.e. on the contents of forms (A) and (B $\rightleftharpoons$ C). The presence of *trans*-enolic forms is observed only in rare cases, which will be discussed separately.

Effect of structural factors and temperature (Tables 1–11). According to NMR data, malonodialdehyde and almost all the aldoesters and ketoaldehydes investigated are completely enolised in both non-polar solvents and as pure liquids (Table 1). On passing from ketoaldehydes to the corresponding diketones and particularly to ketoesters and ketoamides, the percentage of enol falls. For example, in carbon tetrachloride the fractions of the enolic form of acetoacetaldehyde, acetylacetone, acetoacetic ester, and the *N*-benzylamide of acetoacetic acid (in $CDCl_3$) are 100%,[79] 94% [100], 20% [108], and 5% [120] respectively. This effect is associated with the increasing electron density at the carbon atom of the carbonyl group in the above series and the corresponding decrease of the ionisation constants of the dicarbonyl forms[1,9]. It is noteworthy that the ester and amide groups are hardly enolised, in conformity with their low tendency towards nucleophilic addition reactions involving the carbonyl group. The failure of malonic ester to enolise[9] and the increasing degree of enolisation with increasing electron-accepting capacity of the substituents X and Y are consistent with this view[94,121] (Tables 2–4 and 9). A satisfactory linear corelation between the fraction of the enolic form and Hammett's σ constants and particularly Brown's σ^+ constants has been observed for

§ The presence of 76% of the hydrated keto-form of formylacetone in aqueous solution has been demonstrated[79]. For a number of trifluoro-β-diketones in water and alcohols, an equilibrium between the enolic and hydrated or hemiacetal forms has been observed[80,81].

meta- and *para*-substituted benzoyl derivatives of acetic ester[99], acetophenone[94], cyclohexanone[122], and cyclopentanone[121].

Table 1. The screening of the enolic and aldehyde protons, the constants for the spin–spin coupling between them, and the mode of enolisation of β-dialdehydes, β-ketoaldehydes, and β-aldoesters (A ⇌ B, Y = H)[a].

Compound	Medium	τ OH p.p.m.	τ_{CHO}, p.p.m.	J, Hz	[B]/([B]+[C])%	Refs.
OHC–CH_2–CHO	$CDCl_3$	−0.08	1.60	—	50	84 (79, 85)
OHC–CH(CH_3)–CHO	$CDCl_3$	0.61	—	—	50	85
OHC–CH(C_6H_5)–CHO	CCl_4	−4.10	1.35	—	50	86
H_3CCO–CH_2–CHO[b]	$CDCl_3$	−3.58	2.13	—	—	79 (84)
H_3CCO–CH(C_6H_5)–CHO	CCl_4	−5.40	1.85	6.3	—	86
OHC–CH(C_6H_5)–$COOCH_3$[b]	$CDCl_3$	−2.20	2.55	13.3	100	32
OHC–CH(C_6H_5)–$COOC_2H_5$	$CDCl_3$	−2.40	2.45	13.3	100	32 (86)
 $n = 3$[b]	CCl_4	−1.35	2.73	—	78	19 (87, 88)
$n = 4$	CCl_4	−4.27	1.39	3.4	24	19 (86, 87)
	C_6H_6	—	—	—	33	22
$n = 5$	CCl_4	−4.60	2.43	8.0	66	19 (87)
$n = 6$	CCl_4	−4.97	1.89	5.8	44	19
$n = 7$	CCl_4	−5.14	1.57	—	31	19
$n = 8$	CCl_4	−5.11	1.24	—	18	19
$n = 10$	CCl_4	−5.15	1.49	—	28	19
	CCl_4	—	1.49	—	28	19
	CCl_4	—	2.57	9.8	71	19
	CCl_4	—	1.05	1.3	10	19
 b	CCl_4	−2.15	2.98	—	88	19
 b.c.	CCl_4	−0.15	3.29	12	100	19
 $n = 1$	C_6H_6	—	—	—	87	22
$n = 2$	CCl_4	−2.24	2.40	—	—	87
$n = 3$	CCl_4	−4.74	1.84	—	—	87
	CCl_4	−4.20	2.05	—	—	87

a. The values of τ and J quoted in the studies for which the references are enclosed in brackets are close to those in the Table.
b. Several per cent of the formylketone form was observed. All other compounds were fully enolised.
c. 5% of the *trans*-enolic form was detected.

Enolisation is also promoted by the increasing size of the terminal substituents X and Y (Tables 3 and 10), which is apparently due to the instability of the diketo-form owing to the steric interactions between the substituents[95]. Burdett and Rogers[95] attribute to this interaction the lower degree of enolisation of ketoesters compared with diketones. Indeed in ketoesters the alkyl substituent and the carbonyl group are separated by the small oxygen atom and the steric interaction is weakened. However, for large alkyl substituents, such as t-butyl, the stability of the diketo-forms falls and the percentage of the enol increases (Table 3). Such behaviour is characteristic also of ketoamides[124].

Table 2. The content of the enol and the screening of the enolic protons in the series of diketones R–CO–CH_2–CO–R′ in carbon tetrachloride.

R	R′	Enol, %	τ_{OH}, p.p.m.	Refs.
CH_3	CH_3	94	−5.4	89 (90)
t-C_4H_9	CH_3	—	−5.90	91
Mesityl	CH_3	—	−5.40	91
2-Thiono	CH_3	—	−5.66	91
CF_3	CH_3	100	−4.24	90
C_6H_5	CH_3	94.5 (90.5*)	−6.16 (−6.27*)	92 (91, 93)
p-$N(CH_3)_2C_6H_4$	CH_3	77.5*	−6.52*	94
p-$OCH_3C_6H_4$	CH_3	94.7	−6.16	93
p-$CH_3C_6H_4$	CH_3	95.7	−6.00	93
p-BrC_6H_4	CH_3	100	−6.03	93
p-$NO_2C_6H_4$	CH_3	100	−5.92	93
t-C_4H_9	t-C_4H_9	100	−6.30	91
C_6H_5	t-C_4H_9	100	−6.70	91
C_6H_5	CF_3	100	−4.60	91
CF_3	CF_3	100	−3.00	90
CF_3	C_6H_5	100	−7.00	91 (90, 93)
2-Thiono	2-Thiono	100	−6.20	90

* In $CDCl_3$.[94]

Table 3. Enolisation and the screening of the enolic protons of β-ketoesters R–CO–CH_2–COOR′ (pure liquids).

R	R′	Enol, %	τ_{OH}, p.p.m.	Refs.
CH_3	C_2H_5	6–8	−2.17	95, 96, 97
CH_2Br	C_2H_5	6	−1.87	95
CH_2F	C_2H_5	7.2	—	96
CHF_2	C_2H_5	53	—	96
CF_3	C_2H_5	89	−2.00	95, 96
C_6H_5	C_2H_5	22	−2.83	95, 98
CH_3	CH_3	0	—	95
CH_3	n-C_4H_9	15	−2.17	95
CH_3	t-C_4H_9	17	−2.22	95

The α-substituent (Z) has a very marked influence on the keto–enol equilibrium (Tables 5, 6, 8, and 10). Electronegative substituents increase sharply the degree of enolisation. α-Alkyl substituents cause a marked decrease of the percentage of enol. However, here the cause is mainly steric—repulsion between the α- and ring substituents, which makes the chelate ring of the *cis*-enolic form unstable. For example, whereas dibenzoylmethane is fully enolised, its α-methyl analogue exists exclusively in the diketo-form[100]. The replacement of the oxygen of the carbonyl group by sulphur leads as a rule to almost complete enolisation (Tables 7 and 8)[110,125–127]. In alicyclic β-ketoesters the degree of enolisation depends in a complex manner on ring size (Table 7). Possibly this is due to conformational changes on passing from one ring to another[108,109].

A strong intramolecular hydrogen bond is also an important factor stabilising the *cis*-enolic form. The weakness of the intramolecular hydrogen bond in five-membered alicyclic compounds accounts for the relatively low degree of their enolisation (Tables 1 and 7).

With increase of temperature, the content of the enol falls. The thermodynamic parameters of enolisation have been determined for a number of β-dicarbonyl compounds by the NMR method (Table 10). The energy gain on formation of an intramolecular hydrogen bond ($\Delta H < 0$) promotes enolisation but, in view of the higher entropy of the keto-form ($\Delta S < 0$), the latter is not only present in significant amounts in a number of systems but actually predominates[55,78]. Ultimately the position of tautomeric equilibrium is determined by the competing energy and entropy factors. Table 10 shows that the enthalpy of enolisation (ΔH) increases with the dimensions of the terminal substituents and falls with increasing size of the α-substituent.

Table 4. The content of the enol[99] and the screening of the enolic protons[93] of *para*-substituted derivatives of benzoylacetic ester $XC_6H_4-CO-CH_2-COOC_2H_5$ in $CDCl_3$.

X	Enol, %	τ_{OH}, p.p.m.
OCH_3	3	−2.96
H	15	−2.93
Br	—	−2.93
Cl	23	−2.94
NO_2	53	−2.92

Table 5. Enolisation and the screening of the enolic protons of α-substituted acetylacetone derivatives $CH_3-CO-CHZ-CO-CH_3$ (pure liquids).

Z	Enol, %	τ_{OH}, p.p.m.	Refs.	Z	Enol, %	τ_{OH}, p.p.m.	Refs
H	81	−5.56	95, 100	C_6H_5[a]	~100	−6.60	91, 103
CH_3	30	−6.50	95, 100	Br	46	−5.36	95
C_2H_5	26	−6.80	101			(−5.80[a])	
n-C_3H_7	27	−6.80	101	Cl	94	−5.58	95, 100
iso-C_3H_7	0.1	−7.30	102	CN[a]	~100	−6.80	104
s-C_4H_9	0.7	−7.50	102	$COCH_3$[b]	100	−7.41	105
OCH_3[a]	—	−4.09	103	$COOCH_3$[a]	100	−8.62	106
$OCOCH_3$[a]	20	−4.35	103				

a. In carbon tetrachloride.
b. In $CDCl_3$.

Effect of the medium. On dissolution in solvents of low polarity, the percentage of the less polar *cis*-enolic form increases. Conversely polar solvents displace the equilibrium towards the polar diketo-form (Table 11). This can be explained by the solvation of the carbonyl groups by the polar solvent molecules, which increases the stability of the diketo-form[97,100,118]. Thus in dimethyl sulphoxide the enthalpy of enolisation (ΔH) of acetylacetone is lower by more than 1 kcal mole^{-1} compared with pure acetylacetone, which apparently corresponds to an energy gain on solvation of the diketo-form in dimethyl sulphoxide.

Reeves[114] and also Rogers and Burdett[118] compared the experimental keto–enol equilibrium constants for acetylacetone and acetoacetic ester with the values calculated taking into account the dielectric constant of the solvent[128]. For a number of solvents, in particular benzene and acetic acid, satisfactory agreement was obtained between theory and experiment. In other cases (pyrrole, triethylamine) there is a discrepancy between the calculations and experimental data owing to the specific interactions with solvent molecules[114]. The intermolecular hydrogen bond between pyrrole and the carbonyl groups of acetylacetone and acetoacetic ester stabilises the diketo-form. At the same time pyrrole does not interact significantly with the enolic form, as shown by the constancy of the chemical shift of the enolic proton when the concentration of the solution in pyrrole is altered[97,129].

Table 6. Enolisation and the screening of the enolic protons of α-substituted derivatives of acetoacetic ester $CH_3-CO-CHZ-COOC_2H_5$ (pure liquids)[95].

Z	Enol, %	τ_{OH}, p.p.m.
H	8	−2.17
CH_3	5	−2.63
C_2H_5	1	−2.73
n-C_3H_7	1	−2.80
iso-C_3H_7	1	−2.98
s-C_4H_9[a]	0.4	−3.10
s-C_5H_{11}	1.4	−3.30
CH_2—CH=CH_2	3	−2.70
CH_2—C_6H_5	22	−2.83
Br	5	−2.73
Cl	15	−2.28
F	15	—
CN	93 (75[b])	−3.45

a. See Ref. 102.
b. See Ref. 107.

Table 7. The content of the enol and the screening of the enolic protons of the esters of alicyclic oxo-, thiono-, and oxodithio-acids in carbon tetrachloride.

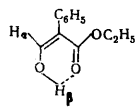
Type of ester	No. of methylene groups in ring	Enol, %	τ_{OH} (SH)
a	3	11.5 (21)[b]	−0.42
	4	85	−2.12
	5	31	−2.68
	6	64	−2.50
	7	38	−2.67
	8	70	−2.88
	9	13	−3.03
	10	7.5	−2.85
	13	7.0	−2.82
c	3	100	−2.51
	4	100	−2.57
	5	46	−2.48
	6	57	−2.33
d	3	99	3.83
	4	99	4.78
e	3	100	−4.01
	4	100	−5.37

a. See Ref. 108. b. See Ref. 98. c. See Ref. 109.
d. See Ref. 110. e. See Ref. 83.

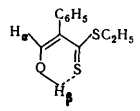
In contrast to pyrrole, acetic acid, which is dimerised, does not form hydrogen bonds with acetylacetone[114] and has little effect on the position of its keto–enol equilibrium (Table 10).

b. Mode of Enolisation

NMR apparently provides a unique possibility of a quantitative estimation of the amounts of the two *cis*-enolic tautomeric forms (B) and (C). Aldo- and keto-esters and their thioanalogues enolise only at the carbonyl oxygen. This has been confirmed in a number of examples (XXIX–XXXIII). For (XXIX) and (XXX), the spin–spin coupling constants $J_{\alpha\beta}$ are characteristic of hydroxymethylene forms, amounting to 13.3 Hz [82] and 13.5 Hz [83] respectively, and are independent of temperature [87].



(XXIX)



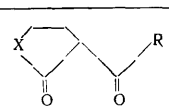
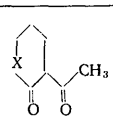
(XXX)

Table 8. Enolisation and the screening of the chelate protons of a number of esters of β-thiono-[110] and β-oxodithio-acids [83] in carbon tetrachloride.

Compound	Enol, %	τ_{OH}, p.p.m.	τ_{SH}, p.p.m.
$H_3C-CS-CH_2-COOC_2H_5$	96	—	2.70
$H_3C-CS-CH_2-COOC_4H_9$-n	94	—	2.65
$H_5C_2OOC-CH_2-CS-CH_2-COOC_2H_5$	96	—	2.75
$C_6H_5-CS-CH_2-COOC_2H_5$	97	—	2.05[a]
$C_6H_5-CS-CH_2-COSC_2H_5$	100[b]	—	2.02
$C_6H_5-CS-CH_2-CONHC_6H_5$	100[b]	—	—
$CH_3-CO-CH_2-CSSH$	100	−4.76	—
$CH_3-CO-CH_2-CSSCH_3$	94	−4.45	—
$CH_3-CO-CH_2-CSSC_2H_5$	94	−4.54	—
$C_6H_5CO-CH_2-CSSH$	100	−5.57	—
$C_6H_5CO-CH_2-CSSC_2H_5$	100	−4.99	—
$CH_3-CO-CH(CH_3)-CSSCH_3$	6	−5.73	—
$CH_3-CO-CH(C_6H_5)-CSSCH_3$	100	−5.67	—
$HCO-CH(C_6H_5)-CSSCH_3$	100	−4.63	—
$CH_3-CO-CH_2-CO-SC_2H_5$	30[c]	—	—

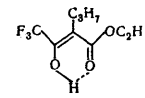
a. 1.65 in the pure liquid [98]. b. See Ref. 111.
c. Bromometric titration (pure liquid) [112].

Table 9. Enolisation and the screening of the enolic protons of a series of alicyclic β-dicarbonyl compounds with a heteroatom in the ring [113].

Compound	Medium	Enol, %	τ_{OH}
 X=NCH_3; R=CH_3	DMSO	0	—
X=O; R=CH_3	$CDCl_3$	0	—
X=O; R=C_3H_7-n	$CDCl_3$	3	
	DMSO	3	−0.2
X=O; R=$COOCH_3$	$CDCl_3$	100	0.0
X=CH_2; R=CH_3[a]	CCl_4	60	−3.08
X=S; R=$COOC_2H_5$	$CDCl_3$	100	−2.17
 X=NCH_3	DMSO	40.8	−5.18
X=CH_2[a]	CCl_4	100	−5.80
X=S	$CDCl_3$	74.6	−4.79
	DMSO	45.6	−4.83

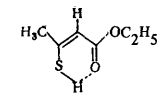
a. See Ref. 88.

In the case of the ketoesters (XXXI)–(XXXIII) a similar conclusion was reached concerning the mode of enolisation, although the ^1H NMR data are more qualitative, since the spin–spin coupling constants are relatively low.



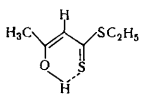
(XXXI)

$J_{CF_3-\overset{\|}{C}-OH} = 2.0$ Hz [102]



(XXXII)

$J_{CH_3-\overset{\|}{C}-SH} = 1.0$ Hz [110]



(XXXIII)

$J_{CH_3-\overset{\|}{C}-OH} = 0.66$ Hz [83]

Table 10. Thermodynamic functions for the enolisation of β-diketones R–CO–CHZ–CO–R′ (pure liquids).

R	Z	R	Temp. range, °C	Enol, % (33°C)	$-\Delta H$, kcal mole^{-1} (±0.2)	$-\Delta S$ (35°), kcal mole^{-1} deg^{-1} (±0.5)	Refs.
CH_3	H	CH_3	33—100	79.5	2.8[a]	6.4[a]	115 (114, 78, 100)
CH_3	H	C_2H_5	33—100	80.5	3.0	7.0	115
CH_3	H	iso-C_3H_7	33—150	89.0	3.2	6.4	115
CH_3	H	t-C_4H_9	33—150	93.5	3.9	7.4	115
iso-C_3H_7	H	iso-C_3H_7	33—150	94.0	3.7	6.6	115
iso-C_3H_7	H	t-C_4H_9	33—150	96.0	4.6	9.0	115
t-C_4H_9	H	t-C_4H_9	33—150	98.5	4.9	8.2	115
CH_3	CH_3	CH_3	(—11)—89	28	1.3	5.6	78 (100)
CH_3	$CH_2-CH=CH_2$	CH_3	25—125	42	2.1	7.3	100
CH_3	$CH_2-C_6H_5$	CH_3	38—170	46	2.5	8.4	100
CH_3	Cl	CH_3	33—80	92	5.9	14±1	78
C_6H_5	H	C_6H_5[b]	90—180	~100	3.2	3.4	100
C_6H_5	$COOC_2H_5$	C_6H_5[c]	—	56	10.1	40.0	116
Dimedone			20—85	—	2.0	—	117

a. In dimethyl sulphoxide ΔH and ΔS are 1.6 kcal mole^{-1} and 5.0 cal mole^{-1} deg^{-1}.
b. In carbon tetrachloride (0.4 M).
c. In chloroform.

Table 11. The content of the enolic form and chemical shifts of the acetylacetone and acetoacetic ester protons in various solvents [118].

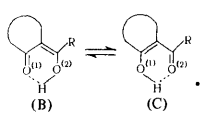
Solvent	Acetylacetone			Acetoacetic ester		
	Enol, %[a]	$\tau_\infty - \tau_0$, p.p.m.[b]		Enol, %[a]	$\tau_\infty - \tau_0$, p.p.m.[b]	
		=CH—	—OH		=CH—	—OH
$N(C_2H_5)_3$	100[c]	—	0	0[B]	—	—
C_6H_{14}	95	0.27	0.10	39.0	0.17	−0.05
CCl_4	96	0.20	0.35	28.0	0.15	0.10
$O(C_2H_5)_2$	95	0.12	0.35	22.0	0.10	−0.05
CS_2	94	0.22	0.27	20.0	0.15	0.12
C_6H_6	89	0.65	−0.68	16.0	0.15	−0.55
$CHCl_3$	87	0.03	0.33	7.5	0.05	0.13
Dioxan	82	0.03	0.63	11.0	0.03	0.03
C_2H_5OH (abs.)	82	−0.02	9.92[e]	10.0	0.03	0.02
Pyridine	82[d]	—	—	—	—	—
Pure liquid	81	0	0	7.5	0	0
Acetone	78[d]	—	—	—	—	—
CH_3OH	74	−0.05	10.42[e]	5.8	−0.02	0.02
CH_3COOH	67	0	0.53	1.9	0.03	0.07
CF_3COOH	66[r]	—	—	—	—	—
CH_3CN	62	−0.07	−0.17	4.9	0	0.02
CH_3SOCH_3	62	−0.13	1.13	2.2	−0.08	0.10

a. In 0.1 M solutions.
b. τ_∞ is the chemical shift extrapolated to infinite dilutions and τ_0 the chemical shift for the pure liquid.
c. Data from Refs. 114 and 119.
d. Data from Ref. 89.
e. Chemical shift of the overall signal of the enolic protons and the hydroxyl protons of the alcohol.

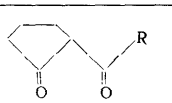
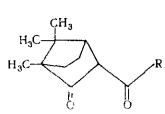
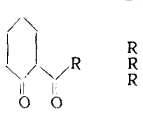
In contrast to aldoesters, β-aldoketones exist in both *cis*-enolic forms (B) and (C). Table 1 presents data on the mode of enolisation in cyclic α-formylketones determined from the chemical shift of the aldehyde (hydroxymethylene) proton; these agree with the spin–spin coupling constants ($J_{=CH-OH}$) [19]. According to Garbisch [130], the differences in the mode of enolisation are associated mainly with the conformations of the rings and their strain. The predominance of the hydroxymethylene form (B) in five-membered rings and of form (C) in six-membered rings is consistent with quantum-chemical calculations indicating that exocyclic carbon–carbon double bonds are energetically favourable for five-membered rings [131]. The ^1H NMR data for α-formylcyclohexanone and 3-formylcamphor are also satisfactorily consistent with the results obtained from ^{17}O NMR spectra [22].

Deutsch and Deutsch [87], who investigated the same compounds as Gabrisch, believed erroneously that rapid (B) ⇌ (C) exchange should lead to the disappearance of the multiplet structure of the hydroxymethylene (aldehyde) and enolic proton signals (as happens in intermolecular exchange). Therefore the very fact that these signals are split was incorrectly interpreted as evidence for the existence of the hydroxymethylene form only. Their work [87] was criticised in detail in a later paper by Garbisch [132].

Table 12. The mode of enolisation and ^{17}O screening (relative to H_2O) in a series of alicyclic β-diketones and β-ketoaldehydes in benzene [22].



(B) (C)

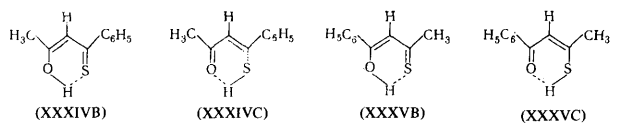
Compound	$\delta_0^{(1)}$, p.p.m.	$\delta_0^{(2)}$, p.p.m.	$\frac{[B]}{[B]+[C]}$, %
 R = CH_3[a]	354	169	70
R = C_6H_5	395	121	80
 R = H	430	88	87
R = CH_3	408	108	83
 R = H	205	360	33
R = CH_3	175	359	30
R = C_6H_5	231	295	43

a. The ^{17}O signal of the diketo-form is observed ($\delta_0^{(1)} \simeq \delta_0^{(2)} \simeq 540$ p.p.m.).

Forsen and Nilsson [86] observed a temperature variation of the $J_{=CH-OH}$ constant for α-phenylacetoacetaldehyde. Possibly it reflects a shift in the (B) ⇌ (C) equilibrium.

Gorodetsky et al [22] succeeded in estimating the contents of the two *cis*-enolic forms for a number of alicyclic β-diketones (Table 12) and benzoylacetone from ^{17}O NMR spectra. Table 12 shows that in β-diketones the effect of ring size on the mode of enolisation is similar to that found for aldoketones. Replacement of a methyl group in the side chain by a phenyl group leads to an increase in the amount of the form with exocyclic double bonds. The stabilisation of this form by the benzene ring owing to the increase in the length of the conjugated chain was predicted by quantum-mechanical calculation [133]. Probably for this reason the enolisation of benzoylacetone (V) at the carbonyl group adjacent to the benzene ring is preferred (about 56%) [22]. These quantitative data were contradicted in a later study by Sardella et al. [94], who did not observe spin–spin coupling between the methyl and vinyl protons of benzoylacetones and thereby concluded that more than 90% is present as the form with an enolised benzoyl group. The resolution of this contradiction requires additional studies, but we believe the data of Gorodetsky et al. [22] to be more convincing.

The problem of the mode of enolisation of thionoketones is interesting. Klose et al. [125] observed the spin–spin splitting of the enolic proton signal by the protons of the methyl group of thiobenzoylacetone (XXXIV) and concluded that thionoketones are enolised at the carbonyl group.



(XXXIVB) (XXXIVC) (XXXVB) (XXXVC)

$J_{CH_3-\overset{\|}{C}-OH} = 0{,}32$ Hz $J_{CH_3-\overset{\|}{C}-SH} = 0{,}20$ Hz

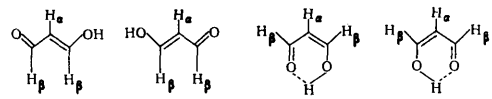
However, Duus and Lawesson [110] observed a splitting of the signal due to the chelate proton in benzoylthioacetone (XXXV) [110], and in accordance with infrared spectroscopic data, suggested that thionoketones are enolised at the thiono-group. The presence of both forms in comparable amounts is quite likely. The sharp increase of the screening of the chelate proton of thionoketones with increase of temperature [110,125] is explained by the shift of the equilibrium towards the thienol form¶ [125] or the dissociation of the intramolecular hydrogen bond [126].

One can postulate a parallel variation of the capacity for enolisation of the RCO–group in aldoketones and diketones, on the one hand, and in the corresponding ketoesters, on the other, with the nature of the substituent R. Indeed a correspondence is observed between the content of the enol in ketoesters (Table 7) and the fraction of the chelate aldo-form (C) in the corresponding aldoketones (Table 1). Furthermore, the preferential enolisation of the benzoyl group of benzoylacetone is consistent with the greater ease of enolisation of the benzoylacetic ester compared with acetoacetic ester (Table 3). Consequently the more pronounced enolisation of ring-substituted benzoylacetic esters with increasing electronegativity of the substituent [93,99] (Table 4) should correspond to an increase of the content of the chelate form with an enolised benzoyl group in the analogous benzoylacetones. This is consistent with the results of a study [93] based on an analysis of the chemical shifts of enolic protons.

¶ The signal of the chelate proton of the thienol form is located in higher fields (Table 8).

c. *trans*-Enolisation

On the basis of the $J_{\alpha\beta} = 9.69$ Hz constant, Bothner-By and Harris[84] concluded that malonodialdehyde exists in chloroform mainly in the *trans*-transoid form (XXXVI, D and E).



(XXXVID) (XXXVIE) (XXXVIB) (XXXVIC)

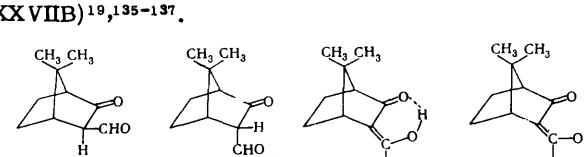
However, according to the data of Shapet'ko et al.[85], this constant is 4.2 Hz in chloroform and acetone and therefore the authors attributed the *cis*-cisoid structure (XXXVI, B and C) to malonodialdehyde. This structure is also indicated by the marked descreening of the enolic proton (about 0 p.p.m.). George and Mansell[79] confirmed Shapet'ko's data ($J_{\alpha\beta} = 3.4-3.8$ Hz in carbon tetrachloride, chloroform, and methylene dichloride), i.e. the structure (XXXVI, B and C). They explained the results of Bothner-By and Harris[84] by the presence of polar impurities in chloroform.

In aqueous solution the enolic forms of malonodialdehyde ($J_{\alpha\beta} = 10.3$ Hz) and also of α-formylacetone ($J_{\alpha\beta} = 9.1$ Hz) have the *trans*-transoid structure according to George and Mansell[79]. This behaviour can evidently be explained by competition between intramolecular hydrogen bonding and strong intermolecular hydrogen bonds with water molecules.

Freshly prepared solutions of α-phenylformylacetic esters in chloroform contain the *trans*-enolic form but after a time are fully converted into the *cis*-enolic and aldo-forms[84].

In 1967 a Japanese group[103] reported the presence of large amounts (up to 50%) of the *trans*-enolic forms of a number of α-alkylacetylacetones in carbon tetrachloride. This conclusion contradicts other data[101,102,134] (^{1}H NMR and bromometric titration), which show that the enolisation of the above compounds is insignificant (about 1% or less) in various media, the enolic tautomer being in the *cis*-form. Possibly the Japanese workers were not dealing with the *trans*-enols but with the enol esters[101].

The *trans*-enolic form of 3-formylcamphor (XXXVIID) was observed in various solvents in slow equilibrium with the aldo-form (XXXVIIA) and the *cis*-enolic form (XXXVIIB)[19,135-137].



(XXXVIIA) (XXXVIIB) (XXXVIID)

In carbon tetrachloride the ratio of the concentrations of the *trans*- and *cis*-forms of the enol D/B increases according to ^{1}H NMR data from 5/95 in 10% solution to 31/69 in 26% solution[19]. The addition of dimethyl sulphoxide to carbon tetrachloride sharply increases the content of the *trans*-enolic form[19,135] (D/B = 78/22 for 14% solution in carbon tetrachloride with 8% of dimethyl sulphoxide). In 10% solution in ether, D/B = 55/45.[136] The increased content of the *trans*-enolic form of 3-formylcamphor is probably due to a competition between intramolecular and intermolecular hydrogen bonding.

The fact that in non-aqueous media the *trans*-enolic form has so far been detected only in 3-formylcamphor (among a large number of compounds investigated) may be tentatively accounted for by the weakness of intramolecular hydrogen bonding in this compound (see below).

On the basis of a private communication by Duus et al., Wamhoff et al.[113] state that α-thioacetyl-γ-butyrolactone contains 37% of the *trans*-enolic form in carbon tetrachloride.

d. Intramolecular Hydrogen Bonds in β-Dicarbonyl Compounds

Intramolecular hydrogen bonding determines the stability of the *cis*-enolic form and with other factors, the position of the keto-enol equilibrium. Therefore here we shall examine the factors which influence the chemical shift of the chelate enolic proton (τ_{OH}). The chemical shift may be a quantitative characteristic of the strength of intramolecular hydrogen bonding in a series of similar compounds. The stronger the intramolecular hydrogen bond, the lower is the value of τ_{OH}.[5] On the other hand, τ_{OH} contains, in principle, information about the enol-enol equilibrium.

The weak dependence of the chemical shift of the ^{1}H NMR signal of the *cis*-enolic proton on temperature[78,102,126] and on the medium (Table 11)[90,138] and also the spin-spin splitting of this signal observed in many cases indicate the stability of the chelate ring with an intramolecular hydrogen bond.

Tables 2, 3, 5, and 6 show that τ_{OH} decreases with increasing size of both the terminal groups and (to an even greater extent) the size of the α-substituent (Z). This finding can be explained by the repulsion of the groups, as results of which the chelate ring contracts, the oxygen atoms come closer together, and the intramolecular hydrogen bond is strengthened[91,95,139]. On the other hand, steric effects account for the shift of the chelate proton signal of α-formyl, α-acetyl, and α-ethoxycarbonyl-pentanones and particularly α-formylcamphor towards higher fields by 2-3.5 p.p.m. relative to the corresponding acyclic compounds (Tables 1, 7, and 9). With increase of the valence angles at the unsaturated carbon atoms in the rings of the above compounds to 107-111°, the intramolecular hydrogen bond becomes weakened owing to the increased distance between the oxygen atoms[19,108].

The more pronounced descreening of the enolic proton in diketones compared with aldoketones and particularly compared with ketoesters is associated with the increase of the electronegativity of substituents in the series Alk < H < OAlk.

In β-ketoesters τ_{OH} depends only slightly on the electronegativity of the terminal substituent (Table 3). This effect is almost absent from *para*-substituted benzoylacetic esters (Table 4).

In β-diketones the electronic influence of the terminal substituent is much more marked. Electronegative substituents reduce the strength of the intramolecular hydrogen bond (Table 2) evidently due to the decreased electron density at the carbonyl oxygen[91]. The benzene ring supplies electrons to the chelate ring and stabilises the intramolecular hydrogen bond, provided that it is conjugated† with the chelate ring. When the mesityl

† The coplanarity of the benzene and chelate rings is confirmed by the descreening of the *ortho*-protons of the ring on the side of the carbonyl group[90].

group is displaced from conjugation, it does not have a significant influence on τ_{OH} (Table 2).

In the majority of compounds the effect of the electronegativity of the α-substituent (Z) on τ_{OH} is masked by steric effects. But if the dimensions of the substituents are similar, ^{1}H NMR data indicate that the screening of the enolic proton decreases with increasing electronegativity in both ketoesters and diketones (cf. Z = Cl and Z = CN, Tables 5 and 6).

The replacement of the −COOAlk group by −CSSAlk in aldo- and keto-esters leads to a marked shift of the enolic chelate proton signal towards lower fields (by 2−3 p.p.m.) (Table 8). On the other hand, the replacement of the acyl group of ketoesters by the thioacyl group causes a sharp shift (by 4−5 p.p.m.) of the resonance of the chelate proton towards higher fields. In β-thionoketones the chelate proton is more highly screened than in the corresponding diketones.

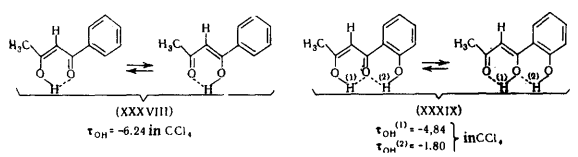
e. Effect of the Enol−Enol Equilibrium on the Chemical Shift of the Enolic Proton

As a result of the migration of the proton of the intramolecular hydrogen bond between the donor atoms, an average chemical shift of the two *cis*-enolic forms (B) and (C) is observed. The marked dependence of τ_{OH} for β-diketones (Y = Alk) on the nature of the terminal substituent X is largely due to changes in electron density at the oxygen atom of the adjacent carbonyl group in the tautomer (B).

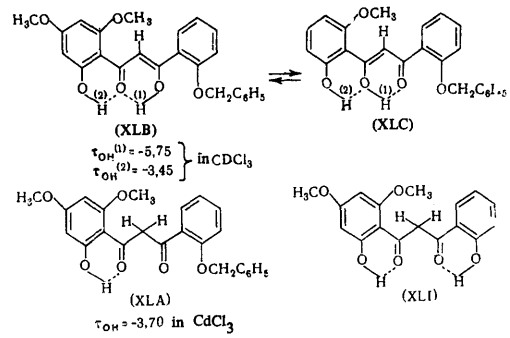
In β-ketoesters (Y = OAlk) the form (B) is absent and the change in electron density at the remote carbonyl group of the tautomer (C) is insignificant. Hence the weak dependence of τ_{OH} on the electronegativity of the substituent in β-ketoesters becomes understandable[93]. The closer the values of τ_{OH} for two chelate forms, the weaker is the influence of the displacement of the intrachelate equilibrium on the observed chemical shift of the enolic proton.

f. Compounds with two Intramolecular Hydrogen Bonds

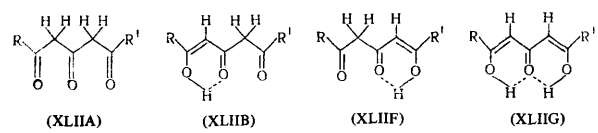
The formation of a second intramolecular hydrogen bond with a chelate oxygen atom reduces the strength of the first intramolecular hydrogen bond. This conclusion was reached after comparing the values of τ_{OH} for compounds (XXXVIII) and (XXXIX) and also for analogous toluene and naphthalene derivatives[140].



Possibly the effect of the second intramolecular hydrogen bond (with the phenolic proton) is one cause of the low content of the enolic form (about 30%) in compound (XL) and other similar compounds[141] compared with dibenzoylmethanes without a hydroxy-group (Table 2). Indeed, in compound (XLI), where both carbonyl groups are stabilised by intramolecular hydrogen bonds, there is no appreciable enolisation[141]. Wagner et al.[141] suggest that, of the two possible enolic forms of (XL), the form (XLB) where the free carbonyl group is enolised, is the more stable:



In the triketones (XLII, R, R′ = CH_3 or C_6H_4X), the contents of the tautomers (A), (B), (F), and (G), (3, 40, 18, and 39% respectively for H = C_6H_5 and R′ = CH_3 in $CDCl_3$) have been determined[99,142]. The low content of the form (G), i.e. the reduced capacity for enolisation of the acetyl and benzoyl groups relative to the corresponding diketones, may be associated with the lower strength of the two intramolecular hydrogen bonds.



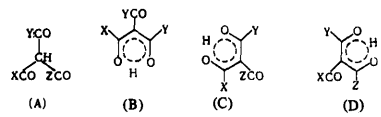
The greater tendency of the benzoyl group towards enolisation compared with the acetyl group is noteworthy.

5. TRIACYLMETHANES AND SIMILAR COMPOUNDS

In general three enolic forms (external tautomers[88]), differing in the group outside the chelate rings (B, C, D), are possible for acyclic tricarbonyl compounds related to triacylmethanes (Table 13). In cyclic tricarbonyl compounds there may be two non-equivalent chelate forms (Table 14). Usually tricarbonyl compounds do not contain the triketo-form (A) in an appreciable amount. However, the compounds with even a single large substituent, such as t-butyl, are not enolised at all[143] and certain acyldibenzoylmethanes and tricarbonyl compounds with ester groups are only partly enolised (Table 13). The content of the enolic forms of these compounds decreases in polar solvents[116]. The interconversions of the external tautomers, which require the dissociation of intramolecular hydrogen bonds, are slow under the usual conditions and the observed ^{1}H NMR spectrum contains the individual signals of the tautomers. The rate of exchange increases sharply in the presence of bases[88,106].

A stronger intramolecular hydrogen bond is characteristic of tricarbonyl compounds compared with the corresponding dicarbonyl compounds (lower values of τ_{OH} and of the vibration frequencies of the C=O and O−H groups in the infrared spectra)[88,148]. The high enthalpy of enolisation of dibenzoylethoxycarbonylmethane (Table 10) and the slow deuterium exchange involving the chelate protons in 2-acetyldimedone[5] are also consistent with the high stability of the intramolecular hydrogen bonds in tricarbonyl compounds. The high stability of the chelate enolic forms of tricarbonyl compounds can be understood by regarding them as β-dicarbonyl compounds with an

Table 13. Tautomeric composition and the screening of the enolic protons of acyclic tricarbonyl compounds.

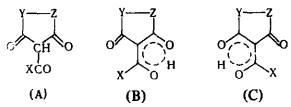


(A) (B) (C) (D)

Compound X	Compound Y	Compound Z	Medium	Tautomers, % A	B	C	Γ	τ_{OH}, p.p.m. B	C	Γ	Refs.
CH_3	CH_3	CH_3	$CDCl_3$	0	33	33	33	−7.41	−7.41	−7.41	105
CH_3	C_6H_5	CH_3	$CDCl_3$	0	100	0	0	−7.05	—	—	143
C_3H_7	C_6H_5	C_3H_7	$CDCl_3$	0	100	0	0	−7.20	—	—	143
C_4H_9	C_6H_5	C_4H_9	$CDCl_3$	0	100	0	0	−4.45	—	—	143
C_3H_7	$OCH_3C_6H_4$	C_3H_7	$CDCl_3$	0	100	0	0	−7.00	—	—	143
C_3H_7	$NO_2C_6H_4$	C_3H_7	$CDCl_3$	0	100	0	0	−7.35	—	—	143
CH_3	C_6H_5	C_6H_5	$CDCl_3$	0	50	50	0	−7.29	−7.29	—	144, 145
C_3H_7	C_6H_5	C_6H_5	$CDCl_3$	>5	<50	<50	0	−7.35	−7.35	—	144, 145
CH_3	$NO_2C_6H_4$	C_6H_5	$CDCl_3$	0	50	50	0	−7.42	−7.05	—	144, 145
C_3H_7	$NO_2C_6H_4$	C_6H_5	$CDCl_3$	0	50	50	0	−7.60	−7.30	—	144, 145
CH_3	$-CH=CH-C_6H_5$	CH_3	CCl_4	0	66	17	17	−7.30	−7.40	−7.40	106
CH_3	H	CH_3	CCl_4	0	80	10	10	−8.30	−7.10	−7.10	86
CH_3	OC_2H_5	H	CCl_4	0	90	10	0	−7.10	−4.40	—	86
CH_3	OCH_3	CH_3	CCl_4	0	100	0	0	−8.62	—	—	106
CH_3	OC_2H_5	CH_3	$CDCl_3$	2	96	1	1	−8.20	—	—	116
CH_3	OC_2H_5	CH_3	DMSO	7	90	1.5	1.5	−7.90	—	—	116
CH_3	OC_2H_5	C_6H_5	$CDCl_3$	16	54	30	0	−7.10	−3.20	—	116, 144, 145
CH_3	OC_2H_5	C_6H_5	DMSO	40	—	60	—	—	—	—	116
C_6H_5	OC_2H_5	C_6H_5	$CDCl_3$	44	13	21.5	21.5	−7.5	−3.7	−3.7	116
C_6H_5	OC_2H_5	C_6H_5	DMSO	94	0	3	3	—	—	—	116
C_6H_5	OC_2H_5	C_6H_5	CCl_4	25	15	30	30	−7.90	−3.7	−3.7	117
CH_3	OC_2H_5	OC_2H_5	CCl_4	43	28.5	28.5	0	—	—	—	110
C_6H_5	OC_2H_5	OC_2H_5	pure liquid	93	3.5	3.5	0	−3.51	−3.51	—	146
t-C_4H_9	OC_2H_5	OC_2H_5	ditto	100	0	0	0	—	—	—	146

a. The representation of the chelate forms employed here implies the possibility of the migration of the proton between the oxygen atoms, i.e. rapid intrachelate tautomerism.

Table 14. Tautomeric composition[a] and the screening of the enolic protons for cyclic tricarbonyl compounds.



(A) (B) (C)

Compound X	Compound Y–Z	Medium	Tautomers, % B	C	τ_{OH}, p.p.m. B	C	Refs.
CH_3	CH=CH	CCl_4	50	50	−2.10	−2.10	88
CH_3	CH=CCl	CCl_4	69	31	−(−1.83)[b]		88
CH_3	$CH=CCH_3$	CCl_4	62	38	−(−2.19)		88
CH_3	$CH_2-C(CH_3)_2$	CCl_4	60	40	−(−4.52)		88
CH_3	$(CH_2)_2$	CCl_4	50	50	−4.75	−4.75	88
CH_3	$(CH_2)_3$	CCl_4	50	50	−8.03	−8.03	88
CH_3	$(CH_2)_4$	CCl_4	50	50	−7.87	−7.87	88
H	$(CH_2)_2$	$CDCl_3$	50	50	−2.32	−2.32	147
H	$CH_2-C(CH_3)_2-CH_2$	CCl_4	50	50	−5.60	−5.60	86
CH_3	$CH_2-C(CH_3)_2-CH_2$	CCl_4	50	50	−8.06	−8.06	88
NH_2	$CH_2-C(CH_3)_2-CH_2$	$CDCl_3$	50	50	−7.78	−7.78	120
CH_3	$C(CH_3)_2-C(OCH_3)=CH$	$CDCl_3$	50	50	—	—	16, 105
iso-C_3H_7	$C(CH_3)_2-C(OCH_3)=CCH_3$	$CDCl_3$	65	35	−9.40	−8.70	16
CH_3	$CH=C(CH_3)-O$	$CDCl_3$	0	100	—	−7.02	148

a. The triketo-form (A) was not detected.
b. Overall signal. The signals due to the protons at the carbon atoms are observed separately.

electronegative α-substituent (–COX). The dependence of τ_{OH} for di- and tri-carbonyl compounds on the substituent and ring size is analogous.

Many studies have been made to determine the mode of chelation of tricarbonyl compounds. In a number of cases the problem has been solved (Tables 13 and 14) despite the difficulty associated with the similarity of the chemical shifts of the acyl groups in the chelate and outside it‡. Nonhebel[143] showed by infrared and ^1H NMR spectroscopy that in diacetylaroylmethanes the aryl group is not incorporated in the chelate and in acetyldiaroylmethanes the acetyl group must be involved in the formation of the chelate (Table 13). The data in this table also show that the ester groups are preferentially located outside the enolic chelate ring.

The contents of the external tautomers of a number of complex tricarbonyl compounds (mainly natural compounds) have been investigated[16,120,149,150]. The intrachelate tautomerism of tricarbonyl compounds has not been specially investigated, but in a number of studies it has been discussed on the basis of indirect data[86,147,150].

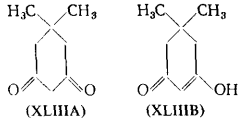
6. CYCLIC β-DIKETONES

In contrast to acyclic and alicyclic β-diketones, in the enolic forms of the cyclic β-diketones considered in this section intramolecular hydrogen bonds stabilising the enolic form cannot be formed owing to steric factors when the ring is not unduly large. Therefore in dilute solutions in non-polar media the contents of the enolic forms of cyclohexane-1,3-dione and dimedone (XLIII) are low. The percentage of the enolic form of the cyclic ketone increases sharply with concentration (in contrast to acyclic β-diketones). With increased concentration of dimedone in chloroform from 0.020 to 0.094 M, the content of its enolic form increases from 5 to 28%.[151] Cyclohexane-1,3-dione is enolised to a greater extent than dimedone, but the form of its concentration dependence is the same for both compounds. A similar variation

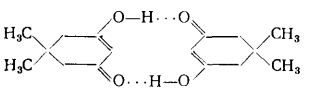
‡ 7.89 and 7.72 p.p.m. for triacetylmethane[143].

of the tautomeric composition of the compounds with concentration is observed also in acetonitrile, despite its high polarity, probably due to the relatively weak proton-acceptor properties of acetonitrile. In proton-accepting solvents the enolic form predominates at all concentrations[16,152]. At higher temperatures, the content of the diketo-form of dimedone and cyclohexane-1,3-dione increases[117]. The dependence of the degree of enolisation on concentration, solvent, and temperature can be explained by the formation of intermolecular hydrogen bonds by the enolic forms with one another and with the proton-accepting solvent molecules.

The ^{1}H NMR spectrum of dimedone contains the signals of both the keto- and enolic forms[72]. The individual signals of the non-equivalent methylene groups of the enolic form§ indicate a low rate of interconversion (the lifetime exceeds one second) of the two equivalent enolic forms of the type (XLIIIB), in contrast to the intrachelate enol-enol transformation of acyclic β-diketones (lifetime $< 10^{-4}$ s).


(XLIIIA)

(XLIIIB)

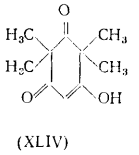

(XLIIIC)

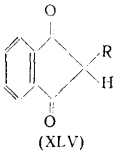
Cyr and Reeves[117] suggested that the tautomerism of dimedone and cyclohexane-1,3-dione in non-polar media can be described by the equilibrium ketone (A) ⇌ monomeric enol (B) ⇌ dimeric enol (B′).

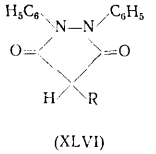
However, Yoge and Mazur[151] demonstrated the presence also of polymeric enolic forms, the fraction of which increases with concentration.

In contrast to β-diketones with intramolecular hydrogen bonds, the enolic proton signal of cyclic β-diketones is significantly displaced towards higher fields on dilution with a non-polar solvent (for dimedone, the values of τ_{OH} extrapolated to high and low concentrations are +0.34 and −2.32 p.p.m. respectively[117]). The observed enolic proton signal is the common signal of the monomeric and all the polymeric enolic forms in view of their rapid interconversion and the increase of τ_{OH} reflects the increase of the relative content of the monomeric form (B) with the free OH group.

^{1}H NMR data[151] indicate a higher rate of inversion of the ring of the diketo-form of dimedone compared with the ring of the enolic form. Bick and Horn[16] showed that the content of the enolic form of syncarpic acid (XLIV) is insignificant in chloroform but increases sharply in the presence of small amounts of water and dimethyl sulphoxide. In acetone the form (XLIV) predominates. The rate of the keto-enol transformation increases sharply (until the merging of the corresponding ^{1}H NMR signals) in the presence of traces of bases.


(XLIV)

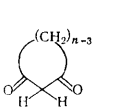

(XLV)

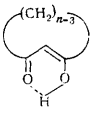

(XLVI)

§ The chemical shifts of the methylene group protons of the enol are close to those of the methyl ether of dimedone[153,154].

The ^{1}H NMR data for five-membered cyclic β-diketones are restricted to indanedione (XLV, R = H) and its 2-phenyl derivative (XLV, R = C_6H_5).[95] The spectra did not show the signals of the enolic form in chloroform and dioxan, in agreement with the general hypotheses concerning the tautomerism of indanediones[155,156]. The enolic form was not observed in any of the 4-alkyl-3,5-dioxo-1,2-diphenylpyrazolidines (XLVI)[157].

There are no literature data on the tautomerism of β-diketones containing between 8 and 10 atoms in the ring¶. For steric reasons, the chelate enolic forms with intramolecular hydrogen bonds are impossible in these compounds. β-Diketones with a large number of ring atoms were investigated by Kirrman and Wakselman[158]. The chelate enolic forms (XLVIIB) of these compounds have been detected; their content increases with ring size (20% for $n = 11$, 60% for $n = 12$, and more than 95% for $n = 14$ and 17 in carbon tetrachloride). The enolic proton signals are close (5 p.p.m.) to the values of τ typical for acyclic β-diketones.


(XLVIIA)


(XLVIIB)

¶ Cyclobutane-1,3-dione[159] and cycloheptane-1,3-dione[160] are weakly enolised.

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