[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Effect of Solvent on the Keto–Enol Tautomerism of Some α-Acylphenylacetonitriles

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The enol contents of solutions of some α-acylphenylacetonitriles have been determined by a spectroscopic method. It has been found that the enol concentration is greater in polar than in non-polar solvents. The results are discussed in terms of the currently accepted theories of keto–enol tautomerism. It is concluded that solvation of the keto form of a tautomeric substance determines the extent of its enolization in hydroxylic solvents while in non-hydroxylic solvents chelation is the decisive factor.

The equilibrium constant of the reaction: keto ⇄ enol, in any solvent is given by the expression[1,2]

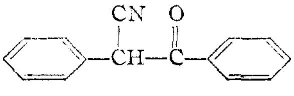
$$K = \frac{C_E}{C_K} = G\frac{S_E}{S_K} \cdots\cdots\cdots\cdots I$$

where C_E and C_K are the concentration of enol and keto forms, G is a constant characteristic of the particular keto–enol system and S_E and S_K are the solubilities of the enol and keto forms in the solvent under consideration. Measurements on acetoacetic ester (see Table II) and on benzoyl camphor[3] show that such compounds are more enolized in non-hydroxylic than in hydroxylic solvents. This conclusion has led to the suggestion that the polarity of the enol is reduced by chelation.

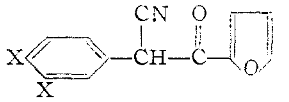
Arndt, Loewe and Ginkök[4] pointed out that since no chelation exists in *o*-hydroxybenzonitrile[5] the enol forms of β-ketonitriles in general should not exist as chelate molecules.[6] Consequently a decrease in enol content might be expected on passing from a hydroxylic to a non-hydroxylic solvent, the polar non-chelate enol being less susceptible to solvation by the latter class of solvents. Unfortunately Arndt, *et al.*,[4] were unable to determine enol contents of solutions of β-ketonitriles in solvents other than ethanol and methanol by the bromine titration method of Meyer.

The application of ultraviolet absorption spectra to the determination of enol contents of solutions of tautomeric substances requires that two conditions be fulfilled. First, the keto and enol forms must absorb light at markedly different wave lengths and secondly, a solution of the pure enol form must be available for comparison of intensity of the enol band. The first condition is satisfied if the double bond of the enol joins into a conjugated system the two isolated chromophores of the keto form. Then solutions of the compound containing appreciable quantities of both forms should show two banded spectra. The second condition is less readily fulfilled since usually the pure enol form is not available. However, the difficulty has been overcome in the past by use of solutions rich in enol,[7] solutions of the enol ether[8] or solutions of the anion of the enol.[9]

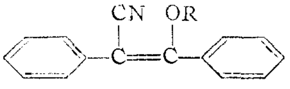
Cyanodesoxybenzoin (I) and α-(2-furoyl)-phenylacetonitrile (II) are ketonitriles which fulfill the first condition mentioned above. Their spectra (Fig. 1, curves 1 and 2) show the expected two-banded form. These two compounds can exist in only one keto and one enol form (exclusive of *cis–trans* isomers of the enol) since the ketenimine (enimine) form (C=C=NH) probably does not exist in neutral solution.[10] This simplifies the allocation of the bands to their respective forms.



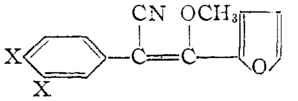
I



II, X = H
VI, X = Cl



III, R = H
IV, R = CH₃



V, X = H
VII, X = Cl

In the case of cyanodesoxybenzoin (I) the allocation of the longer wave length band to the enol form (III) may be made by a comparison with the spectrum of stilbene or α-cyanostilbene (Table I). The comparison of the position of the longer wave length bands in the spectra of I and II with those of the single bands in the spectra of the corresponding methyl enol-ethers (IV and V) (Fig. 1, curves 3 and 4) shows that the maxima of the enols fall at the same wave lengths as the corresponding enol ethers but that the latter have greater intensity. The spectra of IV and V were chosen as the "pure enol" references. In the case of cyanodesoxybenzoin evidence of the association of the short wave length band with the keto form derives from a comparison of its position with that of the maxima in the single banded spectra of the

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[1] G. W. Wheland, "Advanced Organic Chemistry," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 607.

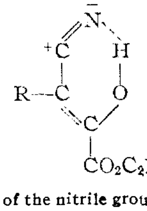
[2] H. Henecka, "Chemie der Beta-Dicarbonyl-Verbindungen, Springer Verlag, Berlin-Göttingen-Heidelberg, 1950, p. 10.

[3] (a) K. H. Meyer, *Ann.*, **380**, 212 (1911); (b) O. Dimroth, *ibid.*, **377**, 127 (1910); **399**, 91 (1913).

[4] F. Arndt, L. Loewe and R. Ginkök, *Rev. Fac. Sci. Istanbul.*, [A XI] 147 (1946).

[5] S. B. Hendricks, O. R. Wulf, G. E. Hilbert and U. Liddel, THIS JOURNAL, **58**, 1991 (1936).

[6] G. S. Skinner, J. A. Gladner and R. F. Heitmiller (*ibid.*, **73**, 2230 (1951)) presented infrared spectroscopic data on substituted ethyl β-cyano-α-hydroxycinnamates which they believe indicate that, in the solid state, these compounds exist in the chelate form. In view of the linear nature of the nitrile groups, however, it is more likely that the hydrogen bonding is intermolecular.



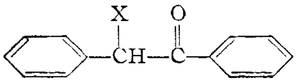
[7] R. A. Morton, A. Hassan and T. C. Calloway, *J. Chem. Soc.*, 883 (1934).

[8] A. Hantzsch, *Ber.*, **43**, 3049 (1910); **44**, 1771 (1911).

[9] Buu-Hoï and P. Cagniant, *Bull. soc. chim.*, [5] **10**, 251 (1943).

[10] F. Arndt, H. Scholz and E. Frobel, *Ann.*, **521**, 95 (1935).

virtually unenolized ketones desoxybenzoin (VIII), α-chlorodesoxybenzoin (IX) and acetophenone (Table I). Since the enol ethers (IV and V) and hence probably the corresponding enols show quite marked absorption in the region of the keto maxima it is not possible to calculate the keto contents of solutions using the above compounds as references.



VIII, X = H
IX, X = Cl

TABLE I

MAIN ABSORPTION SPECTRA OF REFERENCE SUBSTANCES IN REGION 230–400 Mμ

Substance	$\lambda_{\max}$ (ethanol), mμ	ϵ_{mol}
cis-Stilbene[11]	280	13,500
trans-Stilbene[11]	295	27,000
α-Cyanostilbene	313	21,000
Acetophenone[12]	241[a]	12,590
Desoxybenzoin	245	12,600
α-Chlorodesoxybenzoin	250	13,700

[a] $\lambda_{\max}$ (hexane) 235 mμ; (water) 245 mμ intensity same as above.

A source of uncertainty in the spectroscopic estimates of enol contents of solutions of β-ketonitriles such as I and II is the possibility of *cis–trans* isomerism in the enol and further the possibility that the main enol constituent of the solution and the enol ether used as the "pure enol" reference may have different configurations. The extent to which *cis–trans* isomerism could affect the results can be seen by a comparison of the spectra of *cis*- and *trans*-stilbene (Table I). That the enol ether and the main isomer of the enol of cyanodesoxybenzoin (III) in ether have the same configuration is probable since treatment of I (or III) with diazomethane,[13] a procedure believed to involve no *cis–trans* interconversion,[14,15] gives only one enol ether IV in good yield. The assumption that the changes of intensity of the enol band in the spectra of the ketonitriles in various solvents are due mainly to changes in enol content, rather than to changes in the geometrical configuration of the enols themselves, finds confirmation in the corresponding changes in intensity of the keto band. While both the wave length and the intensity of the enol ether maxima are unchanged by change of solvent the enol band of the β-ketonitriles shows a slight bathochromic shift in hydroxylic solvents. This slight shift has been ignored in calculating the enol contents, the intensity at the maximum being used in every instance. For the reasons outlined above it is believed that the absolute accuracy of the enol contents obtained by the spectroscopic method is not great. However, they are adequate to illustrate the phenomena discussed.

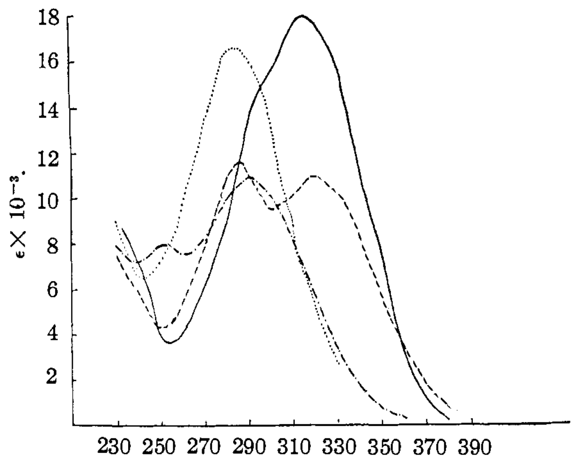


Fig. 1.—·—·—·—, curve 1, cyanodesoxybenzoin; — — —, curve 2, α-(2-furoyl)phenylacetonitrile; ......, curve 3, cyanodesoxybenzoin methyl ether (α,β-diphenyl-β-methoxyacrylonitrile); ——, curve 4, α-phenyl-β-methoxy-β-(2-furyl)acrylonitrile. All in ethanol at 10 mg./l.

The enol contents of solutions of I, II and VI in a variety of solvents are given in Table II.

TABLE II

ENOL CONTENTS OF SOLUTIONS OF β-KETONITRILES

Solvent	I[a,b] $^{\epsilon}\lambda_{\max}$	I[a,b] Enol, %	II[a,c] $^{\epsilon}\lambda_{\max}$	II[a,c] Enol, %	VI[a,d] $^{\epsilon}\lambda_{\max}$	VI[a,d] Enol, %	Ethyl aceto-acetate[3] enol, %
Water	7,700	47	6,200	34	[e]	..	0.4
Methanol	10,000	60	10,900	60	18,000	87	6.9
Ethanol	11,000	67	11,000	61	18,900	91	10.5
n-Amyl alcohol	12,500	76	12,300	68	....	..	15.3
Ether	9,150	55	7,800	43	17,000	83	27.0
Ether:hexane (1:1)	6,520	39	....	..	16,600	81	..
Hexane:ether (9:1)	3,320	20	....	..	10,300	50	..
Hexane	2,200	13	1,500	8	[e]	..	46.4

[a] Concentration 10 mg./l. [b] IV $\epsilon_{\max}$ = 16,500, Fig. 1 curve 3. [c] V $\epsilon_{\max}$ = 18,000, Fig. 1 curve 4. [d] The absorption spectra of VI and its enol ether VII are not shown in the figure. The values for VI in ethanol are: $\lambda_{\max}$ 280 mμ; $\lambda_{\max}$ 340 mμ; in hexane–ether the second maximum is at 328 mμ. The spectrum of VII in ethanol has $\lambda_{\max}$ 325 mμ, ε 20,600. [e] Not sufficiently soluble.

The values of the enol contents given in Table II show clearly that the β-ketonitriles, the enols of which are not chelate, are less enolized in nonhydroxylic than in hydroxylic solvents. This is to be expected since the solubility of the polar nonchelate enol in non-polar solvents should not be high, thus causing a decrease in the relative solubility term S_E/S_K in equation I. Arndt, *et al.*,[4] showed that, contrary to expectation from the above arguments, certain β-ketonitriles are more enolized in ethanol than in methanol. Although I, II and VI appear to be enolized to about the same extent in these two solvents there appears to be an over-all increase in enolization in the series: water < methanol ≤ ethanol < *n*-amyl alcohol, as in the case of β-dicarbonyl compounds the enols of which are capable of chelation.[3] It is apparent that the

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[11] A. Smakula and A. Wassermann, *Z. physik. Chem.*, **155**, 353 (1931).

[12] G. Scheibe, *Ber.*, **59**, 2617 (1926).

[13] P. B. Russell and N. Whittaker, THIS JOURNAL, **74**, 1310 (1952).

[14] F. Arndt and L. Loewe, *Ber.*, **71**, 1627 (1938).

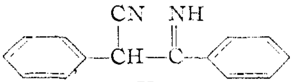
[15] B. Eistert, F. Arndt, L. Loewe and E. Ayça, *Chem. Ber.*, **84**, 156 (1951).

ability to solvate (including hydrate) should decrease from water to *n*-amyl alcohol and thus the above results are explained on the assumption that solvation by hydroxylic solvents of the keto form shifts the keto–enol equilibrium of these non-chelate β-ketonitriles in favor of this form. Consequently the relative solubility term S_E/S_K and with it the enol content, should increase from water to *n*-amyl alcohol. Thus it appears that while solvation of the keto form of a tautomeric substance is the important factor determining the extent of enolization in hydroxylic solvents, in non-hydroxylic solvents the ability to form a chelate enol is decisive.

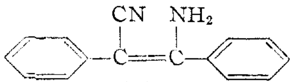
Evidence that the views expressed above are substantially correct is available from other sources. Schwarzenbach and Wittwer[16] have shown that simple monoketones (*e.g.*, acetone) where no possibility of chelation exists are less enolized in aqueous solution than in the pure liquid. Here there is no reason to expect that the solubility of the enol forms should be less in water than in the pure ketone but solvation favors the keto form and the equilibrium is shifted in this direction. Further, Eistert and Henecka[17] have shown that certain derivatives of β-dicarbonyl compounds in which chelation of the enol is prevented are more enolized in alcohol or water than in benzene.

Comparisons of the enol content of solutions of II and VI in any solvent reveal that VI shows a much greater tendency to enolize. Since it differs from II only in carrying chlorine atoms at the 3- and 4-positions of the benzene ring the main effect is probably the increase in the ease of removal of the proton from the α-carbon atom which would in general be expected to aid enolization.

Examination of the spectrum of α-cyano-β-imino-α,β-diphenylethane (X) in alcohol reveals only one intense band (λ_{max} 308 mμ; ϵ = 1300).



Xa



Xb

The position of this sharp band corresponds with that of the band which has been assigned to the enol form of cyandesoxybenzoin (Fig. 1, curve 1). The replacement of C=O by C=N— causes little change in wave length of the absorption maximum of a conjugated chromophore,[18] and thus it appears that, in ethanolic solution, α-cyano-β-imino-α,β-diphenylethane exists almost entirely as the enamine form (Xb) rather than the ketimine form (Xa).

Experimental

Compounds.—The following compounds were prepared by previously described methods: Cyanodesoxybenzoin[19]; α-cyanostilbene[20]; α-(2-furoyl)-phenylacetonitrile[13]; α-(2-furoyl)-3,4-dichlorophenylacetonitrile[13]; α-β-diphenyl-β-methoxyacrylonitrile[13]; α-phenyl-β-(2-furyl)-β-methoxyacrylonitrile[13]; α-(3,4-dichlorophenyl)-β-(2-furyl)-β-methoxyacrylonitrile[13]; α-chlorodesoxybenzoin[21]; α-cyano-β-imino-α,β-diphenylethane.[22]

Before spectroscopic measurements were made the compounds were crystallized from a solvent transparent in the region of the spectrum under consideration (230–400 mμ).

Solutions.—All solutions of tautomeric substances were made up to the required concentration (10 mg./l.) by tenfold dilution of a solution in the solvent under consideration with this solvent. These solutions were allowed to stand at room temperature for one-half hour, a period found to be sufficient for equilibrium to be established.

Absorption Spectra.—The spectra were determined in a Beckman model D.U. quartz spectrophotometer (cell length 1 cm.).

Acknowledgment.—The author wishes to thank Miss Phoebe Lee Graham for the determination of the spectra.

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[16] G. Schwarzenbach and W. Wittwer, *Helv. Chim. Acta*, **30**, 659 (1947); see also reference 1, page 609.

[17] Private communication from Dr. Bernd Eistert (Technische Hochschule, Darmstadt).

[18] E. A. Braude, *Ann. Rep. Chem. Soc.*, **42**, 105 (1945).

[19] W. Wislicenus, H. Eichert and M. Marquardt, *Ann.*, **436**, 88 (1924).

[20] R. v. Walther, *J. prakt. Chem.*, [2] **53**, 454 (1896).

[21] A. M. Ward, *J. Chem. Soc.*, 1541 (1929).

[22] E. F. J. Atkinson, H. Ingham and J. F. Thorpe, *ibid.*, **91**, 578 (1907).