47 kcal. Hence it becomes likely that the actual transition state does not go through an intermediate such as II in which the bond is completely broken and that the rearrangement is a concerted process.

Corroborative evidence is that the reversible *cis–trans* isomerization reaction of 2-methyl[2.1.0]-bicyclopentane appears to have an activation energy of 39 kcal./mole,[13] which is also much larger than the maximum figure of 24 kcal. for complete release of bicyclic strain in the transition state. Hence, strainfree II is also not the transition state for this geometrical isomerization. This reaction will be discussed more thoroughly in another paper.

(13) J. P. Chesick, unpublished work.

Acknowledgments.—This work was supported by the Chemical Science Division, Air Force Office of Scientific Research under contract AF 49 (638) 722. One of us (M. L. H.) wishes to thank the Monsanto Chemical Co. for a summer fellowship in 1961.

This paper comprises a portion of the dissertation to be submitted by M. L. H. in partial fulfillment of the requirements for the Ph.D. in the Graduate School of Yale University.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Nuclear Magnetic Resonance Studies of Keto-enol Equilibria. III. α,β-Unsaturated-β-ketoamines

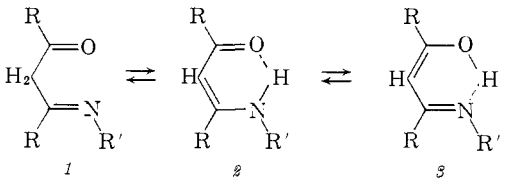
BY G. O. DUDEK AND R. H. HOLM

RECEIVED DECEMBER 12, 1961

The proton resonance spectra of a number of compounds obtained from the 1:1 condensation of a β-diketone with a monoamine have been measured. Of the three tautomeric possibilities, these compounds exist predominantly in the ketamine form —C(=O)—CH=C(—)—NHR. Proof of this structure is obtained from the observed spin-spin splittings of N–H with the α-protons of R. The position of the tautomeric equilibrium could not be altered by large changes in the nature of the solvent nor by variation of the substituent R. The preferential existence of the ketamine form over the ketimine and enimine forms is ascribed to greater stabilization through resonance and hydrogen-bonding.

Introduction

In the first paper[1] of this series proton resonance studies were made of the 2:1 condensation products of acetylacetone and various diamines. These bases are capable of existing in any of three tautomeric forms, the Schiff base *1*, the ketamine *2* and the enimine *3*. The interchange between the last two tautomers involves a small displacement in the



1 *2* *3*

equilibrium position of the acidic proton. It was observed that in solution, with acetone as the sole exception among the solvents studied, these compounds were virtually completely tautomerized in the ketamine form *2*. Structures were inferred from the presence of spin–spin coupling of the α protons of R′ with that on the nitrogen (J = 6–7 c.p.s.). For example, if R′ is a tri- or tetramethylene bridging group, the spectrum of this group is that of form *2* since the α protons are split into a quartet. When the bridging group is dimethylene, a triplet of peculiar shape[2] arises, but in this case the proton is also located on the nitrogen for the signal was found to collapse to a singlet upon deuteration. The prototype of the series, "bis-(acetylacetone)-ethylenediimine," is then properly described as the di-chelated form of N,N′-di-(1-methyl-3-oxobutylidene)-ethylenediamine. The observed composition of the solutions was found to be insensitive to solvent acidity and polarity and to substituent effects at the carbonyl carbon. This behavior is in strong contrast to that of β-dicarbonyls such as acetylacetone and ethylacetoacetate whose enolic content, as assessed by proton resonance or more classical techniques, is strongly dependent on the nature of the solvent.[3–5]

The structure of bases derived from the 1:1 condensation of β-dicarbonyls and primary monoamines has not yet been definitely established, although strong presumptive evidence, principally from infrared studies, favors the ketamine form. Cromwell[6,7] has consistently described these compounds as α,β-unsaturated-β-ketoamines and has reported them to behave chemically more like vinylogs of amides than like ketones or vinylamines.[7] The infrared data of Cromwell, *et al.*,[7] Weinstein and Wyman,[8] Holtzclaw, *et al.*,[9] and Witkop[10] strongly support structure *2* for bases

(1) G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1961).

(2) The nature of this triplet has been further clarified; J. D. Baldeschwieler, R. H. Holm and G. O. Dudek, to be published.

(3) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

(4) M. Geissner-Prettre, *Compt. rend.*, **250**, 2547 (1960).

(5) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., pp. 663–702.

(6) N. H. Cromwell, *Chem. Revs.*, **38**, 83 (1946).

(7) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949).

(8) J. Weinstein and G. M. Wyman, *J. Org. Chem.*, **23**, 1618 (1958).

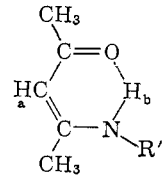
(9) H. F. Holtzclaw, Jr., J. P. Collman and R. M. Alire, *J. Am. Chem. Soc.*, **80**, 1100 (1958).

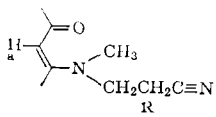
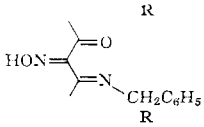
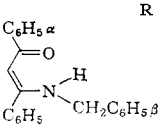
(10) B. Witkop, *ibid.*, **78**, 2873 (1956).

TABLE I

PROTON RESONANCE DATA FOR COMPOUNDS OF THE TYPE

IN P.P.M. RELATIVE TO TETRAMETHYLSILANE



R	Solvent	Methyls	R'^{a} (J)[b]	$H\alpha$	$H\beta$
$-CH_3$	CCl_4	1.86	2.94 (5.1)	4.83	10.6
	$CHCl_3$	1.91, 1.99	2.93 (5.3)	4.98	10.7
	C_6H_6	1.32, 2.05	2.1 (h)	4.90	11.1
$-CH_2CH_3$	CCl_4	1.27,[c] 1.86	3.28[d]	4.78	10.7
$-CH_2C_6H_5$	Neat	1.70, 1.92	4.23 (6.3)[g]	4.99	11.3[e]
	CCl_4	1.83, 1.91	4.41 (6.8)	4.89	11.2
	$CDCl_3$ (0.25 M)	1.91, 2.02	4.45 (6.4)[f]	5.04	11.2
	(0.66 M)	1.89, 2.02	4.43 (6.7)	5.03	11.2
	C_6H_6	1.37, 2.05	3.78 (6.8)	4.92	11.5
	C_5H_5N	1.80, 2.08	4.36 (6.4)	5.09	11.5
	$C_6H_5NO_2$	1.90, 2.05	4.42 (6.4)	5.03	11.3
	CH_2COCH_3 (0.66 M)	[h]	4.49 (6.6)	5.01	11.1
$-CH(C_6H_5)_2$	$CDCl_3$	1.88, 2.03	5.73 (8.2)	5.05	11.7
	CS_2	1.79, 1.87	5.60 (8.9)	4.90	11.5
$-CH_2CH_2C\equiv N$	$CDCl_3$	1.99, 2.01	2.59 (6.8)[e] 3.58 (6.7)[e]	5.05	10.9
	C_6H_6	1.35, 1.97	1.43 (6.8)[c] 2.50 (6.7)[e]	4.82	10.9
$-CH_2CH_2OH$	CCl_4	1.88, 1.92	3.33 (5.4)[c] 3.61 (5.4)[e]	4.82	10.7
$-CH_2CF_3$[i]	CCl_4 (0.26 M / 0.70 M)	1.95	3.78 (7.4)	5.00	10.8
	$CDCl_3$	1.96, 2.04	3.78 (7.4)	5.13	10.9
	C_6H_5N	1.90, 2.04	4.04 (7.0)	5.13	11.3
	$CH_3C\equiv N$	[h]	3.94 (7.0)	5.14	10.8
	$CDCl_3$	2.09, 2.52, 3.02	2.60 (6.7)[c] 3.64 (6.8)[c]	5.11	..
	C_6H_6	2.09, 2.20, 2.29	2.61 (6.7)[c] 1.53 (6.8)[c]	4.84	..
	$CDCl_3$	2.45, 2.56	4.69	..	..
	CCl_4	C_6H_5 = 7.20β' 7.33α'	4.36 (6.9)	5.74	11.8
	CH_3COCH_3	C_6H_5 = 7.29β 7.49α	4.47 (6.7)	5.87	11.8

[a] Band center. [b] In c.p.s. [c] Triplet. [d] Quintet. [e] Quartet. [f] To a singlet upon deuteriation. [g] 6.3 c.p.s. at 40 Mcs. [h] Not observed. [i] J_{HF} = 8.8–9.2 c.p.s.

obtained from a variety of β-dicarbonyl compounds and diverse amines but do not unequivocally eliminate structure *3* in all cases, particularly when the parent keto compound is acetylacetone.[9] Recently, Martin, Janusonis, and Martin[11a] measured the acidic dissociation constants of bases derived from substituted anilines (R′ = aryl) and have suggested the possible major importance of structure *3* in solution, as judged from the inertness of the dissociation constant to the aromatic substituent.

(11) (a) D. F. Martin, G. A. Janusonis and B. B. Martin, *J. Am. Chem. Soc.*, **83**, 73 (1961); (b) G. O. Dudek and R. H. Holm, *ibid.*, **83**, 3914 (1961).

We report here the results of a proton resonance study of a variety of bases obtained from monoamines and β-dicarbonyls, with acetylacetone (R = CH_3) as the principal parent keto compound. These results serve to establish unambiguously the nature of the species in solution and allow further assessment of the stability of the ketamine form *2*. Certain preliminary results have already been reported.[11b]

Experimental

Spectra.—Spectra were obtained on Varian V-4300 or HR-60 spectrometers at 40 and 60 Mc. and on a Varian

A-60 spectrometer. Line positions were determined by an interpolation method using an audio oscillator monitored by a frequency counter and are accurate to ± 0.3 c./sec. or 0.005 p.p.m. at 60 Mc. except when the band width precluded such accuracy. Double resonance spectra were recorded on the HR-60 spectrometer using apparatus constructed by Dr. J. D. Baldeschwieler of this department to whom we are grateful for these spectra.

Solutions.—Solutions were prepared as previously described[1] using tetramethylsilane as the internal zero of reference. Concentrations were approximately 0.2 *M*. Concentration variations produced no significant alterations in the chemical shift data reported in Tables I and II.

Addition of ~0.4 *M* water to a pyridine solution of 4-benzylamino-3-penten-2-one produced no significant change in the spectrum.

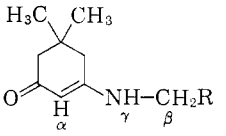
Preparation of Compounds.—The following compounds were prepared by previously published procedures

Compound	M.p., °C. (uncorr.)	Ref.	M.p., °C. (lit.)
4-Methylamino-3-penten-2-one	39–40	9	40–41
4-Ethylamino-3-penten-2-one	Oil	13	
4-Benzylamino-3-penten-2-one[12a]	23–24.5	14	24
4-Benzylimino-pentan-2-one-3-oxime	123–124	14	126–127
1,3-Diphenyl-3-benzylamino-2-propene-one	98–99	15	101
4-(β-Cyanoethyl)amino-3-penten-2-one	89–90	7	89.5–90
4-N-(β-cyanoethyl)methylamino-3-penten-2-one	70.2–70.8	7	69–70
4-(β-Hydroxyethyl)amino-3-penten-2-one	73.6–74.4	16	73
N-benzylsalicylaldimine	24–26	17	

The following compounds were prepared for the first time in this work and were easily obtained from the appropriate amine and carbonyl compound by standard procedures.[6]

TABLE II

PROTON RESONANCE DATA FOR SUBSTITUTED 5,5-DIMETHYL-2-CYCLOHEXENE-ONE'S IN P.P.M. RELATIVE TO TETRAMETHYLSILANE



Solvent	Methyls	Methylenes	$H\alpha$	$H\beta^a$ (J)[b]	$H\gamma$
		R = $-C_6H_5$			
$CDCl_3$ (0.7 *M*)	1.04	2.10, 2.23	5.08	4.20 (5.3)	5.9
(0.3 *M*)	1.06	2.14, 2.22	5.14	4.22 (5.4)[c]	4.8
(0.16 *M*)	1.07	2.18	5.17	4.22 (5.2)	4.7
C_6H_6	0.85	1.94, 2.08	5.28	3.82 (5.3)	5.7
CF_3COOH	1.21	2.63	6.09	4.69 (5.1)	[d]
Pyridine	1.02	2.31, 2.41	5.52	4.36 (5.5)	4.9
		R = $-CF_3$			
$CDCl_3$	1.08	2.19, 2.26	5.23	3.71 J_{HH} = 6.8, J_{HF} = 8.8	
Pyridine	0.99	2.31, 2.37	5.71	4.08 J_{HH} = 6.9, J_{HF} = 9.0	[d]

[a] Center of doublet. [b] Cycles/sec. [c] In deuteriated form, a singlet. [d] Unobservable.

4-(1,1-Diphenylmethyl)-amino-3-penten-2-one.—Colorless prisms from benzene–cyclohexane or acetonitrile, m.p. 139.0–139.8°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found (independent duplicate analyses): C, 81.39; H, 6.63; N, 5.41; and C, 80.71; H, 7.23; N, 5.36.

4-(β,β,β-Trifluoroethyl)-amino-3-penten-2-one.—White plates from cyclohexane or by sublimation, m.p. 66.0–66.6°.

Anal. Calcd. for $C_7H_{10}F_3NO$: C, 46.40; H, 5.56; N, 7.78. Found: C: 46.23; H, 5.73; N, 7.82.

3-Benzylamino-5,5-dimethyl-2-cyclohexen-one.[12b]—White needles from benzene–hexane, m.p. 129.2–130.0°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.82; H, 8.50; N, 6.25.

3-(β,β,β-Trifluoroethyl)-amino-5,5-dimethyl-2-cyclohexen-one.—White plates from ethyl acetate-cyclohexane, m.p. 170.8–171.3°.

Anal. Calcd. for $C_{10}H_{14}F_3NO$: C, 54.29; H, 6.38; N, 6.33. Found: C, 54.55; H, 6.40; N, 6.32.

o,o'-Dihydroxybenzophenone-N-benzylimine.[12b]—Yellow prisms from absolute ethanol-ligroin, m.p. 195.2–196.2°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.97; H, 5.63; N, 4.77.

Results and Discussion

Proton resonance data for compounds examined in this work are set out in Tables I and II. Comparison of chemical shift data of the diamines previously studied[1] with those of bases derived from acetylacetone reveals the expected similarities. The signals of the R′ substituents are simpler than those of the hydrocarbon bridges in the diamine bases, and the clearly resolvable splittings of the α-protons of the R′ group, together with the following evidence, leave no doubt that the highly unshielded protons are bound to nitrogen. Hence, these bases exist in solution in the ketamine form *2*. The spectrum of the R′ = benzyl derivative is shown in Fig. 1. No other signals due to a low

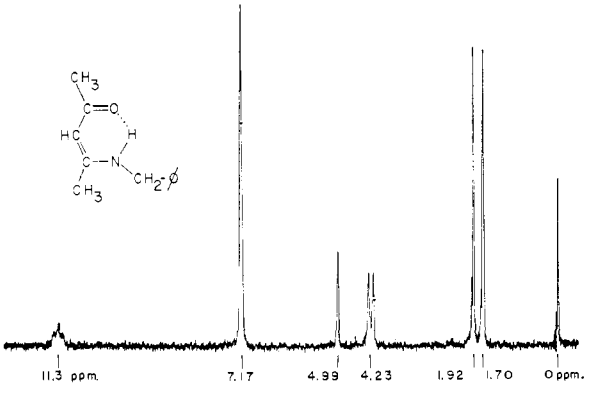


Fig. 1.—Spectrum of neat 4-benzylamino-3-penten-2-one at 60 Mcs.

field proton or R′ group could be detected in any solution, so it is concluded that under these conditions the compounds exist to an extent > 95% in the ketamine form. The presence of a hydrogen-bonded chelate ring is inferred here from large paramagnetic shifts of the N–H protons (compare Tables I and II).

(12) (a) Deuteriated form prepared by shaking oil well with D_2O, separating layers and drying *in vacuo*. (b) Deuteriated forms were prepared by crystallization from warm dioxane solution by addition of excess D_2O.

(13) A. Combes and C. Combes, *Bull. Soc. Chim. France* [3], **7**, 779 (1892).

(14) L. Rügheimer and G. Ritter, *Ber.*, **45**, 1332 (1912).

(15) N. H. Cromwell, R. D. Babson and C. E. Harris, *J. Am. Chem. Soc.*, **65**, 312 (1943).

(16) L. Knorr and P. Rössler, *Ber.*, **36**, 1278 (1903).

(17) J. Hires, *Acta Szegediensis, Acta Phys. et Chim.* [N.S.], **4**, 120 (1958).

The location of the highly unshielded proton in the R′ = benzyl base, which may be considered representative and which has been the most completely studied, can be certified from other evidence: (1) the splitting of the methylene group is identical at 40 and 60 Mc.; (2) deuteriation of the acidic proton results in a collapse of the doublet and results in a single signal (~$2^1/_2$ cycles wide) at 4.45 p.p.m. (60 Mc.); (3) double irradiation under conditions sufficient to destroy the N^{14}-proton spin–spin splitting in pyrrole or dry ammonia has no effect on the doublet; (4) the low field proton signal in the neat liquid is distinctly split into a triplet (J~6 c.p.s.) by coupling with methylene protons (*cf.* Fig. 2b); as is expected from a comparison of the

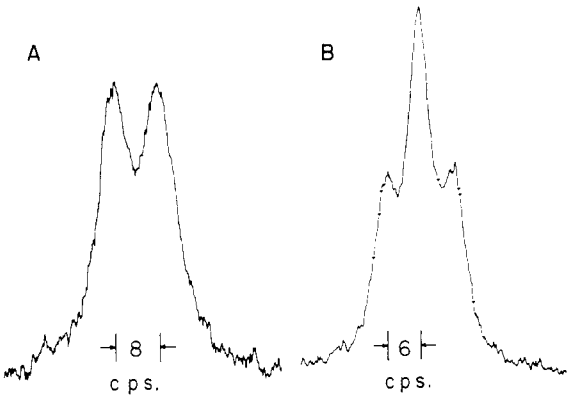
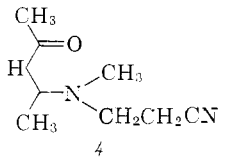


Fig. 2.—Spectra (at 60 Mcs.) of the acidic proton in: (A) 4-(1,1-diphenylmethylamino)-3-penten-2-one (satd. soln. in $CDCl_3$); (B) neat 4-benzylamino-3-penten-2-one.

coupling constant with available J_{N14-H} values,[18] this multiplet is not collapsed by double irradiation; furthermore, the similar signal of the R′ = CH-$(C_6H_5)_2$ compound in $CDCl_3$ is clearly split into a *doublet* with J = 8 c.p.s. (Fig. 2a); (5) the related base 4-N-(β-cyanoethyl)-methylamino-3-penten-2-one, *4*, shows the expected triplet feature for each methylene of the β-cyanoethyl group. This is to be compared with 4-(β-cyanoethyl)-amino-3-penten-2-one in which the α protons of the same group



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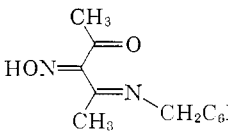
are split into a quartet. We have also examined 4-benzylimino-pentan-2-one-3-oxime, *5*, with a similar result, indicating that the compound is correctly formulated as the tautomer (but not necessarily as the isomer) shown in *5*. In contrast, N-benzylsalicylaldimine exhibits an unsplit methylene signal, indicative of the expected imine structure. The above results buttress our earlier conclusions[1] that the analogous bases derived from diamines exist in the ketamine form and present unequivocal evidence that the acidic proton in the aliphatic bases of Tables I and II is primarily bound to the nitrogen[19] and is exchanging at a rate slower than



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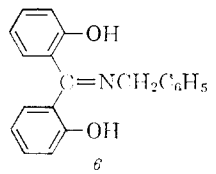


6

~0.03 sec. Whether the proton resides in a single or double minimum cannot be ascertained at present.

As is evident from Table I, wide variations of solvent basicity and polarity have no observable influence on the position of equilibrium, an effect previously found in the diamine compounds.[1] In contrast to the diamine bases, acetone as a solvent has no effect on the spectra of the monoamine bases. The solvent variation in the coupling constant (J), although only slightly above the experimental error, is real as evidenced by the superposition of several spectra of the trifluoroethyl derivatives in various solvents (using the 50 cps. sweep of the Varian A-60).

As with the diamine bases the spectra in benzene reveal strong differentiation of the methyl signals and a diamagnetic shift of the R proton signals exceeding that expected for a normal aromatic solvent effect. Here it appears likely that a specific solute–solvent interaction is operative similar to that previously proposed.[1] One methyl group and the R′ protons gain additional diamagnetic shielding from the ring current effect brought about by a molecule of solvent weakly hydrogen-bonding with the carbonyl oxygen. In the benzyl dimedone base (*cf.* Table II) in which this hydrogen bonding is also possible but without the same consequences, a normal aromatic diamagnetic solvent shift (~0.1–0.2 p.p.m.) is observed.

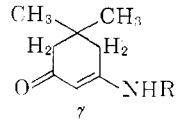
In addition to the inertness of the position of equilibrium to solvent effects, it has not been possible to effect formation of tautomers other than the ketamine by variation of the structure and electronic properties of the R′ group. The insensitivity to inductive effects is seen by the detection of only the ketamine form in compounds carrying R′ substituents of diverse σ^* values, from ethyl (−0.10) to β,β,β-trifluoroethyl (+0.92).[20]

(18) J. D. Baldeschwieler, *J. Chem. Phys.*, **36**, 152 (1962); R. A. Ogg and J. D. Ray, *ibid.*, **26**, 1339, 1515 (1957).

(19) The presence of a split methylene signal is of itself insufficient proof of the existence of an N–H tautomer. For example, we have recently examined the benzyl Schiff base of *o,o′*-dihydroxybenzophenone, the structure of which is anticipated as *6*. The methylene signal at 4.80 p.p.m. in pyridine at 60 Mc. is clearly split into a doublet (separation 3.2 ± 0.2 c./sec.) which persists on deuteration. Examination of a saturated solution in pyridine at 40 and 60 Mc. reveals a simple AB spectrum which upon analysis yields J = 16 c.p.s. and δ ~0.18 p.p.m.; the central doublet splitting at 40 Mc. is predicted to be 1.4 ± 0.2 c.p.s. compared to 1.1 ± 0.3 c.p.s. observed.

(20) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 619.

The trifluoromethyl group, while effective in reducing the basicity of ethylamine by 5 pK_b units,[21] preserves the trifluoroethyl compound in the ketamine form: here the methylene protons are split into a quintet whereas in trifluoroethanol a quartet is observed. It must further be noted that stability of the ketamine form is not necessarily a consequence of intramolecular hydrogen bonding because it also found in the benzyl and trifluoroethyl bases *7* derived from dimedone (*cf.* Table II).



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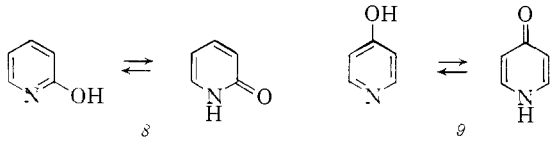
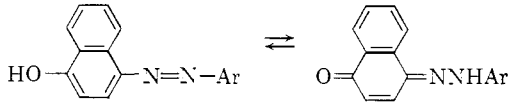
The relative stability of the ketamine form appears to be a particular example of the rather general tendency of nitrogen to form as few double bonds as possible, particularly when carbonyl linkages can be formed. A classic example, discussed in detail by Albert,[22,23] is the lactim-lactam equilibrium which heavily favors the pyridone form

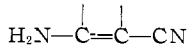


8 *9*

in the solid and neutral aqueous solution. Additionally, the 2- and 4-amino pyridines exist in solution as aromatic amines rather than exocyclic imines.[24,25] Another example is that of the solution equilibrium of arylazonaphthols, *e.g.*

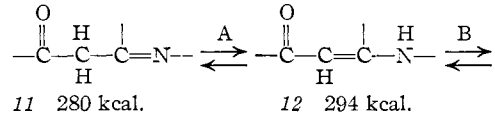


in which the tautomers are often of comparable stability.[26] Recently, Baldwin[27] has shown that enaminonitriles are best represented by *10* rather than by the mono- or diimine forms. Further examples and discussion of this general type of tautomerism are given by Wheland.[28]

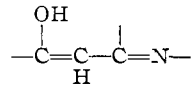


10

In order to explain the marked stability of the ketamine over the enimine and ketimine forms, the free energy changes connected with the general equilibria *11* ⇄ *12* (A) and *13* ⇄ *12* (B) are particularly desirable. However, because of the detection



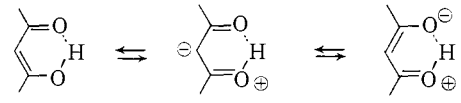
11 280 kcal. *12* 294 kcal.



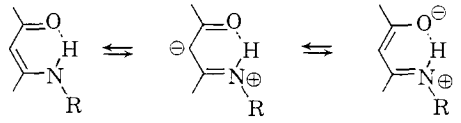
13 295 kcal.

of only one tautomer in all cases, semi-quantitative estimates are not possible other than that $-\Delta F \geq$ 1.8 kcal./mole since the equilibrium constants for A and B equal or exceed 20 from experiment. Nevertheless, the source of the relative stabilization of *12* can be predicted and an estimate of the stabilization energy made. For the fragments *11*, *12* and *13* heats of combustion have been calculated by the method of Klages[29] as described by Wheland.[30] The values obtained (gaseous, 25°, 1 atm.) are set out above. We assume the energy difference between *12* and *13* and *11* to hold approximately in non-polar solvents as well. Lower limits on the enthalpies of the two equilibria can be set by assuming that $\Delta S_B \sim 0$ and that ΔS_A can be approximated by the keto–enol entropy change in pure acetylacetone. Using the data of Reeves[3] $-T\Delta S(25°) \sim 1.8$ kcal./mole is calculated for this reaction. Hence, $-\Delta H_A > \sim 3.6$ kcal./mole and $-\Delta H_B > 1.8$ kcal./mole, but of course the relative magnitudes cannot be fixed.

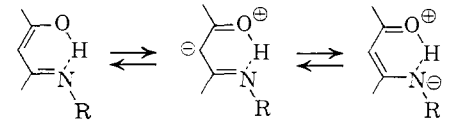
A stabilization energy of $> \sim 1.8$ kcal. is required to account for the stability of *12* relative to *11*. That this is a reasonable estimate can be shown by use of an apparently accurate heat of combustion of acetylacetone. For a liquid of unspecified keto–enol content Nicholson[31] has obtained $-\Delta H_c^0 =$ 642.20 ± 0.36 kcal./mole (25°, 1 atm). Assuming the equilibrium liquid (*i.e.*, 81% enol[3]) we calculate 658 kcal./mole.[30] The difference of ~16 kcal. can be ascribed to additional stability of the enol imparted by hydrogen bonding and resonance of the type



The stabilization of *12* and to a lesser extent, of *13*, must also be accomplished by resonance and hydrogen-bonding of a similar nature. It seems very likely that resonance interaction in the ketamine form is intrinsically more stabilizing



than that in the enimine form in which the negative



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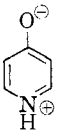
charge cannot be delocalized on oxygen. The difference in stabilization energies between *12* and *13* cannot be fixed other than that it must exceed 1.8 kcal./mole to account for the observed predominance of *12*.

The ketamine resonance is formally similar to that of aliphatic amides for which the resonance energy has been estimated as 16–21 kcal./mole.[32,33] Additionally, 4-pyridone, *9*, is related to *12* in that they both may be considered vinylogous amides. To account for the stability of the keto form, its acidity and aromatic character, contribution from *14* has been given considerable weight.[22,23]

Using an acid–base argument the ketamine stability is reasonable. In water acetylacetone enol has $pK_a \approx 9$,[34] form *2* (R′ = aryl) 13–14[11] and 2:1 condensate of acetylacetone and cyclohexanediamine > 14.[35] A proton on an enolic



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oxygen is more acidic in these cases than a proton on nitrogen by a factor > 10^4 (or $\sim 5^1/_2$ kcal.). It is thus not surprising that substituent variation has no effect on the observable equilibrium composition of the solutions.

Acknowledgments.—Financial support by the National Science Foundation and the Milton Fund of Harvard University is gratefully acknowledged.

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Thermodynamic Data for the Association of Phenol with a Series of Amides

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Thermodynamic data for the formation of addition compounds of phenol with N,N-dimethylformamide (DMF), N,N-dimethylpropionamide (DMP) and N,N-dimethyltrichloroacetamide (DMTCA) are reported. The equilibrium constants can be combined with those previously reported for N,N-dimethylacetamide (DMA) and N,N-dimethylmonochloroacetamide (DMMCA) to give the following series: DMA > DMP > DMF > DMMCA > DMTCA. The heats of formation of the phenol adducts are: -6.4 ± 0.3; -6.4 ± 0.2; -6.1 ± 0.4; -4.7 ± 0.5; -3.8 ± 0.5 kcal. mole^{-1}, respectively. The equilibrium constants obtained do not correlate with the σ^* values of the R substituents in the series $RC(=O)N(CH_3)_2$. An explanation is proposed.

Introduction

In earlier articles we have reported[2,3] equilibrium constants and heats of formation for the adducts of iodine with N,N-dimethylformamide (DMF); N,N-dimethylacetamide (DMA); N,N-dimethylpropionamide (DMP); N,N-dimethylmonochloroacetamide (DMMCA); and N,N-dimethyltrichloroacetamide (DMTCA). It was found that the equilibrium constants for this series of amides $[RC(=O)N(CH_3)_2]$ deviated from that predicted from the σ^* value of the R substituent. The DMP value is too low and the DMTCA value is too high. Even though DMP and DMMCA have similar shapes, a low value was not obtained for DMMCA. These results were explained by considering the rotamers that can exist for these amides. An interaction of the acid with both the oxygen and the chlorine of the rotamer in which the carbonyl oxygen and chlorine have a *cis* configuration[3] was proposed. An entropy effect reduces K for DMP by preferential coördination with the gauche rotamer requiring a rearrangement of amide molecules for coördination.

Since the proposed explanation for the deviation from expected behavior was attributed to the amide, it was felt that the proposal should be tested by utilizing a Lewis acid other than iodine. Phenol was selected because its steric requirements and structure are quite different from those of iodine.

Phenol-amide equilibrium constants deviate from the σ^* plot just as the iodine–amide equilibrium constants do. This is additional support for our proposed explanation.

Experimental

The preparation and purification of the amides has been previously described.[3]

Apparatus.—Preliminary spectra were recorded with a Bausch and Lomb Spectronic 505 recording spectrophotometer. After selection of an appropriate wave length, a Beckman D.U. Spectrophotometer equipped with a temperature controlled, forced air, heating system was employed for all measurements. The temperature of the solution was measured directly with a thermistor located in a well in the sample cell.

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