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The Equilibrium NH Acidity of Organic Compounds

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The literature data of the last decade on the acidity of the N-H bond in organic compounds in aprotic solvents and in the gas phase are examined. The influence of structural factors on the equilibrium NH acidities of arylamines, carboxamides, sulphonamides, polyfluoroaryl compounds, and heterocycles, as well as the acidifying effects of the electron-accepting substituents at the NH acid centre are discussed on the basis of the results of studies of protolytic equilibria in dimethyl sulphoxide. The question of the influence of the *N*-anion stabilisation factors in solution (specific solvation and ion association) on the relative strengths of NH acids is also considered. Data obtained in studies of the NH acidity in the gas phase are presented.
The bibliography includes 103 references.

CONTENTS

I. Introduction 1144
II. The equilibrium NH acidity of organic compounds in dimethyl sulphoxide 1144
III. The influence of the medium on the strength of NH acids 1150
IV. NH acidity in the gas phase 1152

I. INTRODUCTION

Organic compounds whose N–H bonds are involved in a protolytic equilibrium can be regarded as NH acids. They belong to the most common types of Brønsted acids in organic chemistry, like the CH and OH acids. However, in contrast to the latter, which have become the objects of numerous quantitative investigations[1–5], until recently few studies were made on NH acids[6]. Measurements of NH acidity have been used mainly to investigate the cationic forms, i.e. to estimate the basicity of nitrogen-containing compounds. The expansion of the sphere of preparative applications of NH acid anions (*N*-anions)[6] stimulated interest in the structural characteristics which determine the acidity of amino- or imino-group in organic compounds. In many respects they have been discovered in the course of systematic researches carried out during the last decade and to which this review is devoted.

The measure of the acidity of compounds in solution is the p*K*.[1,3] The acidity data are usually referred to the aqueous p*K* scale (pK_a), but, as a consequence of the hydrolysis of the *N*-anions, it is impossible to measure the p*K* of the majority of NH acids in aqueous solution and for this reason studies of the equilibrium NH acidity in non-aqueous media have acquired primary importance.

Considerable advances in the study of NH acids are associated with the application of the method based on the H_- function for media such as mixtures of water with hydrazine[7,8], sulpholan[9], and dimethyl sulphoxide[8–11] and also for alcohols[12,13]. The equilibrium NH acidities of many compounds have been investigated by the indicator method in liquid ammonia[14,15]. The results of these and other studies published up to 1972 have been included in a review[6] and will therefore not be considered here. We shall only mention that the differences between the properties of the solvents employed, their differentiating influence on the relative strengths of the NH acids, have been a serious obstacle to the establishment of a unique NH acidity scale. It was established in the course of studies of NH acids in aprotic polar solvents, in particular, in dimethyl sulphoxide.

II. THE EQUILIBRIUM NH ACIDITY OF ORGANIC COMPOUNDS IN DIMETHYL SULPHOXIDE

The first data on the equilibrium NH acidity of organic compounds in dimethyl sulphoxide (DMSO) were obtained as early as the second half of the 1960's,[10,16,17] while systematic studies of NH acids in DMSO have been carried out, starting from the middle 1970's, by Shatenshtein and co-workers[18–30] and Bordwell and co-workers[31–37]. Both groups of investigators have used the indicator method, based on the spectrophotometric determination of the equilibrium constant K_p of the proton transfer reaction from the NH acid (NH) to the indicator acid AH anion:

$$\rangle NH + A^- \rightleftharpoons \rangle N^- + AH \quad . \qquad (1)$$

The values of K_p, the p*K* of the indicator (pK_{AH}), and the p*K* of the test acid (pK_{NH}) are related:

$$\lg K_p = pK_{AH} - pK_{NH} \quad . \qquad (2)$$

The relation is used to calculate the pK_{NH} from the known values of pK_{AH}.

In the studies of Shatenshtein and co-workers the strengths of NH acids were estimated in terms of the relative acidity scale[38], on which the p*K* for 9-phenylfluorene, established[9] in aqueous sulpholan (18.5), served as a reference, while Bordwell and co-workers used in their studies an absolute scale[39] based on potentiometric data[40,41], on which p*K* = 17.9 corresponds to 9-phenylfluorene. Comparison of the two p*K* scales in dimethyl sulphoxide (DMSO) revealed the following discrepancies between them[42]: on average 0.3 of a logarithmic unit in the range p*K* > 20, 0.6 in the range 14 < p*K* < 20, and ~1.1 in the range p*K* < 14. We took into account these differences in comparing the data of the two groups of investigators. In the Tables below the p*K* are listed in terms of a scale on the basis of which the acidities of the majority of compounds of the given series have been established; together with the recalculated p*K*, the initial values are indicated in brackets.

The reaction centre in all NH acids (we have in mind neutral or anionic forms) is known to contain an unshared electron pair capable of conjugation with the π-electron system of the molecule. Evidently the greater the degree of conjugation and of the delocalisation of the electrons of the unshared pair, the stronger the resonance effects of the substituents at the nitrogen atom on the energy state of the second unshared pair liberated in the heterolytic dissociation of the N–H bond. At the same time, their role in the stabilisation of *N*-anions, one of the unshared pairs in which occupies the σ orbital, is apparently less pronounced than the role of the inductive effects and is not as great as in the stabilisation of carbanions having an analogous structure. Bearing in mind this preliminary remark, we shall consider the influence of structural factors on the equilibrium NH acidity of organic compounds. In the case of acyclic NH acids of the type ArNHR, we shall discuss mainly the effect of substituents in the aryl group Ar and of the groups R directly linked to the acid centre. In the case of heterocyclic NH acids attention will be concentrated on the influence of the structure of the heterocycle and of the substituents in the latter or in the annelated benzene ring.

1. Aniline, Diphenylamine, and Their Substituted Derivatives

Substituted anilines and diphenylamines, particularly the nitro-derivatives, are widely used as indicators in the study of acid–base equilibria and it is therefore useful to quote the full compilation of their p*K* determined in DMSO. The majority of data (Table 1) have been obtained by Bordwell and co-workers, who were the first to measure directly the p*K* of aniline [compound (II)] in DMSO. The acidities of certain other compounds, namely (VIII), (XVIII), (XXII), and (XXIII), were measured in other investigations[43,44] in a buffered system containing phenylacetylene as the proton-donating additive in DMSO. The p*K* found for the NH acids (IV), (IX), (XIII), (XVI), and (XX) are smaller by 1–3 logarithmic units than the values established by Bordwell (see Bordwell et al.[35] concerning the discrepancy) and there is a satisfactory linear relation between the two sets of data ($r = 0.999$), which we used to recalculate in terms of the absolute scale the p*K* determined in a buffer solution. p*K* values similar to those quoted in Table 1 have been obtained for diphenylamine (XXI) (24.8 on the absolute scale[19]) and compounds (XVI), (XVII), (XX), and (XXIV) (potentiometric titration with tetrabutylammonium hydroxide[45]). At the same time, for certain substituted anilines [compounds (XVI), (XVII), and (XX)], Bordwell and co-workers found higher p*K* values than in previous studies[10,16,17,40], in which unduly high estimates were apparently obtained for these and a number of other NH acids in DMSO.

An excellent correlation of the p*K* of aniline and its *meta*-substituted derivatives [compounds (I)–(VII)] and the Hammett σ constants has been obtained ($\rho = 5.67$; $r = 0.9996$),[33] and it is satisfied also by the p*K* of compounds (VIII), (X), (XI), and (XV) (for the last three compounds, values of $\sigma^- = 1.05$, 1.00, and 1.65 respectively must be used[46]). However, the p*K* of 4-benzoyl- and 4-nitro-anilines deviate significantly from the linear relation towards higher acidities even when nucleophilic constants are used.

The available information about the acidities of substituted diphenylamines in DMSO is so far extremely scanty. An approximate estimate of the sensitivity of the NH group of diphenylamine to the electronic influence of the substituents in one benzene ring, based on the three compounds (XXI) to (XXIII), yields $\rho = 4.60$ for the Hammett relation when a nucleophilic constant is used for the nitro-group.

The relative acidities of a large series of polynitrodiphenylamines (17 compounds) have been measured in dimethylformamide (DMF) by potentiometric titration (using tetrabutylammonium hydroxide in methanol as the titrant)[47]. The p*K* found vary in the range from 11.3 for 4′-methoxy-2,4,2′-trinitrodiphenylamine to 1.28 for 2,4,6,2′,4′,6′-hexanitrodiphenylamine. The acidity of 2,4-dinitrodiphenylamine was estimated by extrapolating the relation between the p*K* and Σσ for certain polynitrodiphenylamines and p*K* = 12.65 was obtained. It differs little from the p*K* measured in DMSO [cf. compound (XXIV) in Table 1], which justifies the assumption that the data of Sharnin et al.[47] are a good approximation to the absolute p*K* scale for NH acids in DMSO. For a series of 4′-substituted 2,4,2′-trinitrodiphenylamines, there is a satisfactory correlation between the p*K* and the Hammett σ constants ($r = 0.999$; $n = 5$). The specificity of the effect of the *ortho*-nitro-groups has also been noted; whereas the first is somewhat inferior in its acidifying influence to the *para*-nitro-group, the second appreciably surpasses the analogous *para*-substituent in this respect.

Table 1. The equilibrium NH acidities of aniline, diphenylamine, and their substituted derivatives in DMSO (absolute p*K* scale[39]).

Compound	Substituent	p*K*	Refs.	Compound	Substituent	p*K*	Refs.
Substituted anilines							
(I)	3-CH_3	31.0	[33]	(XI)	4-CN	25.3	[33]
(II)	H	30.7	[31]	(XII)	4-$C_6H_5SO_2$	24.9	[33]
(III)	3-CH_3O	30.5	[33]	(XIII)	2,6-Cl_2	24.8	[35]
(IV)	3-C	28.5	[33]	(XIV)	4-C_6H_5CO	24.4	[33]
((V)	3-B	28.4	[33]	(XV)	4-CF_3SO_2	21.8	[33]
(VI)	3-CF_3	28.2	[33]	(XVI)	4-NO_2	20.9	[33]
(VII)	3-CN	27.5	[33]	(XVII)	4-Cl, 2-NO_2	18.9	[36]
(VIII)	3,4-Cl_2	27.1 (24.5)	[44]	(XVIII)	2,5-Cl_2, 4-NO_2	17.5 (16.2)	[43]
(IX)	2,4-Cl_2	26.2	[35]	(XIX)	2,6-Cl_2, 4-NO_2	17.4	[35]
(X)	4-CH_3SO_2	25.6	[33]	(XX)	2,4-$(NO_2)_2$	15.9	[35]
Substituted diphenylamines							
(XXI)	H	24.95	[36]	(XXIII)	4-NO_2	19.2 (17.7)	[43]
XXII)	3-Cl	23.5	[43]	(XXIV)	2,4-$(NO_2)_2$	12.4 (13.5)	[24]

2. Aminoazines

The data on the acidities of aminoazines in DMSO (Table 2) and aniline made it possible to estimate reliably the acidifying effects of the aza-groups in various positions in the heterocycle (these positions are designated by a numeral in brackets): 3.1 (2), 2.4 (3), and 4.5 (4) logarithmic units (within the limits of ±0.2 of a logarithmic unit)[28]. As a rule, in the presence of several groups, their effects are additive except for two aza-groups in the *ortho*-positions relative to an amino-group in a side chain [compounds (XXIX) and (XXXIV)]; their combined effect is smaller by 0.8–1.0 of a logarithmic unit than the value calculated assuming additivity[28]. It has been suggested that the deviation from additivity is due to the destabilising influence of the free electron pairs of the *ortho*-nitrogen atoms, which cannot be located simultaneously in the *trans*-positions relative to the electron pair of the imino-nitrogen atom, liberated when the proton of the N–H bond is abstracted.

For a series of NH acids, including the aminoazines (XXV) to (XXVIII) and (XXX)–(XXXIII) and aniline, a correlation equation ($r = 0.998$), linking the p*K* to the relative values of

the σ constants of the aza-groups (σ_N), found from the acidifying effects, has been found[28]. Using the ratio of ρ for the given correlation (4.16) to that for substituted anilines (see above), the relative constants σ_N were adjusted to the scale of the Hammett constants: 0.55 (σ_{2N}), 0.44 (σ_{3N}), and 0.78 (σ_{4N}).[48] They are smaller than the corresponding values of σ_N established in water[49,50], because in DMSO there is no possibility for the specific solvation of aminoazines and their *N*-anions (for the formation of a hydrogen bond with the endocyclic nitrogen atoms), which could enhance the electron-accepting properties of the azine ring in a proton-donating medium.

Table 2. The equilibrium NH acidities of aminoazines in DMSO [28] (relative scale[38]).

Compound	Name	p*K*
(XXV)	3-Aminopyridine	28.9
(XXVI)	2-Aminopyridine	28.0
(XXVII)	4-Aminopyridine	26.7
(XXVIII)	5-Aminopyrimidine	26.4
(XXIX)	2-Aminopyrimidine	25.9
(XXX)	2-Aminopyrazine	25.8
(XXXI)	3-Aminopyridazine	25.7
(XXXII)	4-Aminopyridazine	24.1
(XXXIII)	4-Aminopyrimidine	23.9
(XXXIV)	2-Amino-*sym*-triazine	21.5

The influence of substituents in the heterocycle on the NH acidity of aminopyrimidines has been studied in fair detail[23]. It has been established that π-donor groups as a rule deviate from the linear relation between the p*K* and the Hammett constants. The results of a two-parameter correlation analysis (with subdivision of the σ into σ_I and σ_R) have shown that, when the endocyclic nitrogen atom is located between the substituent and the amino-group [the 4-substituted derivatives of compound (XXIX) or the 2-substituted derivatives of compounds (XXXIII)], the electronic effects are transmitted via the pyrimidine ring to a greater extent than via the benzene ring. For the *para*-positions of the substituent and the amino-group, there are conditions for direct polar conjugation (σ_R^- is used in the correlation instead of σ_R), but, if the substituent is then in the *ortho*-position relative to both aza-groups [2-substituted derivatives of compound (XXVIII)], then the best correlation between the p*K* and the Hammett constants is achieved for resonance components represented by the sum $0.6\sigma_R + 0.4\,\sigma_R^-$.

In conclusion, we may note that it is possible to obtain a unique correlation equation describing the dependence of the p*K* on the sum of the Hammett constants (including the values of σ_N presented above) and embracing the 3- and 4-substituted anilines (I)–(VIII), (X), (XI), and (XV), the aminoazines (XXV)–(XXVIII) and (XXX)–(XXXIV), and the majority of the substituted derivatives of compounds (XXVIII) and (XXXIII):[48]

$$pK = 31.0 - 5.38\Sigma\sigma \quad (S = 0.36;\ r = 0.993;\ n = 44)\ .$$

3. Carbonyl Compounds

Data for the equilibrium NH acidities of carbonyl compounds of the type RCONHR′ in DMSO are listed in Table 3. Comparison of the p*K* for carboxamides and arylamines with a similar structure shows that the CO group has a considerable acidifying effect [cf., for example, the p*K* of aniline (II) and compounds (XL)–(XLV)] and appreciably reduces the sensitivity of the acid centre to the electronic effect of the second α-substituent (R′). Thus, whereas the acidities of aniline and 4-aminopyridine exceed the acidity of ammonia (p*K* = 41 in DMSO [34]) by 10 and 14 logarithmic units respectively, the acidities of acetamide (XXXVII) and its phenyl- and 4-pyridyl-substituted derivatives (XL) and (XLVIII) differ by only 4 and 6.5 logarithmic units respectively. The influence of the CO group is manifested also by a weakening of the transmission of the effects of substituents via the benzene ring to the N–H bond. Thus the following values of ρ have been obtained for the three series of NH acids of the type $RCONHC_6H_4X$ in DMSO for the relations between the p*K* and the Hammett constants of the substituents X (the number of the compound corresponding to X = H is indicated in brackets; in all the series $r = 0.995$): −3.22 (XLIV);[26] −3.16 (XLIII);[19] −2.96 (XLVII);[18] in absolute magnitude, they are all smaller than ρ for substituted anilines (see above).

Table 3. The equilibrium NH acidities of the carbonyl compounds RCONHR′ in DMSO (relative scale).

Compound	R	R′	p*K*	Refs.
(XXXV)	NH_2	H	26.6 (25.1) *	[17]
(XXXVI)	$(CH_3)_3C$	H	26.0 (25.7)	[32]
(XXXVII)	CH_3	H	25.8 (25.5)	[32]
(XXXVIII)	H	H	23.8 (23.5)	[32]
(XXXIX)	C_6H_5	H	23.7 (23.4)	[31]
(XL)	CH_3	C_6H_5	21.8 (21.5)	[31]
(XLI)	C_6H_5NH	C_6H_5	20.9	[26]
(XLII)	$(CH_3)_2CHCH_2O$	C_6H_5	20.7	[19]
(XLIII)	CH_3O	C_6H_5	20.3	[19]
(XLIV)	$C_6H_5NCH_3$	C_6H_5	19.9	[26]
(XLV)	H	C_6H_5	19.7	[27]
(XLVI)	C_6H_5	NH_2	19.5 (18.9)	[36]
(XLVII)	C_6H_5	C_6H_5	19.3 **	[18]
(XLVIII)	CH_3	C_5H_4N ***	19.2	[27]
(XLIX)	$(CH_3)_2CHCH_2S$	C_6H_5	17.4	[19]
(L)	C_6H_5	C_5H_4N ***	17.1	[27]
(LI)	CCl_3	C_6H_5	13.4	[27]
(LII)	CN	C_6H_5	12.5	[26]

*Recalculated[17] taking into account the difference between the p*K* of urea (XXXV) and diphenylamine.
**19.4 (18.8).[31]
***4-Pyridyl.

In connection with the study of the effects of substituents in the benzene ring, we may point out that the p*K* of 4-fluoro-derivatives of acetanilide and formanilide (21.3 and 19.4)[27] and of a series of 2′-substituted benzanilides[18] have also been determined in DMSO. In particular, it has been shown that the influence of the 2′- and 4′-nitro groups on the NH acidity of benzanilide (XLVII) is virtually the same (the p*K* of the substituted derivatives are 15.5 and 15.4 respectively[18]); this has also been observed for *N*-phenylcarbamate (XLIII).

The nature of the substituent R at the carbon atom of the CO group also has appreciable influence on the strength of the carbonyl NH acids [cf., for example, the p*K* of compounds (XL), (XLV), (XLVII), (XLIX), (LI), and (LII)]. The correlation between the p*K* and the Taft σ* constants ($\rho^* = 4.69$; $r = 0.997$) for substituents R, which are mainly alkyl and chloroalkyl groups, has been obtained for the chloralamides $CCl_3CH(OH)NHCOR$ whose acidity has been measured

potentiometrically in a mixture of benzene and methanol[51]. The inductive influence of R is a decisive factor also in the NH acidity of dichlorovinylamides CCl_2 = CHNHCOR (R = alkyl, chloroalkyl, phenyl, or substituted phenyl; potentiometric measurements in DMF; $\rho^* = 2.36$; $r = 0.996$).[52] A linear relation of a similar kind has also been established for the carboxamides R"CH_2CONH_2 (R" = H, F, C_6H_5O, CH_3O, C_6H_5, C_6H_5S, etc.; $\rho^* = 2.8$; $r = 0.908$),[32] but, for R" = alkyl, no correlation is observed between the pK and σ^*.[32]

On the other hand, certain data in Table 3 also cannot be interpreted from the standpoint of the predominant inductive influence of the substituent R on the acidity. If that were so, urea (XXXV) should be a more acid compound than acetamide (XXXVII) and N-phenylcarbamate (XLVII) should be more acid than formanilide (XLV). Since the actual relative strengths of the above NH acids are the reverse of expectation, the hypothesis that the π-donor capacity of the substituents R (for example, NH_2 and CH_3O) also plays an appreciable role suggests itself. A confirmation of this may be seen in the two-parameter correlations

$$pK = 24.3 - 9.1\sigma_I - 4.7\sigma_R^- \quad (S = 0.4;\ r = 0.971),$$
$$pK = 20.1 - 9.7\sigma_I - 4.9\sigma_R^- \quad (S = 0.12;\ r = 0.999),$$

deduced for the $RCONH_2$ [compounds (XXXV)–(XXXIX)] and $RCONHC_6H_5$ [compounds (XL), (XLIII), (XLV), (XLVII), and (LII)] series respectively, from which it follows that, apart from the inductive contribution to R to the stabilisation of N-anions, account must be taken also of its resonance effect.

The influence of substituents in the benzene ring attached to the CO group on the NH acidity has been investigated in relation to benzanilides. The relative pK of compounds having the general formula 4-$XC_6H_4CONHC_6H_4OCH{=}CH_2$ were determined potentiometrically in DMF, pyridine, and other solvents and linear relations between the pK and the Hammett constants of the substituents X were established (the values of ρ vary from −6.18 to −7.85 depending on the medium)[53].

The replacement of the oxygen atom in the CO group by sulphur entails an increase of the NH acidity by 4–6 logarithmic units, which follows from a comparison of the pK of urea[15,17] or N-phenylcarbamate[19] and their thio-analogues. The acidities of certain thiocarbonyl compounds have been investigated potentiometrically in DMF, in which the pK of the thioamides 4-XC_6H_4NHCSR (R contains a CH group linked to powerful electron acceptors—the CN, $C_6H_5SO_2$, etc. groups)[54] and the acylthioureas RCONHCSNHR′ (R = 2-furyl substituted in the 5-position or 4-substituted phenyl; R′ = phenyl or 4-substituted phenyl) were determined[55,56]. In the case of thioamides the second dissociation constant corresponds to the ionisation of the N–H bond (the first refers to the C–H bond); the range of variation is small: from 0.8 to 1.6 logarithmic units on passing from X = H to X = NO_2 for different R.

In the series where R = $CH(SO_2C_6H_4Cl\text{-}4)CONH_2$ the pK are correlated with the σ^0 constants of the substituents X ($\rho = -1.95$). Only one dissociation step, attributed to the N–H bond between the CO and CS groups, has been noted for acylthioureas (the terminal NH group forms a hydrogen bond with the oxygen atom of the CO group[55]). The influence of the nature of the substituents in the furan or benzene ring (for R′ = C_6H_5) on the NH acidity of acylthioureas is more appreciable than in the thioamides indicated above: the values of ρ in the Hammett relations are respectively −6.8 and −5.3. In the series where R = 2-furyl and R′ = C_6H_4X the sensitivity of the acid centre to the effects of the substituents X is fairly low: the pK vary in the range 8.9–11.3 [X = 2-NO_2 and 4-$(C_2H_5)_2N$ respectively] and for the 3- and 4-substituted derivatives it was not possible to discover a dependence of pK on the Hammett constants.

4. Sulphonamides

The equilibrium NH acidity of sulphonamides (Table 4) is lower by 6–7 logarithmic units than that of their carbonyl analogues (cf. Table 3). This large difference is due to the fact that, in terms of the negative inductive effect $-I$, which plays the most important role in the stabilisation of N-anions, the SO_2 group is significantly superior to the CO group. Accordingly, the acidifying influence of the substituents R at the sulphur atom in the RSO_2 group on the N–H bond is apparently also even more inductive in its character than the influence of the analogous substituents on the N–H bond in carboxamides. In particular, we may note that the pK of sulphonamides of the type RSO_2NH_2 [compounds (LIV), (LVII), and (LXI)] vary linearly with the Taft constants of the substituents R, including the phenyl group:

$$pK = 18.3 - 2.86\sigma^* \quad (r = 0.998).$$

Alkyl substituents at the nitrogen atom of benzenesulphonamide reduce the NH acidity in conformity with their inductive effects[27] [see compounds (LIII) and (LV)–(LVIII)].

Table 4. The equilibrium NH acidities of the sulphonamides RSO_2NHR' in DMSO (relative scale.

Compound	R	R′	pK	Refs.
(LIII)	C_6H_5	$(CH_3)_3C$	18.2	[27]
(LIV)	CH_3	H	18.1 (17.5)	[31]
(LV)	C_6H_5	$(CH_3)_2CH$	17.9	[27]
(LVI)	C_6H_5	C_2H_5	17.7	[27]
(LVII)	C_6H_5	CH_3	17.5	[27]
(LVIII) *	C_6H_5	H	16.8	[27]
(LIX)	C_6H_5	C_6H_5	12.6	[27]
(LX)	C_6H_5	C_5H_4N **	11.3	[27]
(LXI)	CF_3	H	10.8 (9.7)	[31]
(LXII)	CF_3	C_6H_5	6.8 (5.7)	[36]

*pK = 16.7 (16.1) has been quoted[37] for compound (LVIII).
**4-Pyridyl.

The acidities of benzenesulphonanilides substituted in the benzene ring attached to the nitrogen atom are described by a linear correlation between the pK and the Hammett constants ($\rho = -2.7$ and $r = 0.990$ for the *meta*- and *para*-substituents and $\rho = -2.53$ and $r = 0.998$ for the *ortho*-substituents[27]).

5. Polyfluoroaryl-substituted Compounds

The complete substitution of hydrogen atoms by fluorine in the aryl groups of arylamines or carboxamides is accompanied by an increase of the equilibrium NH acidity by 6–8 logarithmic units [cf. the pK of compounds [LXIII)–(LXVII) in Table 5, compounds (II), (XXVII), (XXI), (XL), and (XLVII) in Tables 1–3, and compounds (LXV) and (LXVIII) in Table 5]. The high electron-accepting capacity of the polyfluoroaryl groups is due to the negative inductive effect of fluorine atoms[57]. Like the sulphonyl group, they therefore activate the N–H bond to a greater extent than the carbonyl group and are superior in this respect also to the p-nitrophenyl group[24].

The equilibrium NH acidity of compounds C_6F_5NHAr is described satisfactorily by a two-parameter correlation equation, where the chemical shift δ_F of the signal of the *para*-fluorine atom of the C_6F_5 group in the ^{19}F NMR spectra has

been suggested as a measure of the resonance influence of the aryl group Ar: [24]

$$pK = 20.0 - 3.88\sigma^* + 0.36\delta_F \quad (r = 0.988) .$$

Table 5. The equilibrium NH acidities of polyfluoroaryl-substituted compounds C_6F_5NHR in DMSO [24] (relative scale).

Compound	R	pK
(LXIII)	H	23.1
(LXIV)*	H	19.2
(LXV)	C_6H_5	19.2
(LXVI)	CH_3CO	15.5
(LXVII)	C_6H_5CO	13.0
(LXVIII)	C_6F_5	12.6
(LXIX)	$C_{10}F_7$**	11.8
(LXX)	C_6F_5CO	10.8
(LXXI)	$2,4\text{-}(NO_2)_2C_6H_3$	10.2***
(LXXII)	C_5F_4N	9.4

*Instead of the C_6F_5 group, compound (LXIV) contains the 2,3,5,6-tetrafluoropyridyl group C_5F_4N.
**2-Heptafluoronaphthyl.
***Taken from Vlasov et al.[29]

Table 6. The acidifying effects (ΔpK) of the substituents R in NH acids.

R	I	II	III
C_6H_5	10.3	5.8	3,9
CH_3CO	15.5	9.2	7,6
HCO	17.5	11.6	—
C_6H_5CO	17.6	11.9	10.1
C_6F_5	18.2	11.8	10.5
CN	24.0	—	—
$C_6H_5SO_2$	24.9	19.2	—
$2,4\text{-}(NO_2)_2C_6H_3$	25.1	18.3	12.9
CF_3SO_2	31.3	25.0	—

Note. The ΔpK were found as the differences between the pK of ammonia [~41 (Algrim et al.[34]), series I], aniline [30.7 (Bordwell and Algrim[31]), series II], and pentafluoraniline [22.8 (Vlasov et al.[24]), series III], on the one hand, and the pK of the corresponding *N*-substituted derivatives on the absolute scale; apart from the data in Tables 1–5, pK = 17.0 for cyanamide[37] has been used.

Satisfactory linear relations (r = 0.988–0.998) between the pK and the Hammett constants for the substituents X have been obtained for four series of NH acids of the type $4\text{-}XC_6F_4NHR$ (dialkylamino-groups, which exhibit an extremely weak electron-donating effect in the above series, were not included in the correlation). The constants ρ vary as follows (the substituents R are indicated in brackets)[29]: −6.43(H); −3.93(C_6F_5); −3.23(C_6H_5CO); −3.01[$2,4\text{-}(NO_2)_2C_6H_3$]. The differences between them and the ρ in the correlations for the analogous series of non-fluorinated compounds (see above) are insignificant, i.e. the degree of transmission of the electronic effects of the *para*-substituents via the benzene ring to the NH acid centre changes little when the *ortho*- and *meta*-hydrogen atoms are replaced by fluorine[29]. This is also supported by the results of a quantum-chemical calculation (by the CNDO/2 method) of the parameters of the highest occupied molecular orbital in the *N*-anions containing the phenyl or pentafluorophenyl group at the nitrogen atom[29].

6. The Acidifying Effects of the Substituents in Acyclic NH Acids

In conclusion of the discussion of data for the equilibrium NH acidity of acyclic compounds in DMSO, it is useful to compare the acidifying effects of α-substituents, which provide a clear idea about the relative strengths of NH acids of different types. Table 6 presents the values of ΔpK characterising the acidifying influence of a series of groups on the N–H bonds of ammonia, aniline, and pentafluoroaniline.

The sequence in which the ΔpK vary is virtually the same in all three series and there is a linear relation between the ΔpK for series I and II:

$$\Delta pK_I = 1.06\Delta pK_{II} + 5.1 \quad (S = 0.6;\ r = 0.996) .$$

On the other hand, the absolute magnitude of the acidifying effect of a given substituent decreases from series I to series II and further to series III. This can be partly due to the increased steric hindrance to the conjugation of the substituent R with the nitrogen atom on replacement of a single hydrogen atom in ammonia by the phenyl (series II) and pentafluorophenyl (series III) groups. However, this is not the only cause and apparently not the main cause of the inconstancy of the ΔpK noted above. For example, the steric environments of the acid centres in aniline and 4-aminopyridine are identical and yet the acidifying effects of the CH_3CO, C_6H_5CO, and $C_6H_5SO_2$ groups in aniline are greater by 1–3 orders of magnitude than in aminopyridine [cf. the differences between the pK of compound (XXVII) and compounds (XLVIII), (L), and (LX) with the corresponding ΔpK in series II]. Furthermore, the steric hindrance should not be reflected in the stabilisation of the *N*-anions via the inductive mechanism and yet the tendency towards a decrease of the ΔpK can be distinctly traced also for substituents which exert a predominantly inductive influence on the N–H Bond (C_6F_5, $C_6H_5SO_2$, and CF_3SO_2).

An analogous situation has been observed for the CH acidity[58,59] and has been interpreted as a consequence of the mutual weakening of the electronic effects of the substituents at the acid centre[34,42]. Evidently this phenomenon is of a general character and must be taken into account also in the consideration of the NH acidity†.

7. Nitrogen-containing Heterocycles

The principal data on the acidity in DMSO of heterocycles containing the imino-group in the ring are presented in Table 7. The majority of the NH acids of this type are azoles and their derivatives. The equilibrium NH acidity of azoles increases with increase in the number of aza-groups in the ring and the influence of such groups in the β-positions on the N–H bond is greater than that of those in the α-positions [cf. the pK of compound (LXXIX) and those of (LXXXII) and (LXXXIV) or the pK of the last two compounds and (LXXXIX), Table 7].

† New values of the constants σ^-, whereby one can take into account the influence of the substituents in CH acids, have been proposed recently[60], but it is not possible to obtain even a satisfactory linear relation between these constants and the pK of NH acids measured in DMSO.

The influence of the ring substituents on the acidity of azoles is predominantly inductive. Thus a linear relation has been obtained between the pK of 2-substituted and 2,3-disubstituted pyrroles and the sum of the inductive constants σ_I of the substituents ($\rho = -17.4$; $r = 0.994$) and the transmission of the effect of the substituent from the 3-position is twice as weak as the transmission of the effect from the 2-position[22]. The acidity of substituted pyrazoles and imidazoles can be described by correlations between the pK and the sum of the constants σ_m regardless of the number of substituents and their positions in the ring ($\rho = -8.8$ and -9.5 and $r = 0.987$ and 0.999 respectively)[21].

Table 7. The equilibrium NH acidities of nitrogen-containing heterocycles in DMSO (relative scale).

Compound	Name	pK	Refs.
(LXXIII)	1,2,3,4-Tetrahydroquinoline	32.1	[20]
(LXXIV)	1,2,3,4-Tetrahydroquinoxaline	32.1	[20]
(LXXV)	Indoline	30.5	[20]
(LXXVI)	2,2-Pentamethylenebenzimidazoline	29.3	[20]
(LXXVII)	3,4-Dihydro-2*H*-benzo-1,4-thiazine	28.8	[20]
(LXXVIII)	Acridan	25.2	[30]
(LXXIX)	Pyrrole	23.3	[21]
(LXXX)	Phenothiazine	22.8	[21]
(LXXXI)	Indole	21.3	[21]
(LXXXII)	Pyrazole	20.4	[21]
(LXXXIII)	Carbazole	19.6	[21]
(LXXXIV)	Imidazole	18.9	[21]
(LXXXV)	Indazole	18.8	[21]
(LXXXVI)	Phenanthridinone	18.3	[30]
(LXXXVII)	Benzimidazole	18.1	[21]
(LXXXVIII)	9-Acridone	16.4	[30]
(LXXXIX)	1,2,4-Triazole	15.4	[21]
(XC)	Benzotriazole	12.6	[21]
(XCI)	Tetrazole	9.3 (8.2)	[36]

Note. The statistical correction for two NH groups has been introduced for compounds (LXXIV) and (LXXVI). For compounds (LXXIX) and (LXXXI), Bordwell et al.[37] obtained similar pK values, equal to 23.35 (23.05) and 21.25 (20.95) respectively, while for compound (LXXXIII) a higher pK, amounting to 20.5 (19.9), was obtained.

When the azole ring is annelated to the benzene ring, the NH acidity increases on average by two logarithmic units. A satisfactory linear relation ($r = 0.995$) has been established between the pK of compounds (LXXIX), (LXXXI), (LXXXII), (LXXXIV), 2-phenylimidazole, and their benzo-derivatives; with its aid, the acidity of 1,2,3-triazole (pK = 14.7) has been estimated from the pK of benzotriazole[21]. The influence of the benzo-group should apparently be attributed to the strengthening of the delocalisation of the unshared pair of the electrons of the "pyrrole" nitrogen atom over the π-electron system of the molecule, although one cannot rule out the possibility that the inductive effect of the sp^2-hybridised carbon atoms of the benzo-group also plays an appreciable role. In this connection one may note that the inductive effect of the phenyl group in the 2-position of pyrrole increases the NH acidity by 1.7 logarithmic units[22].

However, the role of conjugation in the stabilisation of the N-anions of certain heterocycles is apparently nevertheless greater than in the case of acyclic NH acids. Structural changes which affect the p,π-conjugation system in the molecules of azoles can lead to an appreciable weakening of the NH acidity. Thus the rupture of the o,o'-C–C bond between the benzene rings of carbazole (LXXXIII) or its replacement by a methylene bridge, is accompanied by a decrease of acidity by more than 5 logarithmic units [cf. with diphenylamine (XXI) in Table 1 or with acridan (LXXVIII)]. The consequences of a decrease in the size of the π-electron system of benzoheterocycles and of the "dearomatisation" of the heterocyclic ring following its partial hydrogenation at the C=C or C=N bond are even more appreciable (10–12 logarithmic units) [cf. the pK of compounds (LXXV) and (LXXXI) and of (LXXVI) and (LXXXVII)]. On the other hand, the annelation of the benzoheterocycles (LXXIII) and (LXXVII) to a second benzene ring with simultaneous replacement of the aliphatic C–C bond by an aromatic bond leads virtually to a doubling of the size of the π-electron system and the consequent increase in the NH acidity by 6–7 logarithmic units [cf. with compounds (LXXVIII) and (LXXX)]. The analogous structural change in the case of a five-membered heterocycle is accompanied by an increase of the NH acidity by 11 logarithmic units [cf. compounds (LXXV) and (LXXXIII)].

When the methylene group of acridan is replaced by the carbonyl group, the NH acidity increases by ~9 logarithmic units [cf. with 9-acridone (LXXXVIII)], which is close to the acidifying effect of the acyl groups in aniline (9–12 logarithmic units—see Table 6, series II). In view of the considerable remoteness of the acid centre of 9-acridone from the CO group, presumably the contribution of its inductive effect to the stabilisation of the given N-anion is smaller than in acyclic carbonyl-containing N-anions. The planar conformation of the 9-acridone molecule apparently favours the manifestation of the resonance effect of the CO group, which is the maximum possible for NH acids. It has been suggested that this is the reason why the sensitivity of the acid centre of 9-acridone to the resonance influence of substituents in the 2-position (the *para*-position relative to the nitrogen atom) is weakened[30].

The benzoheterocyclic compounds (LXXIII)–(LXXVII) with a partially reduced heterocyclic ring can be regarded by convention as the corresponding *ortho*-substituted N-alkylanilines. It is not therefore surprising that their acidities are similar to that of aniline. It is remarkable that the acidity of compounds with a five-membered heterocycle is appreciably higher than that of their six-membered analogues [cf. compounds (LXXIII) and (LXXV), (LXXIV), and (LXXVI)]. This difference persists also for their p-nitro-substituted derivatives (when the nitro-group is introduced, the acidity increases by 10–12 units)[20]. This behaviour was first observed in a potentiometric determination of the NH acidities of anthraquinones containing the imino-group in the annelated five- or six-membered heterocycle (the range of the pK for the compounds investigated is from 11.4 to 20.7).[51] The increase of acidity following a decrease in the size of the heterocycle has been explained by the increase of the s character of the orbital of the N–H bond as a consequence of the endeavour of the nitrogen atom to rehybridise due to the tendency of the five-membered ring annelated to the benzene ring to weaken the strain.

The above data exhaust the information currently available about the influence of the structure of organic compounds on the acidity of the N–H bond in DMSO. Measurements of the pK of NH acids in other aprotic solvents (mainly in dimethylformamide[47,52–54], nitromethane[62,63], and a number of others) covered a much smaller number of compounds and did not yield fundamentally new information about the influence of the structure of the compounds on their equilibrium NH acidity compared with data for solutions in DMSO.[64] On the other hand, the relative strengths of the NH acids frequently change significantly on passing from proton-donating to relatively non-polar solvents, which is due primarily to

factors stabilising *N*-anions such as specific solvation or association with the counterion[42,65].

Studies of NH acids using proton-donating media (water, alcohols, mixtures of DMSO with hydroxylated components, etc.) are being prosecuted at the present time. Thus a number of investigations of the NH acidities of arylamines[50,66,67], derivatives of guanine[68] and barbituric acid[69], and certain azoles[70,71] in the above solvents have been published during the last 5–7 years. The equilibrium NH acidities of certain heterocycles and carbonyl compounds have been measured also in a weakly polar aprotic solvent—1,2-dimethoxyethane[18,19,21,72]. It is therefore of interest to consider to what extent the differences between the proton-donating capacities or polarities of the solvents are reflected in the strength of the NH acids.

III. THE INFLUENCE OF THE MEDIUM ON THE STRENGTH OF NH ACIDS

The overall pattern in the change of the equilibrium NH acidity of organic compounds when DMSO is replaced by water is illustrated in Fig.1, where the p*K* for NH acids of different structural types, determined relative to the corresponding standard states in both solvents, are compared. The pK_a employed (the subscript *a* indicates the assignment of the p*K* to the acidity scale in aqueous solutions[3]) were either measured directly in water or were obtained by the authors[50,73] by recalculating the values for mixed solvents using methods taking into account the activities of the species involved in the protolytic equilibrium. It has been shown for a large number of CH and NH acids that the results of the recalculation by two such methods[78,79] are in good agreement[80].

Analysis of the relation between the p*K* of NH acids in both solvents shows easily that the equilibrium NH acidities of the majority of compounds in DMSO are lower than in water—the circles in Fig.1 are distributed mainly above the dashed straight line passing through the origin of coordinates at an angle of 45°. This difference has come to be explained by the fact that, by virtue of the specific character of the solvation in water (the formation of hydrogen bonds), the *N*-anions are stabilised in this solvent to a greater extent than in DMSO. The reduced NH acidity in DMSO is partly, but apparently to a lesser extent, caused by the formation of stronger hydrogen bonds between the molecules of the NH acids and the solvent (see Trofimov et al.[22] and Karjalainen and Ruostesno[81] concerning this topic) whose basicity is higher than that of water[39]. For *N*-anions with a highly delocalised charge, the degree of specific solvation in water is diminished, while the solvation of the anion in DMSO via the dispersion interaction mechanism is actually enhanced[40,41]. This is probably why the NH acidities of the corresponding compounds, for example, of 2,4-dinitrodiphenylamine (see point 14 in Fig.1), are higher in DMSO than in water.

The data presented in Fig.1 also show that, when the solvent is changed, the strengths of the NH acids change unequally: the differences between the pK_{DMSO} and pK_a vary from 2.5 to 6 logarithmic units, i.e. a differentiating effect of the medium on the equilibrium NH acidity is observed. At the same time, linear relations between both parameters can be found for structurally similar NH acids (see the straight line in Fig.1 and the data in Table 8).

The pK_{DMSO} and the pK_a of anilines and unsubstituted aminoazines (Table 8, series I and II) are correlated most effectively and the form of the linear relation I hardly changes when aniline and diphenylamines are combined into a single series (cf. series I and II). The considerable scatter of the points in the case of azoles (see points 21–28 in Fig.1) precludes a conclusion concerning a distinct linear relation between pK_{DMSO} and pK_a. One can only speak of a parallel variation of these quantities. Relations with a satisfactory correlation coefficient and standard deviations greatly superior to the accuracy of the determination of the p*K*, which is to within 0.1, can be obtained for monocyclic azoles (series IV) and benzazoles (series V). The excellent linear correlation obtained for benzenesulphonanilides (series VI) is appreciably impaired when benzenesulphonamide (series VII) is included in the above series. On the basis of the foregoing, one can conclude that the solvation effects responsible for the shift of the protolytic equilibrium on replacement of an aprotic solvent by a proton-donating solvent depend specifically on the structure of the NH acid. At the same time their contributions to the energetics of the acid dissociation process vary in proportion in a series of NH acids of a given structural type.

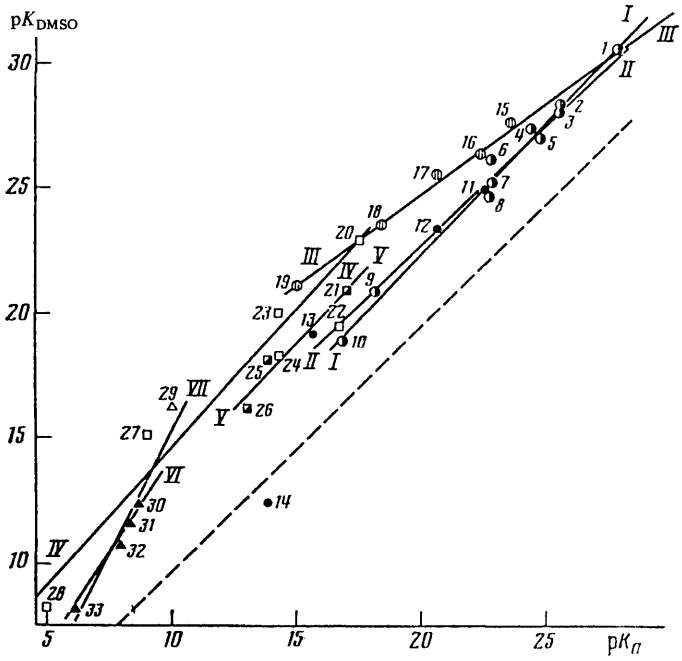


Figure 1. The equilibrium NH acidities of organic compounds in dimethyl sulphoxide (pK_{DMSO}) and in water (pK_a) (the pK_a are indicated in brackets); aniline and its substituted derivatives[73] (the substituents are indicated): 1) H (27.8); 2) 3-Cl (25.5); 3) 3-CF_3 (25.4); 4) 3-CN (24.3); 5) 3,4-Cl_2 (24.6)l 6) 2,4-Cl_2 (22.6); 7) 4-CN (22.7); 8) 2,6-Cl_2 (22.6); 9) 4-NO_2 (18.1); 10) 4-Cl, 2-NO_2 (16.8); diphenylamine and its substituted derivatives[73]: 11) H (22.4); 12) 3-Cl (20.6); 13) 4-NO_2 (15.5); 14) 2,4-$(NO_2)_2$ (13.8); aminoazines[50]: 15) 2-aminopyridine (23.5); 16) 4-aminopyridine (22.3); 17) 2-aminopyrimidine (20.5); 18) 4-aminopyrimidine (18.4); 19) 2-amino-*sym*-triazine (14.9); azoles: 20) pyrrole (17.5);[74] 21) indole (17.0);[75] 22) carbazole (16.7);[76] 23) pyrazole (14.2);[74] 24) imidazole (14.2);[74] 25) indazole (13.8);[75] 26) benzimidazole (12.9);[75] 27) 1,2,4-triazole (8.9);[70] 28) tetrazole (5.0);[70,71] 29) benzenesulphonamide (10.0) [77] and benzenesulphonanilides[77] (the substituent in the 4'-position is indicated); 30) CH_3 (8.7); 31) H (8.3); 32) Cl (7.9); 33) NO_2 (6.2).

It is also of interest to note the following factors. The regression coefficient b in the correlation equation (Table 8) shows that, when the solvent is replaced, the sensitivity of the acid centre in compounds of the given structural type to the electronic effects of the substituents is altered. In particular, for phenyl-substituted NH acid (series I, II, and VI), the coefficient b is determined by the ratio of the constants ρ of the Hammett relations between the pK and σ in DMSO and in water (it has been assumed that the Hammett σ constants are identical for the two solvents). In the majority of the series of NH acids considered the coefficient b exceeds unity, which indicates a smaller sensitivity of the NH acidity to structural factors in the aqueous solution (cf., for example, the values of ρ for substituted anilines—$\rho = 5.20$ in water[50] and $\rho = 5.67$ in DMSO [34]). As a result of this, the replacement of DMSO by water entails a smoothing out of the differences between the NH acid strengths within a given series.

Table 8. Correlations of the type $pK_{DMSO} = a + bpK_a$ for NH acids in different structural series.

Series	Compound	a	b	S	r	n
I	Anilines (Nos. 1-10)	1.5±1.3	1.05±0.06	0.4	0.994	10
II	Anilines and diphenylamines (Nos. 1-13)	3.0±0.9	0.99±0.04	0.5	0.991	13
III	Aminoazines (Nos. 1 and 15-19)	10.1±0.4	0.74±0.02	0.2	0.998	6
IV	Azoles (Nos. 20, 23, 24, 27, and 28)	3.6±1.7	1.12±0.13	1.3	0.979	5
V	Benzazoles (Nos. 21, 25, and 26)	2.6±3.5	1.09±0.24	0.7	0.976	3
VI	Benzenesulphonanilides (Nos. 30-33)	−2.2±0.8	1.65±0.1	0.2	0.996	4
VII	Benzenesulphonamides (Nos. 29-33)	−5.3±0.7	2.07±0.08	0.7	0.979	5

Note. The numbers of the series correspond to the numbers of the straight lines in Fig.1, while the numbers of the compounds correspond to the numbers of the points in the same Figure.

Such levelling of the acidity in a hydroxylated solvent can be explained by the specific solvation of N-anions. The higher the basicity of the N-anion (the greater the pK of its conjugate NH acid), the stronger the hydrogen bond between it and the solvating molecules of the hydroxylated solvent and the greater the decrease of the pK on passing from DMSO to a proton-donating medium. Thus the coefficient b can be regarded also as a measure of the sensitivity of N-anions to the stabilising effect of specific solvation. Judging from the data in Table 8, it is a maximum for sulphonamides (series VI and VII), which is probably due to the involvement of the oxygen atoms of the SO_2 group in the formation of hydrogen bonds.

Series III, in which the regression coefficient is significantly less than unity, attracts attention in this connection. This implies that an "anomalous" tendency is observed for unsubstituted aminoazines—the levelling of acidity on passing from water to an aprotic medium. The most probable cause of this anomaly is specific solvation of the aminoazine anions at the endocyclic nitrogen atoms, which enhances the electron-accepting influence of the latter on the acid centre (indeed, as mentioned earlier, the Hammett constants for the aza-groups in water are larger than for the same groups in DMSO [48]). This factor is apparently more important than the decrease of the sensitivity of the anionic centre to the effects of the aza-groups in water (decrease of ρ) and the difference between pK_{DMSO} and pK_a therefore increases with increasing sensitivity of the aminoazines, in contrast to what is observed for other NH acids.

An analogous phenomenon can probably occur also for azoles. For example, the difference between pK_{DMSO} and pK_a (i.e. ΔpK) increases with increase of acidity in the sequence pyrroles (5.5) < pyrazole (5.8) < triazole (6.2) (Fig.1). However, there is no doubt that the actual situation may be more than complex because the pyrazole and triazole anions each contain two equivalent nitrogen atoms, which function as both anionic centres and substituents simultaneously.

We shall now consider how the change from a polar to a weakly polar medium is reflected in the relative strengths of NH acids. In a weakly polar medium the protolytic equilibrium involves species resulting from the association of the free anions with the counterion (M^+), in particular ion pairs, and not the free ions themselves (Eqn.(1)):[42,82]

$$\rangle NH + A^-M^+ \rightleftharpoons \rangle N^-M^+ + AH\,. \qquad (3)$$

The pK_{NH} calculated by Eqn.(2) from the equilibrium constant of reaction (3) characterises the so-called "ion-pair" acidity (pK_p) and is related to the "free-ion" (pK_i) value of pK_{NH} determined for equilibrium (1):

$$pK_p = pK_i - \lg (K_{AM}/K_{NM}) \qquad (4)$$

where K_{AM} and K_{NM} are the dissociation constants of the ion pairs A^-M^+ and $\rangle N^-M^+$ into free ions. Evidently the stronger the association of the N-anion with the counterion (other conditions being equal) the greater the displacement of equilibrium (3), the greater the difference between pK_p and pK_i, and the greater the relative strength of the conjugate NH acid.

The effectis of ion association have been investigated in detail for CH acids[83-86], for which appreciable differences between the pK_i, measured in DMSO, and the pK_p, determined relative to the same standard in 1,2-dimethoxyethane (DME), have been established in many instances. The difference is particularly large (up to 8 logarithmic units) when the CH acid molecule contains a heteroatom (nitrogen or oxygen) to which there is a partial transfer of the anionic charge on ionisation of the C–H bond. The coordination of the counterions to such "hard" nucleophilic centres takes place with formation in DME of very stable contact ion pairs (for the varieties of the latter, see Szwarc[87]).

An analogous study has been carried out also for NH acids: the pK_p have been determined in DME for ~20 compounds, incorporating the Li^+ or Cs^+ counterions, relative to 9-phenylfluorene ($pK = 18.5$).[72] It has been shown that they are appreciably smaller than the corresponding pK_p, measured in DMSO and for Li^+ the difference between the pK values is greater than for Cs^+, since in the contact ion pair the anion is stabilised to a greater extent than the cation with a smaller radius. Since a "hard" nucleophilic centre (the nitrogen atom) is already present in N-anions, the introduction of other heteroatoms into such species is not accompanied by such an appreciable differentiation of the equilibrium "ion-pair" acidity as for the CH acids with analogous structures. Furthermore, satisfactory linear relations have been obtained for the entire set of NH acids investigated in DME:

$$pK_p(Li^+) = 0.89\,pK_i - 2.6 \quad (S = 1.0;\ r = 0.971)\,,$$
$$pK_p(Cs^+) = 1.01\,pK_i - 1.5 \quad (S = 0.6;\ r = 0.992)\,.$$

In the first equation the regreession coefficient is significantly less than unity, which indicates an enhancement of the stabilising effect of the lithium cation with increase of the intrinsic basicity of the N-anions. In the case of a

weaker interionic interaction (with the caesium cation), the stabilising effect of the counterion hardly changes in the acidity range investigated (18 logarithmic units).

The K_{NM} (M = Cs) in DME have been determined conductimetrically for a series of compounds (diphenylamine, carbazole, nitrophenyl-substituted NH acids, and certain others) and the pK_i in DME have been calculated by Eqn.(4).[72] The majority of the constants are slightly (by 0.3–0.5 of a logarithmic unit) smaller than the corresponding pK_i in DMSO, but the differences for the nitro-derivatives reach 1.4–1.9 logarithmic units. Such an appreciable difference can be a consequence both of the marked stabilisation of the nitrophenyl-substituted NH acids in the more basic DMSO and of the relatively less effective solvation of the corresponding *N*-anions in this solvent. At any rate, these results show that differentiation of the NH acid strengths is observed in protic solvents, but it does not occur for the analogous CH acids[42,82].

Thus our comparison of the quantitative data for the equilibrium NH acidities of organic compounds in media differing in their polar and proton-donating properties shows that specific solvation and ion association have a differentiating effect on the stability of their *N*-anions in solution. As a result of this, the available information about the NH acid strengths in a hydroxylated or weakly polar solvent can give rise to a distorted idea about the true structural rules governing the equilibrium NH acidity. In order to discover such rules, one can employ the NH acidity scale in DMSO or a similar p*K* scale established in a weakly polar solvent (for example in DME) with a counterion having a large radius (Cs^+). The most reliable information about the influence of the structure of compounds on their acidity is provided by the results of studies of protolytic equilibria in the gas phase.

IV. NH ACIDITY IN THE GAS PHASE

Studies of equilibria involving proton transfer in the gas phase have been prosecuted quite vigorously during the last decade. The usefulness of such research is undoubted because it gives rise to the possibility of separating the purely structural effects in acidity from the solvation effects[88]. However, as in the condensed phase, the main objects of investigations have been OH and CH acids. Data concerning the gas phase NH acidities of organic compounds are so far scanty and studies have been made mainly on the cationic forms of NH acids: alkylamines[89–92] and substituted pyridines[93] and anilines[94]. The results of such investigations have been analysed in fair detail in two reviews[88,95], which have been supplemented by an extensive communication by Taft and co-workers[96].

The relative strengths of the neutral forms of NH acids in the gas phase were first compared by Brauman and Blair[97], who established the following sequence in which acidity varies in the series of primary and secondary aliphatic amines: Et_2NH > t-$BuCH_2NH_2$ ≧ t-$BuNH_2$ ≧ Me_2NH ≧ iso-$PrNH_2$ > $PrNH_2$ > $EtNH_2$ > $MeNH_2$ > NH_3. Later Mackay et al.[98] determined the free energies ΔG of abstraction of a proton from the N–H bond in certain amines (Table 9) and showed that the acidity of amines is higher than that of ammonia. Thus it follows from the data presented that alkyl groups, which are usually regarded as electron donors, exhibit electron-accepting properties in the gas phase, stabilising amide anions. According to the above investigators[97,98], the stabilisation is due to the interaction between the negatively charged nitrogen atom and the polarisable alkyl group.

The ΔG for a series of other NH acids have been found by Kebarle and co-workers[100,101]. Having observed that the acidity of diacetamide is lower than that of its CH analogue, namely acetylacetone, the above investigators suggested that the ΔG found for barbituric acid (327.3 kcal mol^{-1})[100] characterises the acidity of the CH_2 group, while the energy of the deprotonation of the N–H bond should be somewhat higher (by ~2 kcal mol^{-1}). McIver and co-workers[99,102] determined the difference $\delta\Delta G$ in the gas phase between the ΔG for *p*-xylene (adopted as the standard acid), on the one hand, and pyrrole, aniline, and phenyl-substituted anilines, on the other. According to their estimate, $\delta\Delta G$ for the pair of NH acids methylamine and aniline is 35.9 kcal mol^{-1}, which makes it possible to calculate the ΔG indicated for aniline in Table 9 (we may note that ΔG = 353 kcal mol^{-1} has been obtained for pyrrole by an analogous procedure; cf. Table 9).

Table 9. The free energies of the deprotonation (ΔG) of certain NH acids in the gas phase.

Compound	ΔG, kcal mol^{-1}	*T*, K	Refs.
Ammonia	396.1	298	[98]
Methylamine	395.7	298	[98]
Ethylamine	391.7	298	[98]
Dimethylamine	389.2	298	[98]
Aniline	359.8	320	[99]
Pyrrole	351.8	300	[100]
Acetanilide	345.8	300	[100]
Acetylurea	341.1	300	[100]
Diacetamide	339.8	300	[100]
Succinimide	338.0	300	[100]

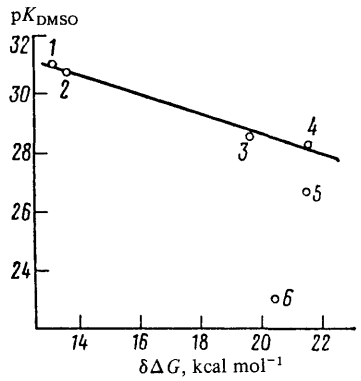


Figure 2. The equilibrium NH acidities of compounds in the gas phase (the relative deprotonation energies $\delta\Delta G$) and in DMSO (pK_{DMSO}): 1) 3-methylaniline; 2) aniline; 3) 3-chloroaniline; 4) 3-trifluoromethylaniline; 5) acetanilide; 6) pyrrole (according to the data in Tables 1, 3, 7, and 9).

It has been shown[99] that the $\delta\Delta G$ for *meta*- and *para*-substituted anilines are satisfactorily correlated with the Hammett σ constants (ρ = 10.4), but the points for the 3-F, 4-MeO, and 4-CF_3 substituents then deviate significantly from the straight line (r = 0.948). On the other hand, the two-parameter relations obtained for both series of substituted

anilines using the σ_I and σ_R^- constants are characterised by a high correlation coefficient (0.991). Bartmess et al.[99] note that the effects of the substituents are greater in the gas phase than in solutions. For example, in liquid ammonia and DMSO the parameters ρ of the Hammett relations (5.3 and 5.7 respectively) are smaller almost by a factor of two than in the gas phase (10.4). Furthermore, the ratio ρ_R^-/ρ_I for *meta*-substituted compounds decreases and that for *para*-substituted compounds increases on passing from the gas phase to the condensed phase.

For substituted anilines, a satisfactory agreement is observed between the acidities in the gas phase and in DMSO,[99] while in other cases there is an inversion of the acidity sequence (cf., for example, acetanilide and pyrrole in Fig.2). Consequently an appreciable superposition of solvation effects on structural effects cannot be ruled out even in an aprotic solvent. The view according to which the rules governing the variation of the "intrinsic" acidity (i.e. the acidity determined only by the molecular structure) of compounds can be established only by methods for the investigation of gas-phase proton-transfer processes is therefore apparently quite valid[88].

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In conclusion we may note that the expansion of studies on protolytic equilibrium in the gas phase and in an aprotic medium is in our view quite promising. The result of such investigations not only make it possible to obtain the correct idea about the relation between NH acidity and the structure of a compound but also one can solve the practically important problem of the quantitative estimation of solvation effects, including the effect of specific solvation, in acid–base interactions. The study of processes involving the transfer of a proton in the N–H bond in the excited states of acid and conjugate base molecules is of both theoretical and practical interest[103].

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