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REVIEW

Basicity and Nucleophilicity of Aryl-Containing N-Anions

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Abstract—New data on the basicity of N-centered anions in the gas phase and in DMSO solution are analyzed. The results of quantitative studies on the reactivity of N-anions in nucleophilic substitution are systematized, and general factors determining their nucleophilicity are discussed.

I. INTRODUCTION

N-Anions are usually generated from NH acids by the action of strong bases. They are used in the synthesis of amino derivatives by replacement of halogen atoms in alkyl and aryl halides. Extension of the scope of preparative applications of N-anions has aroused interest in structural factors determining the acidity of NH group in organic compounds, taking into account that the basicity of N-anions is quantitatively described by pK_a of the conjugate NH acid. Here, it is most important to examine NH acidity in nonaqueous media, for pK_a values of most organic NH acids in water could not be measured because of protonation of the N-anion. Measurement of equilibrium NH acidity in the gase phase and in a dipolar aprotic solvent, such as DMSO, makes it possible to estimate both the effect of substituents and solvation effect, which are significant factors determining nucleophilic reactivity of N-anions generated from NH acids. Studies of these factors are also necessary for systematization of quantitative data on nucleophilic reactivity. Analysis of the reactivity of aryl-containing N-anions is also important from the viewpoint of developing methods for functionalization of aromatic amines in order to obtain monomers, antioxidants, medical preparations, and dendrimers which are used in various fields of technics [1–3].

In the recent years, new data have been reported on both equilibrium NH acidity of organic compounds and nucleophilicity of N-anions in substitution reactions. The present review analyzes these data with the goal of systematizing general relations between the structure of NH acid, bacisity of the conjugate anion, and nucleophilicity of the latter in substitution processes.

II. EQUILIBRIUM NH ACIDITY

Starting from the middle 1970s, equilibrium NH acidity has become the subject of systematic studies in terms of the two existing equilibrium acidity scales in DMSO: relative [4–9] and absolute [10, 11]. Both scales are based on the results of the indicator

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procedure which utilizes spectrophotometric determination of the equilibrium constant (K_{eq}) for proton transfer from NH acid to anion of an indicator acid:

$$ArNHR + Ind^- \underset{}{\overset{K_{eq}}{\rightleftharpoons}} Ar\bar{N}R + IndH$$

The pK value of an NH acid is calculated using the equation $\log K_{eq} = pK_{IndH} - pK_{ArNHR}$, where pK_{IndH} is pK of indicator acid.

In the framework of the relative scale, the strength of an NH acid is estimated with respect to pK of 9-phenylfluorene (18.5), determined in aqueous sulfolane [12]. The absolute scale was built up on the basis of potentiometric data, according to which pK of 9-phenylfluorene is equal to 17.9 log units [10].

Values of pK of Brønsted acids depend on the solvent, i.e., on the solvent ability to solvate proton, anion, and undissociated acid. There are solvents, e.g., DMSO, which ensure determination of acidity data without influence of ion association effects. The high dielectric constant of DMSO (ε = 49 at 20°C) makes it very advantageous for acidity measurements by various methods [10]. The NH-acidity data obtained in DMSO are characterized by the least deviations from the true pK values of NH acids, since stabilization of N-anions in DMSO is weaker than in protic solvents due to the absence of specific solvation. On the other hand, hydrogen bond formation between NH acid and DMSO cannot be ruled out [10, 13–15]. More precise data on equilibrium NH acidity can be obtained from the results of gas-phase studies, according to which the effect of substituents on the acidity in the gas phase is several times stronger than in solution [16].

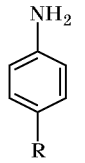
Published data on NH acidity in aprotic solvents and in the gas phase, reported by the beginning of 1980s, were summarized by Petrov [17]. The author discussed the effect of structural factors on the equilibrium NH acidity of arylamides, carboxamides, sulfonamides, polyfluoroaryl-containing compounds, and heterocycles, as well as acidifying effects of electron-acceptor substituents at the NH center. Also, stabilization of N-centered anions in solution (via specific solvation and ion association) on the relative NH acidity was considered. The data on gas-phase NH acidity were presented. The relative and absolute equilibrium NH-acidity scales were compared, and it was shown that the difference between these scales should be taken into account, which depends in turn on the range of pK values.

The present review summarizes experimental data on the equilibrium NH acidity, which were reported during the last 15 years.

II.1. Aniline and Its Derivatives

Alkylamines are too weak NH acids to determine their pK values in DMSO, but the acidity of the N–H bond in aniline, its *meta*- and *para*-substituted derivatives, and such NH acids as pyrroles, indoles, carbazoles, and imidazoles can be measured [18]. Bordwell *et al.* [19, 20] reported on the equilibrium NH acidities of aniline and its 26 derivatives in DMSO, which were measured by the indicator procedure. Table 1 lists previosuly unknown pK values for substituted anilines and diphenylamines. A Hammett plot with ρ = 5.67 was obtained for aniline and five its *meta*-substituted derivatives. The pK values of anilines, given in Table 1, fall into a range typical of known compounds of the same series. The points for strong donor and acceptor *para*-substituents deviate from the Hammett plot. According to [19], the reason is overestimated solvation of substituents in DMSO due to direct conjugation with the N-anionic center. In order to obtain a common Hammett plot for 3- and 4-substituted anilines, the substituent constants σ_p^- should be corrected. The increased NH acidity of *N*-methylaniline (by 1.1 log unit) is explained by polarizability of the methyl group [21]. Introduction of a phenyl group to the nitrogen atom of aniline increases the NH acidity by 5.6 log units. The presence of a phenylamino group in position *4* of the benzene ring in diphenylamine reduces the NH acidity by 0.6 log unit. Substituent in the *para*-position of the second benzene ring in diphenylamine does not exert an appreciable effect on the NH acidity, for its conjugation with the N-anionic center is sterically hindered (Table 1). In going from 4-substituted anilines to 4-substituted 1-naphthylamines, the NH acidity increases due to stronger electron-acceptor effect of the naphthyl group compared to phenyl and higher sensitivity of the NH acidity of naphthalene derivatives to substituent effect [22]. The acidity of 4-substituted 1-aminoanthraquinones is greater than the acidity of 4-substituted 1-naphthylamines owing to greater electron-acceptor power of the system through which the substituent effect is transmitted [23]. The series of 4-substituted 1-aminoanthraquinones is characterized by higher sensitivity of the NH acidity to substituent effect (ρ = –7.75), as compared to 4-substituted anilines (ρ = –6.85), but lower, as compared to 4-substituted 1-naphthylamines (ρ –8.06) [23]. This means that increase in NH acidity should not necessarily be accompanied by increase in its sensitivity to substituent effect. We showed in [23] that the sensitivity of NH acidity to substituent effect, estimated as the ρ value in the Hammett equation, is linearly related to the squared orbital coefficient

Table 1. Equilibrium NH acidities of anilines, diphenylamines, naphthylamines, and aminoanthraquinones in DMSO at 25°C (absolute scale [19–23])



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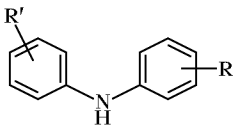

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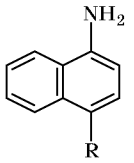

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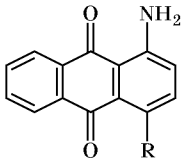

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Comp. no.	R	p*K*	Comp. no.	R	p*K*	Comp. no.	R	p*K*
1	4-F	30.7	**13**	4-Ac	25.3	**25**	4-Me	29.5
2	N-Me	29.5	**14**	2-CN	24.3	**26**	H	29.1
3	4-Cl	29.4	**15**	2,4,6-Cl_3	23.5	**27**	4-Cl	27.1
4	4-Br	29.1	**16**	4,4′-$(MeO)_2$	26.7	**28**	4-Br	26.8
5	2-F	28.7	**17**	4-MeO	25.8	**29**	4-CN	22.5
6	2,4-F_2	28.6	**18**	4-PhNH	25.8	**30**	4-NO_2	18.0
7	3-Br	28.4	**19**	4,4′-$(PhNH)_2$	25.6	**31**	4-MeO	22.7
8	3-CF_3	28.2	**20**	4-Me	25.5	**32**	H	22.6
9	2-Cl	27.6	**21**	3-Me	25.3	**33**	4-Cl	20.6
10	4-CF_3	27.0	**22**	3-Cl	23.4	**34**	4-Br	20.5
11	3-CF_3SO_2	26.2	**23**	4,4′-Br_2	22.2	**35**	4-NO_2	12.3
12	3,5-$(CF_3)_2$	25.8	**24**	4-NO_2	16.9			

of the carbon atom to which the substituent is attached in the HOMO of the N-anion: $\rho = -24.5(C_R)^2 - 2.52$; $r = 0.993$, $s = 0.06$, $n = 8$.

II.2. Cyclic NH Acids

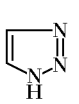
The known data on the acidity of nitrogen-containing heterocycles [17] were supplemented in [11, 20, 21, 24, 25] by p*K* values of some azines and azoles (Table 2). The acidity of 1,2,3-triazole is greater than the acidity of 1,2,4-triazole by about an order of magnitude. Introduction of halogen atoms into positions *2* and *2,6* of carbazole, as well as benzene ring fusion, enhances the NH acidity.

Insertion of an oxygen bridge into diphenylamine molecule increases the acidity by 3.4 log units. Insignificant change of NH acidity in going from diphenylamine to cyclic structures like iminostilbene and iminodibenzyl is explained by acoplanarity between the bridging atoms and benzene rings [20].

The acidity variation in the series of 5-substituted indoles conforms to the Hammett equation with $\rho = -3.9$, and aromaticity of the pyrrole ring is responsible for a weak influence of the 5-substituent on the acidity of the N–H bond [24]. Table 3 contains p*K* values of cyclic carboxamides and thiocarboxamides in DMSO [25, 26]. The acidity increases by 1.3–2.3 log units on introduction of C=X (X = O, S) moiety into heteroring; the cyclization effect is estimated at 0.1–3.4 log units [26]. The higher acidity of 2-pyridinone relative to its saturated analog, 2-piperidinone, stems from the aromatic character of the conjugate base of the former. Increase in the NH acidity in going from 2-pyridinone to 4-oxo analog ($\Delta pK = 2.2$) may be attributed to the greater energy of the aromatic base owing to stronger charge separation and repulsion between unshared electron pairs on the oxygen and nitrogen atoms [25]. 2-Quinolinone is a weaker NH acid than 2-pyridinone. Obviously, the negative charge on the oxygen atom in the conjugate base of 2-quinolinone is not delocalized over the benzene ring. Replacement of the oxo group in 2,3-dihydro-1*H*-indol-2-one, 2-piperidinone, 2- and 4-pyridinones, and 2-quinolinone by thioxo leads to considerable increase in the NH acidity. This may be explained by higher energy of the corresponding sulfur-containing bases as compared to their oxygen analogs, as well as by greater ability of sulfur to delocalize negative charge [27].

The acidity of 4-substituted urazoles originates from the presence of an acylhydrazyl moiety and heterocyclic nature of the urazole ring (Table 4). The Hammett dependence for 4-(*p*-R-phenyl)urazoles is

Table 2. Equilibrium NH acidities of nitrogen-containing heterocycles in DMSO at 25°C (absolute scale [11, 20, 21, 24, 25])



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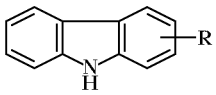

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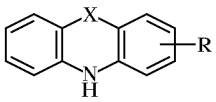

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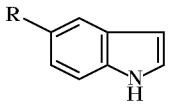
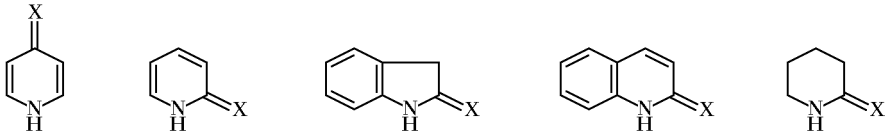


43–46

Comp. no.	NH acid	p*K*	Comp. no.	NH acid	p*K*
36	1,2,3-Triazole	13.9	**42**	Iminostilbene	26.1
37	2,6-Dibromocarbazole	17.15	**43**	5-Methoxyindole	21.7
38	1*H*-Dibenzo[*a*,*i*]carbazole	17.7	**44**	5-Chloroindole	20.2
39	2-Chlorocarbazole	18.52	**45**	5-Bromoindole	19.3
40	Phenoxazine	21.65	**46**	5-Nitroindole	15.7
41	Iminodibenzyl	25.5			

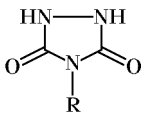
Table 3. Equilibrium NH acidities of cyclic carboxamides and thiocarboxamides in DMSO at 25°C (absolute scale [25, 26])



X = O, S.

NH acid	p*K*	NH acid	p*K*
2,3-Dihydro-1*H*-indole-2-thione	10.0	Quinolin-2(*H*)-one	17.6
Pyridine-4(1*H*)-thione	11.8	2,3-Dihydro-1*H*-indol-2-one	18.2
Pyridine-2(1*H*)-thione	13.3	3,3-Dimethyl-2,3-dihydro-1*H*-indol-2-one	18.5
Quinoline-2(*H*)-thione	13.7	3,3-Dibenzyl-2,3-dihydro-1*H*-indol-2-one	18.7
Pyridin-4(1*H*)-one	14.8	2-Piperidinone	26.4
Pyridin-2(1*H*)-one	17.0		

Table 4. Equilibrium NH acidities of 4-substituted urazoles (tetrahydro-1*H*-1,2,4-triazole-3,5-diones) in DMSO at 25°C (absolute scale [28])



R	p*K*	R	p*K*
CH_3	12.2	Ph	11.0
4-$CH_3C_6H_4$	11.4	4-ClC_6H_4	10.6
4-$CH_3OC_6H_4$	11.3	3-ClC_6H_4	10.4

characterized by a ρ value of 1.94 (r = 0.991) which indicates a weak transmittance of the substituent effect [28].

Analysis of the above data on equilibrium NH acidity of cyclic NH acids shows that incorporation of nitrogen atom in a cyclic structure reduces the sensitivity of NH acidity to substituent effect owing to aromatic character of the conjugate base.

II.3. Amides, Amidines, and Related Compounds

Table 5 contains p*K* values of carboxamides RCONHR′, sulfonamides RSO_2NHR', and thiocarboxamides RC(=S)NHR′, which supplement the set of

previously known data [17]. Replacement of hydrogen atom of the amino group in aniline derivatives by RCO group considerably increases the NH acidity (approximately by 10 orders of magnitude) and reduces the sensitivity to substitution pattern. The ρ value in the Hammett equation for nine *para*-substituted acetanilides is considerably smaller than the corresponding value for *meta*-substituted anilines (5.7 and 3.1, respectively) [29]. The nature of the alkyl group in the RCO fragment relatively weakly affects the NH acidity [30]. Introduction of a methyl group to the nitrogen atom of acetamide reduces the NH acidity only slightly, whereas analogous replacement of hydrogen by *tert*-butyl group in *t*-$BuCONH_2$ reduces the NH acidity by 2.45 log units, primarily because of steric hindrance to solvation. *p*-Methoxyacetanilide is a weaker NH acid than acetanilide (ΔpK = 0.6), while the presence of a cyano group in the same position increases the acidity by 2.9 log units. Such substituent effects should be considered from the viewpoint of conjugation with the acid center, which destabilizes or stabilizes the corresponding conjugate base. An analogous influence of substituents is observed on introduction of *para*-methoxy- and *meta*-trifluoromethyl groups into benzamide molecule: as a result, the NH acidity decreases by 0.65 log unit and increases by 1.5 log unit, respectively [30]. Replacement of the C=O group in carboxamides by $C-SO_2$ and C=S increases the NH acidity, presumably due to greater ability of sulfur to stabilize negative charge in the $RC(=X)NH^-$ anions, as compared to oxygen.

The NH acidity rises by about 10 orders of magnitude on replacement of one hydrogen atom in the amino group of carboxamides by hydroxy group [31]. As applied to sulfonamides, analogous structural transformation increases the NH acidity only by 0.7 log unit [29]. These data indicate essential difference in the structures of hydroxamic acids and their sulfonamide analogs. The sulfur atom in $PhSO_2NHOH$ has a tetrahedral configuration, and the S=O bond parameters are quite different from those of the C=O bond. Therefore, (1) stabilization of the sulfur-containing anion through formation of intramolecular hydrogen bond is impossible and (2) π-acceptor power of the sulfonyl group is much weaker than that of the carbonyl group, so that the negative charge in $PhSO_2N(OH)^-$ is localized on the nitrogen atom. Repulsion between unshared electron pairs on the nitrogen and oxygen atoms exerts a destabilizing effect which is sufficiently strong to compensate for the acidifying effect of the N−OH group [29]. O-Alkylation of hydroxamic acids leads to much smaller reduction of the NH acidity (by about an order of magnitude), as compared to the reduction of OH acidity caused by N-alkylation (~5 log units) [28]. These differences indicate that acetohydroxamic and benzohydroxamic acids behave in DMSO as NH acids. Hammett equations with ρ values of 2.8 and 2.7 were derived by Bordwell and co-workers [29] for the series of 3- and 4-substituted benzamides and benzohydroxamic acids, respectively.

Factors responsible for the acidity of compounds like $RC(=X)NH_2$ (X = O, NH, S) were analyzed in terms of a three-parameter equation [33]. The major contribution was found to be that of the field/induc-

Table 5. Equilibrium NH acidities of hydroxamic acids, carboxamides, sulfonamides, and thiocarboxamides in DMSO at 25°C (absolute scale [11, 26, 27, 29–32])

R	R′	p*K*
	RCONHR′	
Ph	OH	13.65
Me	OH	16.1
3-$CF_3C_6H_4$	H	21.85
3-ClC_6H_4	H	22.3
4-ClC_6H_4	H	22.6
$HOCH_2$	H	23.0
$PhOCH_2$	H	23.0
$PhSCH_2$	H	23.0
Ph	H	23.35
4-$CH_3OC_6H_4$	H	24.0
NH_2CH_2	H	24.7
NH_2	H	26.95
Me	4-$NO_2C_6H_4$	17.6
Me	4-CNC_6H_4	18.6
Me	4-$CF_3COC_6H_4$	19.5
Me	4-$CH_3OC_6H_4$	22.0
Me	CH_3	25.9
Me_3C	*t*-Bu	28.05
$PhCH_2$	Ph	20.6
PhS	Ph	23.0
PhO	Ph	23.0
	RSO_2NHR'	
Ph	OH	15.4
CF_3CH_2	Ph	5.7
	RC(=S)NHR′	
PhNH	Ph	13.4
CH_3	Ph	14.7
Ph	H	16.9
CH_3	H	18.45

Table 6. Effect of phenyl group on the NH acidity of carboxamides, thiocarboxamides, and amidines [27, 34]

Amide	p*K* (DMSO, 25°C, absolute scale)
$AcNH_2$	25.5
AcNHPh	21.45
$BzNH_2$	23.35
BzNHPh	18.77
$Ph(C=NH)NH_2$	26.7
Ph(C=NPh)NHPh	20.8
$Ph(C=NPh)NHNMe_2$	22.9
$(H_2N)_2C=NH$	28.5
$(PhNH)_2C=NH$	22.45
$(H_2N)_2C=O$	26.9
$(PhNH)_2C=O$	19.5
$(H_2N)_2C=S$	21.0
$(PhNH)_2C=S$	13.4

tive effect: it constitutes about 50% of the overall effect. The contributions of polarizability and resonance effect are approximately similar. Bordwell and Guo-Zhen [34] analyzed the effect of the above three factors on the NH acidity of acetamide, acetamidine, and thioacetamide and showed that the field/inductive effect should decrease in the series C=S > C=O > C=N, in parallel with the corresponding dipole moments. The polarizability and resonance effects should be greater for thioacetamide. A combination of these factors makes thioacetamide more acidic than acetamide and acetamidine. Replacement of the methyl group in acetamide, acetamidine, and thioacetamide by amino group reduces the NH acidity by 1.4–2.5 log units. The data in Table 6 illustrate the effect of phenyl group at the amide nitrogen atom of carboxamides, thiocarboxamides, and amidines. It is seen that in going from acetamide to acetanilide the NH acidity increases by about 4 log units, which is typical of such replacement. *N*-Phenylbenzamide is more acidic than benzamide by 4.6 log units, and the acidifying effect of replacement of hydrogen atoms at each nitrogen atom in benzamidine by phenyl groups is almost 6 orders of magnitude. At first glance, it seems to be surprising, for a much greater effect might be expected. The reason is that the two *N*-phenyl groups are incapable of effectively delocalizing negative charge in the conjugate anion because of steric hindrance. Replacement of the phenyl group at the amino nitrogen atom in *N*,*N*′-diphenylbenzamidine by dimethylamino group reduces the NH acidity of $Ph(C=NPh)NHNMe_2$ by 2.1 log units. Introduction of a phenyl group to each nitrogen atom of guanidine increases the NH acidity by 7.6 log units, i.e., the effect is somewhat stronger than that observed in going from benzamidine to *N*,*N*′-diphenylbenzamidine. A similar effect (ΔpK = 7.4) was observed on introduction of phenyl groups to each amino group of urea.

Table 7. Equilibrium NH acidities of hydrazines in DMSO at 25°C (absolute scale [35])

NH acid	p*K*
$PhNHNH_2$	28.8
PhNHNHPh	26.2
$PhNHNPh_2$	24.5
$EtCO_2NHNH_2$	22.2
$PhCONHNH_2$	18.9
$3\text{-}C_5H_4NCONHNH_2$	17.5
$PhSO_2NHNH_2$	17.1
$4\text{-}C_5H_4NCONHNH_2$	16.8
$PhSO_2NHNMe_2$	15.8
$2,4\text{-}(NO_2)_2C_6H_3NHNPh_2$	12.1

The acidifying effect of replacement of the C=O group by C=S is 6 log units, i.e., it is lesser by 2 orders of magnitude than the corresponding effect in indole derivatives [24].

As follows from the above data on equilibrium NH acidities of amides, amidines, and related compounds, introduction of an electron-acceptor group into the α-position with respect to the N-anionic center increases the NH acidity but reduces its sensitivity to substituent.

II.4. Hydrazines and Hydrazides

The equilibrium NH acidities of hydrazines are given in Table 7. Replacement of hydrogen atom in the amino group of anilines and carboxamides gives, respectively, hydrazines, and hydrazides and is accompanied by a small increase in the NH acidity (ΔpK = 1–3). The acidity slightly increases (by about 0.16–1.95 log unit) in going from anilines to phenylhydrazines [19]. A satisfactory Hammett equation was obtained for substituted phenylhydrazines. The corresponding ρ value (5.34) is slightly smaller than that found for substituted anilines (ρ = 5.67).

Introduction of the second phenyl group into the hydrazine molecule increases the acidity by 2.3 log units, and the third phenyl group exerts an effect equal to 2 log units. In the presence of two nitro groups in the *ortho*- and *para*-positions of the benzene ring in position *2* of 1,1,2-triphenylhydrazine, the NH acidity rises by 12.4 log units. Phenylhydrazines having an RC=O, RC(O)O, or RSO_2 group are more acidic

than phenylhydrazine [35]. When the hydrazine moiety is incorporated into a ring, the resulting structure is characterized by greater acidity, five-membered rings being more acidic than six-membered (ΔpK = 3.1–4 and 0.5–1, respectively) [28, 35]. Pyridinecarbohydrazides are by 4–5 orders of magnitude more acidic than the corresponding carboxamides. The greater acidifying effect of nitrogen atom in position *4* rather than *3* of the pyridine ring is typical not only of hydrazides, but also of amides and aminopyridines. The observed increase in the acidity of hydrazides relative to amides may be explained by the field/inductive effect of the α-NH_2 group in the anion $PhCON(NH_2)^-$. Reduction of the NH acidity by an order of magnitude on replacement of the NH_2 group in $PhSO_2NH_2$ by hydrazino group may be due to effect of charge localization in $PhSO_2N(NH_2)^-$, which overcomes acidifying effect of the α-NH_2 group. The α-NMe_2 group in sulfonamides enhances the acidity by an order of magnitude, presumably because of polarization effect; the reverse situation with carboxamides is likely to result from steric reasons [29]. Thus the transition from anilines and carboxamides to hydrazines and hydrazides is accompanied by rise in NH acidity and somewhat weakening of the substituent effect transmission.

II.5. Scale of Equilibrium NH Acidity in DMSO

Bordwell [11] summarized the data on equilibrium acidities in DMSO of more than 70 NH acids, including azines, azoles, hydrazines, carbonyl compounds, and sulfonamides. Also, references were given to papers where effects of structural variations (such as introduction of electron-acceptor groups and aromatization) on the equilibrium NH acidity are discussed. Hammett plots were built up for series of NH acids in which the substituent is remote from the N-anionic center, and the corresponding ρ values were calculated (Table 8), which can be used to estimate p*K* of new compounds belonging to those series.

Thus structural variations intrinsic to the transition from ammonia to aniline induce twice as large growth of NH acidity (about 10 orders of magnitude) as that observed in going from aniline to diphenylamine and from diphenylamine to carbazole. The presence of a carbonyl group between the benzene ring and amino group in benzamide gives rise to a ~10^7-fold increase of the NH acidity, and the acidifying effects of thiocarbonyl and sulfonamide groups are considerably stronger and approximately similar to each other (~14 log units). Replacement of one hydrogen atom in the amino group of benzamide by hydroxy group increases the NH acidity by ~10 orders of magnitude.

Table 8. Parameters of the Hammett equations for equilibrium NH acidities in DMSO at 25°C [11, 22–24]

NH acid series	$-\rho$	*n*	r^2
1,4-$RC_{10}H_6NH_2$	8.1	6	0.986
4-R-1-Aminoanthraquinones	7.7	5	0.994
$ArNH_2$	5.7	6	0.998
ArNHAr′	5.4	3	0.997
Phenothiazines	5.2	5	0.982
$ArCONHCH_3$	4.1	6	–
5-R-Indoles	4.0	5	0.980
ArCONHOH	2.6	4	0.989

In going from aniline to phenylhydrazine, the NH acidity rises by only 2 orders of magnitude, whereas analogous transition from benzamide to benzohydrazide is characterized by twice as strong effect. The magnitude of acidifying effects caused by the above structural variations depends on the degree of stabilization of the conjugate anions. In the case of NH acids whose ionization in DMSO gives rise to highly delocalized anions, increase in the acidity may be due to enhanced solvation through dispersion interactions. The effect of structural factors on the NH acidity can be separated from solvation effects by considering equilibrium acidities in the gas phase.

II.6. Equilibrium NH Acidity in the Gas Phase

Taft and Bordwell [36] compared the equilibrium NH acidities of some NH acids in DMSO and in the gas phase. Table 9 contains differences between p*K* values of NH acids and 9-phenylfluorene in the gas phase and in DMSO and variations of the NH acidity in going from the gas phase to DMSO. For an NH acid NA, the effect of the medium is a measure of the solvent (DMSO) ability to stabilize anion A^- relative to 9-phenylfluorenyl anion minus the ability of DMSO to stabilize the NH acid NA relative to 9-phenylfluorene. Positive sign of $\delta_s\Delta G^0$ corresponds to acidifying effect.

Replacement of hydrogen atom in the NH group by phenyl group could stabilize the corresponding N-anion through charge delocalization over the aromatic π-system due to polarization and field/inductive effects. All these effects in N-anion are stronger than in the initial NH acid, and each acts to increase the acidity (cf. $-\Delta G_g^0$ values for ammonia, aniline, diphenylamine, acetamide, trifluoromethylacetamide, and the corresponding benzanilides). Introduction of a nitro group into the aniline molecule also exerts

Table 9. Influence of structural ($-\Delta G_g^0$) and solvation factors ($\delta_s\Delta G^0$) on the relative NH acidity (with respect to 9-phenylfluorene,[a] kcal/mol [36]

NH acid	$\delta_s\Delta G^0$ [b]	$-\Delta G_g^0$	$-\Delta G_s^0$
NH_3	~29	–60.6	~–32
$PhNH_2$	6.2	–23.6	–17.4
p-$NO_2C_6H_4NH_2$	–3.3	–0.7	–4.0
Ph_2NH	–1.3	–8.3	–9.6
$AcNH_2$	9.2	–19.6	–10.4
CF_3CONH_2	2.2	–1.2	1.0
$CH_3CONHPh$	–0.1	–5.1	–5.0
$CF_3CONHPh$	–2.0	9.1	7.1
4-Aminopyridine	2.5	–14.3	–11.8
3-Aminopyridine	3.3	–17.8	–14.5
2-Aminopyridine	6.7	–20.1	–13.4
Pyrrole	8.4	–15.4	–7.0
Pyrazole	8.1	–10.9	–2.8
Imidazole	6.3	–7.3	–1.0
Indole	2.3	–6.4	–4.1
Carbazole	–0.9	–1.9	–2.8

[a] Data for 9-phenylfluorene: 335.5 kcal/mol (gas phase) and 24.5 kcal/mol (DMSO).
[b] $\delta_s\Delta G^0 = \Delta G_g^0 - \Delta G_s^0$.

an acidifying effect (22.9 kcal/mol in the gas phase and 13.4 kcal/mol in DMSO). Destabilizing effect of repulsion between *p*-electron pairs belonging to contiguous atoms is well illustrated by variation of the gas-phase acidity of aminopyridines, pyrazole, and imidazole. The reverse order of variation of the acidity of 2- and 3-aminopyridines in DMSO is explained by stronger solvation of the 2-aminopyridine anion. Fusion of a benzene ring increases the gas-phase acidity in going from pyrrole to indole and carbazole by 13.5 kcal/mol, while in DMSO the increase in acidity is only 4.2 kcal/mol. When an N-anionic center is incorporated into a ring, the acidity also rises (cf. $-\Delta G_g^0$ values for aniline and diphenylamine with those of indole and carbazole).

Koppel *et al.* [37] measured the gas-phase NH acidities of various classes of NH acids, such as anilines, diarylamines, nitrogen-containing heterocycles, imides, and amides. The range of variation of the gas-phase acidity of the above NH acids is about 100 kcal/mol. In going from the gas phase to DMSO, this range decreases almost by half. The gas-phase NH acidities were correlated with p*K* values in DMSO for the series of anilines, imides, amides, heterocyclic NH acids, and diphenylamines. Approximately similar weakening of the substituent effect on proton transfer equilibrium due to solvation (i.e., reduction of the sensitivity of N-anionic center to substituent in going from the gas phase to solution) was observed for the series of anilines having π-acceptor group in the *para*- and *ortho*-positions or fluorine atom, heterocyclic NH acids and ammonia, and diphenylamines. These NH acid series are characterized by strong stabilization of the anionic form relative to the conjugate NH acid in going to solution. The slopes of the Δ*G*—p*K* dependences are also similar (1.44–1.58). A slightly greater weakening of the substituent effect on proton transfer equilibrium in going from the gas phase to DMSO was observed for imides (1.75) and amides (1.61). The strongest solvent effect was found for *meta*-substituted anilines (2.83) whose conjugate anions poorly delocalize the negative charge.

It should be noted that measurements of the equilibrium NH acidity in the gas phase and in a dipolar aprotic solvent (DMSO) allows separation of proper structural effects from those produced by the solvent. This is important for studying nucleophilic reactivity of N-anions generated from NH acids.

III. NUCLEOPHILICITY OF ARYL-CONTAINING N-ANIONS

Nucleophilic substitution reactions are extensively studied and are widely used in organic synthesis. Their efficiency can be increased through application of charged nucleophiles in aprotic dipolar solvents [38, 39]. Therefore, systematization of quantitative data on the nucleophilicity of aryl-containing N-anions in substitution reactions is important for establishing factors responsible for their reactivity [40].

The problem of quantitative description of nucleophilic reactivity can be solved in terms of several approaches which allow prediction of the rate and direction of nucleophilic substitution to be made for a series of structurally related reagents [40, 41]. Among such approaches, that utilizing the Brønsted equation is used especially widely. It implies estimation of the reactivity of a nucleophile with regard to its basicity [40]. Quantitative reactivity measurements require generation of N-anions at high concentrations, which can be achieved through the use of dipolar aprotic solvents [42, 43].

III.1. Nucleophilicity of Aryl-Containing N-Anions in S_N2 Reactions

Bordwell and Hughes [44, 45] studied the kinetics of reactions of benzyl halides in DMSO with a series of N-anions derived from anilides, carbazoles, pheno-

Table 10. Rate constants (l mol^{-1} s^{-1}) of reactions of N-anions with benzyl chloride and 3-trifluoromethylbenzyl chloride in DMSO at 25°C [44]

NH acid	pK[a]	k_{PhCH_2Cl}	$k_{3\text{-}CF_3C_6H_4CH_2Cl}$
Carbazole	19.90	0.337	0.841
3-Chlorocarbazole	18.50	0.111	0.286
3,6-Dibromocarbazole	17.16	4.44×10^{-2}	9.06×10^{-2}
13*H*-Dibenzo[*a*,*i*]carbazole	17.69	3.15×10^{-3}	–
Diphenylamine	24.95	3.85	16.90
3-Chlorodiphenylamine	23.50	0.820	3.31
4,4′-Dibromodiphenylamine	22.20	0.490	–
N-Ethyl-3,5-dibromoaniline	26.30	10.10	–
Phenothiazine	22.72	2.56	22.45
2-Chlorophenothiazine	20.79	0.603	3.42
3,7-Dibromophenothiazine	20.13	0.378	–
3-Tosylphenothiazine	18.46	2.83×10^{-2}	0.114
Phenothiazine 5,5-dioxide	15.75	6.20×10^{-4}	9.39×10^{-4}
Acetanilide	21.45	0.101	–
Benzanilide	18.80	3.19×10^{-3}	–

[a] Absolute scale.

thiazines, and diphenylamines, which cover the basicity range from 17 to 25 log units. The rate constants are given in Table 10. Comparison of the reactivity of N-anions with the reactivity of structurally related carbanions revealed some similarity in the steric effects, Brønsted coefficients, and structure–reactivity relation. It was presumed that S_N2 reactions of N-anions, as well as of carbanions, with alkyl halides involve electrons of *p*-orbital rather than lone electron pair on sp^2-orbital. Brønsted relations between the rate constants and pK of the conjugate NH acids in the basicity range covering about 12 orders of magnitude indicate that the basicity of N-anions is the main factor determining their nucleophilicity and that solvation and steric effects are accessory. All Brønsted plots are characterized by approximately similar slopes β = 0.32–0.33, the straight line for the carbazole series extends that plotted for the phenothiazine series, and the plot for diphenylamines is located to the right from the first two. The deviations observed for some phenothiazinide ions from the Brønsted plot for the carbazole–phenothiazine series may be attributed to enhanced solvation of N-anions having strong electron-acceptor substituents in positions conjugated with the anionic center. According to [44], the sixfold reduction of the reactivity of N-anions derived from diphenylamines, as compared to carbazoles and phenothiazines of the same basicity, is explained by steric factors. The nucleophilicity of N-anions toward alkyl halides in DMSO is lower by a factor of 80 than the nucleophilicity of structurally similar carbanions possessing the same basicity.

The Brønsted coefficients for S_N2 reactions with alkyl halides of C-, O-, and N-centered anions are roughly similar; therefore, the nucleophilicities of different kinds of anions can be compared within the same basicity range [44]. The following reactivity series is observed: $C^- > O^- > N^-$. Factors responsible for this reactivity series may be the length and strength of the C–C, C–O, and C–N bonds and electronegativity of the donor atom in the anionic center. Insignificant differences between the Brønsted coefficients for C-, O-, and N-anions suggest similar structures of the corresponding transition states despite different natures of the anionic reaction center. Assuming that the Brønsted coefficient reflects the fraction of charge which is transferred from anion to substrate in the transition state, the above results show that reactions of a given substrate with delocalized anions of different structures involve transfer of similar amounts of charge over a wide range of basicity variation.

Correlations were found between the basicity of carbazole N-anions and rate constants of their reaction with cyclohexyl bromide (E_2) in DMSO at 25°C, the Brønsted coefficient β being equal to 0.40 [46]. These reactions are slower than S_N2 reactions of the same nucleophiles with benzyl halides (Tables 10, 11).

A considerably greater value of β (0.8) was found while studying the kinetics of isomerization of 3-butenonitrile in DMSO in the presence of sulfon-

Table 11. Rate constants (l mol^{-1} s^{-1}) of reactions of carbazole N-anions with cyclohexyl bromide in DMSO at 25°C [46]

NH acid	pK[a]	$k \times 10^3$
Carbazole	19.90	21.20
3-Chlorocarbazole	18.50	5.80
3,6-Dibromocarbazole	17.16	1.69

[a] Absolute scale.

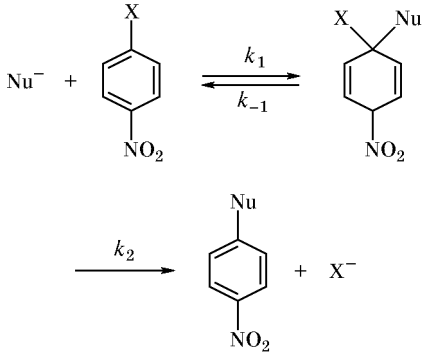
amide N-anions [47]. Analogous values of β were obtained for deprotonation of α-cyano CH acids in water with amines. Presumably, this is the result of formation of delocalized α-cyano carbanions [47].

Niyazymbetov *et al.* [48] proposed to use oxidation potentials of N-anions generated from nitrogen-containing heterocycles to estimate their reactivity toward alkyl halides. It was shown that N-anions derived from heterocyclic NH acids are characterized by much lower sensitivity of the rate constant to variation of the oxidation potential, as compared with sulfur-, oxygen-, and carbon-centered anions. This was explained in terms of essential differences between heterocyclic N-anions and N-anions of other structural types, namely by the fact that S_N2 reactions of heterocyclic N-anions are likely to involve the second σ-orbital rather than π-HOMO [48].

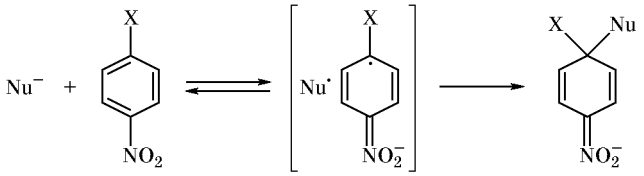
III.2. Nucleophilicity of Aryl-Containing N-Anions in S_NAr Reactions

The reaction of nitrodiphenylamine potassium salts with 2,4-dinitrofluorobenzene at 80 and 110°C in DMF and HMPA follows the second-order kinetics [49]. The kinetic data were compared with basicities of the corresponding secondary aromatic amines in DMFA, and a log$k$—pK correlation was found for the series of 2,4,2′-trinitro-4′-R-diphenylamine potassium salts (R = OMe, Me, H, Cl). The obtained data are consistent with the S_NAr mechanism involving the corresponding N-anions. The reaction in HMPA is faster than in DMF, which may be due to greater ability of the former to specific solvation [49].

The nucleophilicity of N-anions in S_NAr reactions in DMSO was quantitatively studied using the reactions of phenothiazine N-anions with *p*-nitrophenyl halides (Hlg = F, Cl, Br) and *p*-nitrodiphenyl ether as examples [50] (Table 12). It was shown that most S_NAr reactions follow the addition–elimination pattern with formation of carbanionic intermediates [51, 52]:



It is also probable that the first stage involves nonchain one-electron transfer [50]:



The observed series of the leaving group effect on the rate constant (F > Cl ≈ Br > OPh) is also consistent with the addition–elimination mechanism. The Brønsted plot for the reaction of phenothiazinide ions with *p*-nitrofluorobenzene is characterized by a slope β of 0.51, and for the reactions with *p*-nitrophenyl chloride and bromide, β ≈ 0.7. The donor atoms are arranged in the order $C^- > O^- > N^-$ with respect to their effect on the rate of S_NAr reaction, i.e., it is the

Table 12. Rate constants (l mol^{-1} s^{-1}) of S_NAr reactions of N-anions derived from substituted phenothiazines in DMSO at 25°C [50]

R	pK[a]	$k_{p\text{-}NO_2C_6H_4Cl}$	$k_{p\text{-}NO_2C_6H_4F}$	$k_{p\text{-}NO_2C_6H_4Br}$	$k_{p\text{-}NO_2C_6H_4OPh}$
H	22.72	9.95×10^{-3}	9.41×10^{-1}	9.76×10^{-3}	5.78×10^{-4}
2-Cl	20.79	4.35×10^{-4}	9.31×10^{-2}	4.50×10^{-4}	–
3,7-Br_2	20.13	–	4.50×10^{-2}	–	–

[a] Absolute scale.

Table 13. Rate constants ($l\ mol^{-1}\ s^{-1}$) of reactions of N-anions derived from aryl- and diarylamines with *p*-nitrophenyl halides in DMSO

NH acid	pK^a	$k_{p\text{-}NO_2C_6H_4F} \times 10^3$, 25°C [53]	$k_{p\text{-}NO_2C_6H_4Cl} \times 10^3$, 60°C [55]
Pentafluoroaniline	23.10	143	111.20
4-Nitroaniline	21.50	29.60	33.30
4-Aminotetrafluoropyridine	19.20	7.56	11.20
4-Cyanotetrafluoroaniline	17.90	4.81	4.25
Diphenylamine	25.55	330	–
3-Chlorodiphenylamine	24.10	210	–
4-Nitrodiphenylamine	17.45	3.53	–
N-(4-cyanotetrafluorophenyl)aniline	14.70	1.16	–

[a] Relative scale.

same as in S_N2 reactions, but in the former case the reactivity is lower by 1–3 orders of magnitude. The Brønsted coefficients for aromatic nucleophilic substitution with participation of C-, N-, and O-anions change over a range of 0.5–0.7, which is considerably wider than the corresponding range for S_N2 reactions (0.2–0.5); this indicates a greater charge transfer in the transition state of S_NAr reactions [50].

We studied in [53] the kinetics of reactions of *p*-nitrophenyl fluoride in DMSO at 25°C with N-anions generated from aryl- and diarylamines:

$$ArRN^-\ Na^+ + 4\text{-}O_2NC_6H_4F \longrightarrow ArRNC_6H_4NO_2\text{-}4$$

R = H, Ar′.

The corresponding Brønsted dependences were built up for the two series, β_{Nu} = 0.24 and 0.28 for diarylamines and arylamines, respectively. The rate constants (Table 13) were found to be lower than those reported previously for phenotiazine N-anions in the same reaction (Table 12). An analogous order of variation of the rate constants for diarylamines and phenothiazines was observed in S_N2 reactions of the corresponding N-anions with benzyl chloride in DMSO at 25°C (Table 10). These relations suggest approximately similar effects of steric factors on the reactivity of aryl- and diarylamine N-anions toward *p*-nitrophenyl fluoride. The effects are stronger than that found for phenothiazine N-anions, for they reduce the reaction rate by a factor of 5–10.

Unlike S_N2 reactions where the value of β_{Nu} for N-anions with different structures remains constant (~0.33), the Brønsted coefficient β for S_NAr reactions changes over a fairly wide range (from 0.14 to 0.74), i.e., the role of steric factor in the nucleophile increases [54].

Analysis of the nucleophilicities of arylamine N-anions in reactions with *p*-nitrophenyl chloride at 60°C [55] (R = H, Ar′):

$$ArRN^-\ Na^+ + 4\text{-}O_2NC_6H_4Cl \longrightarrow ArRNC_6H_4NO_2\text{-}4$$

and with *p*-nitrophenyl fluoride at 25°C [53] in DMSO shows that the chloride reacts at a lower rate than the fluoride (Table 13) and that the sensitivities of the rates of the two reactions to the basicity of arylamine N-anions are similar. One should not expect an appreciable effect of the nature of leaving group on β_{Nu} in S_NAr reactions, for such effect is not observed even in S_N2 reactions where rupture of the bond with leaving group occurs in the rate-determining stage.

Variation of the rate constants for reactions of diarylamine N-anions with pentafluoropyridine in DMSO at 25°C (Table 14) is described by the Brønsted equation [54], indicating linear relations between the effects of steric and solvation factors on both the basicity and the nucleophilicity of N-anions derived from diarylamines.

We measured the rate constants for reactions of aryl- and diarylamine N-anions with hexafluoroben-

Table 14. Rate constants ($l\ mol^{-1}\ s^{-1}$) of reactions of N-anions derived from diarylamines ArNHAr′ with pentafluoropyridine in DMSO at 25°C [54]

Ar	Ar′	pK^a	$k \times 10^3$
C_6F_5	C_5F_4N-4	9.4	2.31
C_6F_5	C_6F_5	12.6	31.10
C_6F_5	$C_6F_4CH_3$-4	13.3	84.10
Ph	C_5F_4N-4	15.1	169

[a] Relative scale.

Table 15. Rate constants (l mol^{-1} s^{-1}) of reactions of N-anions derived from aryl- and diarylamines ArNHR with hexafluorobenzene in DMSO at 25°C [54]

Ar	R	pK[a]	$k \times 10^3$
C_6F_5	H	23.1	4.43×10^4
$C_6H_4NO_2$-4	H	21.5	3.04×10^3
C_5F_4N-4	H	19.2	41.7
$C_{10}H_6NO_2$-1,4	H	18.0	10.8
C_6F_4CN-4	H	17.9	5.42
Ph	$C_6H_4NO_2$-4	17.45	2.47
Ph	C_6F_4CN-4	14.7	1.53
C_6F_5	C_6F_4Cl-4	12.0	0.373
C_6F_5	C_5F_4N-4	9.4	0.212

[a] Relative scale.

zene [54, 56] and found that the reactions of diarylamine N-anions with hexafluorobenzene (Table 15) occur at a lower rate than their reactions with pentafluoropyridine (Table 14).

$$ArRN^-Na^+ + C_5F_5N \longrightarrow 4\text{-}(ArN)C_5F_4N$$

R = H, Ar′.

The Brønsted dependences for reactions of aryl- and diarylamine N-anions with hexafluorobenzene [54, 56] suggest that the major contribution to the nucleophilicity of these anions is provided by their basicity. The Brønsted coefficient β_{Nu} increases with rise in electrophilic properties of the substrate, i.e., in going from hexafluorobenzene (0.14) to pentafluoropyridine (0.34) and from *p*-nitrophenyl fluoride (0.24)

Table 16. Brønsted coefficients β_{Nu} ($\log k = \beta_{Nu}\, pk + c$) and β_{ox} ($\log k = \beta_{ox}\, E_{ox} + c$) for reactions of aryl- and diarylamine N-anions with aryl halides in DMSO at 25°C[a]

N-Anion	Aryl halide	β_{Nu}	β_{ox}
$ArNH^-$	C_6F_6	0.74	–9.36
$ArNH^-$	*p*-$O_2NC_6H_4F$	0.28	–3.15
$ArNH^-$	*p*-$O_2NC_6H_4Cl$	0.26[b]	–3.11[b]
$ArAr'N^-$	C_5F_5N	0.34	–3.92
$ArAr'N^-$	*p*-$O_2NC_6H_4F$	0.24	–4.00
$ArAr'N^-$	C_6F_6	0.14	–1.73
Phenothiazinide	*p*-$O_2NC_6H_4F$	0.51 [50]	–6.82[c]

[a] Data of [54].

[b] At 60°C.

[c] Calculated from the data of [50] and [58].

to hexafluorobenzene (0.74) within the same range of basicity variation. These data indicate enhanced charge transfer from nucleophile to substrate in the transition state of S_NAr reactions [54]. The observed increase of β_{Nu} with rise in the basicity of N-anions for the reaction with hexafluorobenzene was interpreted in terms of the Marcus equation as a result of considerable change in heights of internal barriers, i.e., assuming different structures of transition states in the two reactions [54].

Analysis of the relations between oxidation potentials and logarithms of the rate constants for reactions of N-anions with aryl halides in DMSO [56] showed that the slope of the straight lines for the same substrate increases as the negative value of oxidation potential rises. The larger Brønsted coefficient β_{Nu} corresponds to the greater sensitivity β_{ox} of the reaction rate to oxidation potential E_{ox} of N-anion (Table 16) [54]. It is known that many reactions of nucleophiles with electrophiles can follow the SET (single electron transfer) mechanism [58]. Bordwell and Harrelson [59] showed that the probability for reactions of the same electrophile to follow the SET mechanism increases as the negative value of oxidation potential of the nucleophile rises. It was presumed that the main factors responsible for the transition from S_N2 and S_NAr reactions to SET are the ease of nucleophile oxidation and the ease of electrophile reduction [59–61]. Therefore, β_{ox} values may be used to estimate the probability of change of the reaction mechanism from S_NAr to SET.

Thus analysis of published data shows that nucleophilic reactivity of aryl-containing N-anions in substitution reactions can be estimated from their basicity and sensitivity of the reaction rate to basicity variation. In going from S_N2 to S_NAr reactions, the effect of steric factors on the nucleophilicity increases, which leads to extension of the range of variation of the Brønsted coefficients for S_NAr processes.

IV. CONCLUSION

New data on the equilibrium NH acidity of organic compounds were systematized, and the relation between the structure of a compound and its NH acidity was analyzed. The equilibrium NH acidities in the gas phase and in DMSO solution were compared, which allowed us to separate proper structural effects from those exerted by the solvent. Analysis of the data on equilibrium NH acidities is important for studying nucleophilic reactivity of N-anions since their basicity is measured as pK of the conjugate NH acid.

Published data on the nucleophilicity of N-anions in substitution reactions were summarized. As follows from these data, if the effects of solvation and steric factors remain constant, the reaction rate is determined by the basicity of the anion (p*K* of the conjugate NH acid) and by the sensitivity of the rate constant to basicity variation (Brønsted coefficient). The Brønsted coefficient for aromatic nucleophilic substitution changes over a wider range than that typical of S_N2 reactions due to increased steric requirements in the transition state of S_NAr reactions. The Brønsted coefficient characterizes the degree of bond formation in the transition state of the rate-determining stage, and application of the Marcus equation makes it possible to correlate variation of the Brønsted coefficient with the height of internal barrier.

Analysis of the relations between the basicity and nucleophilicity of N-anions provides new possibilities for interpretation and prediction of the reactivity of these nucleophilic species in substitution reactions and forms the basis for their purposeful utilization in organic synthesis with the goal of obtaining practically valuable compounds.

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