THERMODYNAMICS OF PROTON DISSOCIATION. II.*
SOME *ortho*-SUBSTITUTED ANILINE DERIVATIVES

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The values ΔH^0, ΔG^0 and ΔS^0 of dissociation of seven *o*-substituted or disubstituted anilinium ions have been determined by combination of direct calorimetry and photometric pK_a measurements in aqueous solutions at 25°C. The influence of *o*-substituent has been discussed from the point of view of its interactions with the protonated amino group and water medium, electrostatic and other factors.

An *ortho* substituent affects substantially the equilibria of acid–base reactions, complex formations and other reactions of aromatic amines and their derivatives. The present report tries to contribute to elucidation of the mechanism of those influences on the basis of dissociation of the monoprotonated forms of selected *o*-derivatives of aniline in aqueous solution. In the next Part* the electrostatic factors due to the shape of the molecules are pointed out, the kind of *o*-substituent being not taken into account. These factors overlap with the factors connected with the chemical character of the substituent. Besides that most of the aniline *o*-derivatives used represent intermediates of biologically efficient anilides, their efficiency being dependent on the reaction equilibria mentioned. In the case of two derivatives it was also possible to compare the calorimetric $\Delta H°$ values of dissociation with those calculated by Bolton and Hall[1] from a precisely determined temperature dependence of pK_a.

EXPERIMENTAL

Chemicals. The following aniline derivatives were used: 2-methoxyaniline (*I*), 2-ethoxyaniline (*II*), 2-chloroaniline (*III*), 2-methyl-3-chloroaniline (*IV*), 2-methyl-5-chloroaniline (*V*), 2-amino-acetanilide (*VI*), and 2-aminobenzamide (*VII*). The first three substances were inland commercial products, the further two ones were of Light production (*purum*). They were purified by vacuum distillation on a column (13 Torr, without manostat); intermediate fractions boiling in a range of $1-2°C$ were taken and stored in sealed glass ampoules under nitrogen. The derivative *VI* was prepared and recrystallized according to ref.[2], m.p. 132—133°C; the sample *VII* (Anthranilsäure-amid, Fluka, *purum*) was repeatedly recrystallized from ethanol, m.p. 110°C.

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* Part I: This Journal **35**, 576 (1970).

Photometry. Acidity pK_a's of all the derivatives were determined by means of spectrophotometric method in UV region[3] using a Spektromom 202 apparatus equipped with a thermostated cell-holder ($25 \cdot 0 \pm 0 \cdot 1°C$). The measurements were carried out in succinate buffers having known ionic strengths I and acidity functions[4] p($a_H \gamma_{Cl}$), or in aqueous solutions of hydrochloric acid whose acidity functions were computed by interpolation of published data[4,5]. The values of acidity functions were corrected with respect to protonation of aniline (p($a_H \gamma_{Cl}$)') by a recommended iteration procedure[3]. The concentration ratio of the protonated and unprotonated forms was detected spectrophotometrically and used for the calculation of the approximate pK_a' value:

$$p K_a' = p_{(aH\gamma Cl)}' + \log([BH^+]/[B]) - 1 \cdot 023 \sqrt{I}/(1 + \sqrt{I}) . \qquad (1)$$

The last term of Eq. (*1*) corresponds to the first part of Davies formulation[6] of a simplified calculation of log γ. The pK_a value for $I = 0$ was calculated on the basis of the further part of Davies formula by a linear extrapolation using the least squares method:

$$p K_a = p K_a' + 2BI . \qquad (2)$$

The pK_a' values were calculated from the absorbance of five solutions of mixtures of the protonated and unprotonated forms of each derivative. The ionic strength of buffers was within 0·015 and 0·100 (derivatives *I, II, IV, V* and *VI*), the molal concentration of hydrochloric acid was within 0·03 and 0·07 (derivatives *III* and *VII*). The pK_a values linearly extrapolated to $I = 0$ are summarized in Table I. The values of s were calculated as standard deviations of absolute term (intercept) of linear equation (*2*). The coefficient B together with the pK_a values enable a reverse calculation of smoothed pK_a' values up to the upper limit of the given range of ionic strengths or molalities of hydrochloric acid. The differences between the original experimental and the smoothed pK_a' values did not exceed 0·006 units. For the sake of comparison the pK_a values of the derivatives *VI* and *VII* were determined potentiometrically by a procedure described earlier[7], the respective results being $3 \cdot 32 \pm 0 \cdot 02$ and $2 \cdot 92 \pm 0 \cdot 02$. However, the photometric values given in Table I were used in all the cases for calculation of ΔG^0 (Table V) and the [BH$^+$] values necessary for calorimetry.

Calorimetry. The modified calorimeter[7,8] was used again. The thermistor resistance was measured by comparison with a standard resistance decade using a Temperatur-Messgerät ap-

TABLE I

pK_a Values of Aniline Derivatives at Zero Ionic Strength

s Standard deviation, B coefficient of Eq. (2), λ_{max} position of the maximum used (nm).

Derivative	p$K_a \pm s$	B	λ_{max}
I	$4 \cdot 528 \pm 0 \cdot 002$	$-0 \cdot 60$	284
II	$4 \cdot 482 \pm 0 \cdot 004$	$-0 \cdot 21$	284
IV	$3 \cdot 608 \pm 0 \cdot 005$	$-0 \cdot 20$	286
V	$3 \cdot 342 \pm 0 \cdot 005$	$-0 \cdot 55$	286
VI	$3 \cdot 337 \pm 0 \cdot 003$	$-0 \cdot 15$	287
III	$2 \cdot 655 \pm 0 \cdot 003$	$-0 \cdot 60$	287
VII	$2 \cdot 941 \pm 0 \cdot 005$	$-2 \cdot 4$	318

paratus (Knauer). The evaluation of the corrected change of the thermistor resistance was carried out by graphical extrapolation[9], the way of calculation of thermal effect being the same. The run of the calorimeter was adjusted in such a way that the mean of the initial and final reaction temperatures did not deviate from the limits $25.00 \pm 0.02°C$. The overall procedure of the measurements of dissociation heats of the aniline derivatives studied was the same as in ref.[7], the corresponding calorimetric data are summarized in Tables II and III. The ionic strength of solutions was not adjusted, so that it equaled preactically the total hydrochloric acid concentration h. On the basis of regression analysis the dependence $q = f(BH^+)$ seems to be, however, sufficiently

TABLE II

Heats of Mixing (q, cal) of Aqueous Solutions of Aniline Derivatives with 0.5m-HCl (4.2 mmol)

b Resulting total concentration of the base (molality), BH^+ resulting amount of the protonated form (mmol), ΔH heat of dissociation (cal/mol), s standard deviation. Resulting total concentration of HCl h 0.03 m, resulting amount of H_2O 140 g. The measured $-q$ 0.84 cal for $BH^+ = 0$ in all the cases.

b	I		II^a	VI		IV			V		
	BH^+	$-q$	$-q$	BH^+	$-q$	b	BH^+	$-q$	b	BH^+	$-q$
0.018	2.519	20.21	20.14	2.430	13.93	0.014	1.931	13.92	0.010	1.369	9.59
0.015	2.100	16.82	16.81	2.038	11.76	0.012	1.657	12.13	0.0085	1.166	8.32
0.011	1.540	12.50	12.45	1.503	8.89	0.009	1.245	9.25	0.007	0.961	7.09
0.007	0.980	8.26	8.31	0.961	6.05	0.004	0.555	4.64	0.004	0.550	4.46
0.003	0.420	4.07	4.04	0.413	3.07	0.002	0.278	2.78	0.002	0.276	2.67
$\Delta H \pm s$	$7\,656 \pm 19$		7635 ± 36	5370 ± 17		6768 ± 23			6385 ± 45		

^{a} The values BH^+ are the same for the derivative II as for I.

TABLE III

Heats of Mixing (q, cal) of Aqueous Solutions of Aniline Derivatives with 1m-HCl (7.0 mmol)

h 0.05; the measured $-q$ 2.18 cal for $BH^+ = 0$; for the other data see Table II.

b	III		VII	
	BH^+	$-q$	BH^+	$-q$
0.018	2.362	15.95	2.429	14.69
0.015	1.978	13.66	2.030	12.58
0.011	1.458	10.64	1.494	9.81
0.007	0.932	7.65	0.953	7.18
0.003	0.401	4.54	0.409	4.27
$\Delta H \pm s$	$5\,810 \pm 17$		$5\,134 \pm 28$	

TABLE IV

Thermodynamic Functions of Dissociation $BH^+ \rightarrow B + H^+$ of Aniline o-Derivatives

Temperature 25°C, zero ionic strength. For standard deviations of ΔG^0 and ΔH^0 see Tables I—III, standard deviation of ΔS^0 was average ± 0.09 cal mol^{-1} K^{-1}.

Derivative	ΔG^0, cal mol^{-1}	ΔH^0, cal mol^{-1}	ΔS^0, cal mol^{-1}K^{-1}
I^a	6 177	7 656	4·96
II	6 114	7 635	5·10
III^b	3 622	5 810	7·34
IV	4 922	6 768	6·19
V	4 559	6 385	6·12
VI	4 552	5 366	2·73
VII	4 012	5 123	3·72

[a] Ref.[1] gives ΔG^0 6179·9 cal mol^{-1}, ΔH^0 7411 cal mol^{-1} and ΔS^0 4·12 cal mol^{-1} K^{-1}. [b] Ref.[1] gives ΔG^0 3633·9 cal mol^{-1}, ΔH^0 5902 cal mol^{-1} and ΔS^0 7·60 cal mol^{-1} K^{-1}.

linear in all the cases given in Table V. Therefore the dissociation heats ΔH given in Tables II and III were calculated by the previously described method, too, the dilution heats of hydrochloric acid solutions being considered as independent of the concentration of the derivative used. As the ΔH value of isoelectric dissociation of primary amines is obviously little affected by ionic strength[7], no corrections were used for transformation to the standard state of zero ionic strength. Because of using our pK_a values for [BH$^+$] calculation now, the present values ΔH^0 of derivatives I and II differ somewhat from the previously given preliminary results[10].

Dependence of ΔS^0 on ΔG^0 of meta and para substituted aniline derivatives. It may be useful to compare the thermodynamic functions obtained for dissociation of o-derivatives with m- and p-derivatives which fulfil a mutual linear relation[7,10]. This can be expressed for our purposes as

$$\Delta S^0 = \alpha + \beta \, \Delta G^0 . \tag{3}$$

The coefficients of Eq. (3) were computed by the least squares method from the mean values of ΔS^0 and ΔG^0 of the seven m- and six p-derivatives taken from[7] Part I, Fig. 1. and completed by newer data[11]. p-Nitroaniline deviates markedly from the dependence of the other derivatives, and it was, therefore, excluded from the calculations. The coefficients of Eq. (3) also demonstrate that, within the natural scattering, the relation (3) is quite identical for m- and p-derivatives.

Derivatives	$\alpha \pm s$ cal mol^{-1} K^{-1}	$(\beta \pm s) \, 10^4$, K^{-1}
Meta	8·15 $\pm$ 0·86	$-6·89 \pm 0·53$
Para	8·07 $\pm$ 0·61	$-6·80 \pm 0·34$
Meta + para	8·13 $\pm$ 0·11	$-6·87 \pm 0·26$

RESULTS AND DISCUSSION

Table IV gives our results along with the results of Bolton and Hall[1] for derivatives I and III. The values ΔG^0 (pK_a, Table I) obtained by the same photometric method stand quite in accord to each other with overlapping intervals of standard errors. Our calorimetric ΔH^0 value of dissociation of the derivative III also agrees well with that calculated by the abovementioned authors from the temperature dependence of photometric pK_a's. Calorimetric ΔH^0 value of the derivative I is, however, higher than the value calculated from $d(pK_a)/dT$ by about 3%, wherefrom follows a greater difference in ΔS^0.
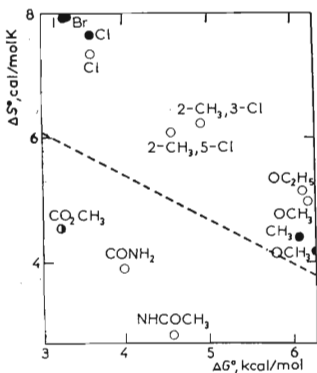

Fig. 1

Dependence of ΔS^0 on ΔG^0 of Dissociation of Aniline o-Derivatives

○ The present work, ● ◑ the data taken from ref.[1] (halogeno and methoxy derivatives), ref.[3] (methyl derivative) and ref.[14] (methoxycarbonyl derivative).

It is, therefore, interesting to compare the thermodynamic functions of the two slightly different derivatives I and II. As it could be expected, the derivative with longer side chain in the vicinity of amino group has lower ΔG^0 (pK_a). The decrease is due to a slightly lower ΔH^0 and especially to a higher value of the term $T\Delta S^0$. Consequently, the lower basicity of II as compared to I could be caused first of all by a change of conformation states of the longer ethyl chain during dissociation, thus forming a positive contribution to ΔS^0. As the differences of the thermodynamic functions are very small, this example also shows their very good mutual consistency. The higher basicity of IV as compared to the isomer V (the respective ΔS^0 are almost the same) indicates a mutual secondary steric influence of the three crowded neighbouring substituents on the benzene nucleus. With respect to the continuity with our conclusions the thermodynamic functions of dissociation of the o-derivatives studied are dealt with in the form of the dependence of ΔS^0 on ΔG^0 represented in Fig. 1.

Further literature data are included here, too, the common linear dependence of *m*- and *p*-derivatives according to Eq. (*3*) is represented by a dashed line.

Generally, the ΔS^0 values of not only *o*-derivatives but also *m*- and *p*-derivatives of aniline (represented by the abovementioned line) are much higher than the dissociation entropies of primary aliphatic amines. *E.g.* ΔS^0 of methylamine equals[12] $-4\cdot 7$ e.u. (cal mol^{-1} K^{-1}); even if we take into account the considerably higher[12] ΔG^0 14404 cal/mol, this value would lie below the dashed line of extended Fig. 1 by 2·9 e.u. Further primary amines, even those with a quite different alkyl group (*e.g.* tert-butylamine), would be placed very similarly, as far of, course, as the ΔS^0 values corrected with respect to the change of conformation states[12] were used. Therefore, one of the reasons can be a higher hydratation of the protonated amino group of anilinium derivatives as compared to aliphatic amines.

Together with *m*- and *p*-derivatives, the *o*-derivatives maintain a negative trend of ΔS^0 with increasing ΔG^0 (Fig. 1), too, which follows from the discussed ion–dipol interaction. However, *o*-derivatives form two different groups located above and below the line of *m*- and *p*-derivatives. The latter derivatives with a negative deviation of ΔS^0 were discussed to some extent previously[7]. As it can be seen in Fig. 1, they all have an *o*-substituent with a proton–acceptor character (*o*-nitroaniline belongs to them, too) which enables a direct interaction with the protonated amino group perhaps of an intramolecular hydrogen bond type. Their dissociation is accompanied by a release of less hydratation water[7], and this, in fact, chelate effect results in a ΔS^0 decrease. The derivative *VI* shows a greater decrease in ΔS^0 than the derivative *VII*; the protonated form of the former derivative can be considered to form a bridge of a $-\overset{(+)}{N}-H\cdots N-$ type closing a five-membered ring.

The group of derivatives having positive deviations of ΔS^0 (above the line) is characterized by a comparatively inert substituent in *o*-position. According to the next Part the positive deviations of ΔS^0 are caused by the prevailing electrostatic contribution which follows from the shape of the molecules of *o*-derivatives. However, even in the case of an inert substituent the electrostatic factors overlap with primary steric effects, and if it is a methyl group, then with the consequences of the so called hydrophobic hydratation, too. At least two of the hydrogen atoms of the *o*-methyl group lie wholly within 3·5 Å from the charge centre, which distance is decisive for the influence of hydrophobic hydration on the dissociation functions[12,13]. At the same time, the restriction of hydratation of the protonated amino group by the steric hindrance and the restitution of hydrophobic hydratation of methyl group form negative contributions to ΔS^0 which are subtracted from the electrostatic contributions. Perhaps for this reason *o*-toluidine shows a small positive deviation, whereas the derivative *III* and the further *o*-halogeno derivatives (in which the influence of hydrophobic hydratation is diminished) show the greatest positive deviation of ΔS^0. The derivatives *IV* and *V* are approaching to them, which is connected pro-

bably with the change of molecular shape due to a further substituent in m-position· The fact that the both o-alkoxy derivatives (I and II) belong to this group too, indicates that an eventual intramolecular hydrogen bond is not very significant in this case.

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