TABLE I

R	$N\langle^{R'}_{R''}$	Synthesis	Yield, %	Solvent	M. p., °C. or b. p. (mm.)	Formula	N, % Calcd.	N, % Found
$—CH_2—$	NC_4H_8O	E	84	H_2O	98–103[f] or 96–98	$C_{13}H_{14}N_2O_3 \cdot H_2O$	10.60	10.59
				Ether–alc.	195–196 (dec.)	$C_{13}H_{14}N_2O_3 \cdot HCl$	9.92	9.53
$—CH_2—$	NC_5H_{10}	E	35	Alc. 80%	94–95[a]	$C_{14}H_{16}N_2O_2$		
				Ether–alc.	186–187	$C_{14}H_{16}N_2O_2 \cdot HCl$	9.98	9.55
$—CH_2CH_2—$	$N(CH_3)_2$	A	2.5	Pet. ether	104–105	$C_{12}H_{14}N_2O_2$	12.84	12.93
$—CH_2CH_2—$	$N(C_2H_5)_2$	C	59	Pet. ether	45–47[b]	$C_{14}H_{18}N_2O_2$		
					235–236	$C_{14}H_{16}N_2O_2 \cdot HCl$		
$—CH_2CH_2—$	$N(i\text{-}C_3H_7)_2$	C	30	Alc.–ether	207–209	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.96
$—CH_2CH_2—$	$N(n\text{-}C_4H_9)_2$	C	36	Pet. ether	161–167 (2.5)	$C_{18}H_{26}N_2O_2$	9.26	9.25
$—(CH_2)_3—$	$N(CH_3)_2$	A	37	Alc. abs.	203–204	$C_{13}H_{16}N_2O_2 \cdot HCl$	10.43	10.37
$—(CH_2)_3—$	$N(C_2H_5)_2$	A or B	83	Alc.–ether	79–80	$C_{15}H_{20}N_2O_2 \cdot HCl \cdot C_2H_6O$	8.17	8.46
			85	Acetone	181–182[c]	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.41
$—(CH_2)_3—$	$N(i\text{-}C_3H_7)_2$	D	15	Alc.–ether	214–216	$C_{17}H_{24}O_2N_2 \cdot HCl$	8.62	8.55
		C	53					
$—(CH_2)_3—$	$N(n\text{-}C_4H_9)_2$	C	43	Pet. ether	190(3)	$C_{19}H_{28}N_2O_2$	8.85	9.17
			70	Acetone	115–116	$C_{19}H_{28}N_2O_2 \cdot HCl$	7.94	7.52
$—(CH_2)_3—$	$N(n\text{-}C_5H_{11})_2$	A	70	Water	87–88	$C_{21}H_{32}N_2O_2 \cdot HCl \cdot 2H_2O$	6.73	6.75
$—(CH_2)_3—$	$N(\text{cyclo-}C_6H_{11})_2$	D	30	Alc.–pet. ether	>265	$C_{23}H_{32}N_2O_2 \cdot HCl$	6.92	6.89
$—(CH_2)_3—$	NC_4H_8O	C		Alc. abs.	247–248 (dec.)	$C_{15}H_{18}N_2O_3 \cdot HCl$[d]	9.01	8.83
$—(CH_2)_3—$	$\underbrace{NCH(CH_3)(CH_2)_4}$	C	31	Alc.–ether	190–192	$C_{17}H_{22}O_2N_2 \cdot HCl$	8.68	8.50
$—CH_2CH(CH_3)—$	$N(C_2H_5)_2$	C	40	Acetone	178–179	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.33
$—CH(CH_3)CH_2—$	$N(C_2H_5)_2$	C	29	Acetone	184–185	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.36
$—(CH_2)_3—$	$NHCH_3$	A	2.8	Alc.–ether	204–207	$C_{12}H_{14}N_2O_2 \cdot HCl$	11.00	10.75
$—(CH_2)_3—$	$NH(i\text{-}C_3H_7)$	A	28	Ether Pet. ether	58–60	$C_{14}H_{18}N_2O_2$	11.38	11.72
$—(CH_2)_3—$	$NH(n\text{-}C_4H_9)$	A	9.5	Alc. abs.	195–197	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.50
$—(CH_2)_4—$	$N(C_2H_5)_2$	D	35	Alc. abs.	183–184	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.73
$—CH_2CH_2CH(CH_3)—$	$N(C_2H_5)_2$	D	4	Acetone	158–159	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.65
$—(CH_2)_5—$	$N(C_2H_5)_2$	D	62	Alc.–ether	175–176	$C_{17}H_{24}N_2O_2 \cdot HCl$	8.62	8.46
$—CH(CH_3)(CH_2)_3—$	$N(C_2H_5)_2$	A	57	Pet. ether	174–182(5)	$C_{17}H_{24}N_2O_2$[e]	9.72	9.84
$—(CH_2)_6—$	$N(C_2H_5)_2$	D	65	Alc–ether	206–208	$C_{18}H_{26}N_2O_2 \cdot HCl$	8.27	8.07
$—(CH_2)_6—$	NC_4H_8O	D	30	Pet. ether	40–42	$C_{18}H_{24}N_2O_3$	8.85	8.53

[a] Sachs (ref. 2(a)) m.p. 117–118°. [b] Walls (ref. 2(b)) m.p. 46–47°. [c] Shriner and Hickey m. p. 144–145°. [d] Prepared by Dr. M. T. Leffler. [e] Kharasch and Fuchs (ref. 2(d)) obtained this compound as a mixture with its isomer. The preparation from the diamine eliminates the rearrangement which they describe. [f] Hot stage melting point.

responding increase in efficiency, and branching of this chain is unfavorable. Increasing the size of R′ and R″ does not increase the efficiency in wheals to any marked extent, but does increase corneal anesthetic effect. When either R′ or R″ is H, the efficiency is decreased, even for a compound of the same molecular weight. The compounds in which R is methylene were not tested, because the hydrochlorides, soluble in water, rapidly decomposed and deposited a precipitate of phthalimide.

Acknowledgment.—Thanks are due Messrs. E. F. Shelberg and L. F. Reed for the microanalyses herein reported.

Summary

A series of N-alkamine substituted phthalimides is reported, most of whose members are effective local anesthetics, especially for parenteral rather than topical use.

NORTH CHICAGO, ILLINOIS RECEIVED APRIL 29, 1946

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Metalation of Benzotrifluoride

BY JOHN D. ROBERTS[1] AND DAVID Y. CURTIN

Aromatic substituents groups which direct *ortho–para* in electrophilic substitution reactions such as nitration and sulfonation appear to exert a similar influence in the nuclear metalation of substituted benzenes.[2] No studies have been reported of the influence in metalation reactions of groups which lead to *meta* substitution with electrophilic reagents. In general, reaction of such groups with the customary metalating agents occurs more rapidly than nuclear metalation. In the present work the metalation of benzotrifluoride has been investigated since the trifluoromethyl group is known to be resistant to chemical attack[3,4] and strongly *meta*-directing in nitration[4] and in chlorination[5] reactions.

Benzotrifluoride is readily metalated in refluxing ether solution by *n*-butyllithium. Carbonation of the metalation products gave a 48% yield of a

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(1) National Research Fellow, 1945–1946.

(2) See Morton, *Chem. Rev.*, **35**, 1 (1944), for a summary of work on orientation in nuclear metalation reactions notably by Gilman, Morton and Wittig and their collaborators.

(3) Gilman and Woods, THIS JOURNAL, **66**, 1981 (1944).

(4) Swarts, *Bull. sci. acad. roy. Belg.*, **6**, 389 (1920); *Chem. Zentr.*, **92**, II, 32 (1921).

(5) Wertyporoch, *Ann.*, **493**, 153 (1932).

mixture of solid acids which was found to consist of *o*- and *m*-trifluoromethylbenzoic acids in a ratio of about five to one. Little, if any, of the *p*-isomer appeared to be present.

A competitive metalation experiment was carried out with anisole and benzotrifluoride. The reaction of 0.1 mole of *n*-butyllithium with a mixture of 0.1 mole of anisole and 0.1 mole of benzotrifluoride resulted after carbonation in a 40% yield of almost pure *o*-anisic acid.

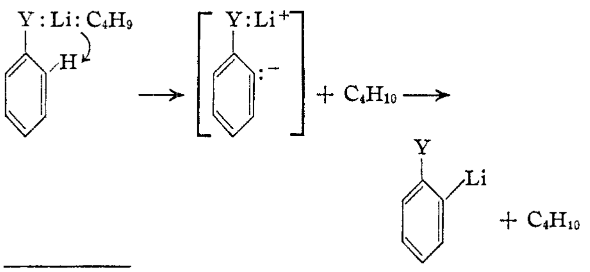
Since benzene is metalated only slightly under the conditions used in the metalation of benzotrifluoride,[6] it is clear that the trifluoromethyl group activates the benzene ring toward metalation. However, the result of the competitive experiment indicates that the activating influence of a trifluoromethyl group is less than that of a methoxyl group.

From a number of previous experiments on the relative rates of substituted benzenes[7] and from the present work the following approximate relationships between the degrees of activation of the aromatic nucleus by various substituent groups may be inferred

$\mathrm{F} > \mathrm{Cl}$
$\mathrm{F} > -\mathrm{OCH_3} > -\mathrm{CF_3} > \mathrm{H}$
$\mathrm{F} > -\mathrm{N(CH_3)_2}$
$\mathrm{O} > \mathrm{S} > \mathrm{N}$

These relationships are the ones that would be predicted if the inductive effect were most important in determining the ease of reaction. The inductive effects of the groups mentioned are such as to be expected to increase the acidity of the ring hydrogens. Hence, if the inductive effect determines the reaction rate, the primary process of the reaction seems best formulated as the removal of a ring hydrogen (as a proton) by a nucleophilic attack by the anion of the metalating agent.[8]

The predominantly *o*-orientation observed with the substituents mentioned above is best accounted for by assuming that the reaction involves an initial coördination of the metallic atom of the metalating agent with an unshared electron pair on the substituent group followed by the removal of an *o*-hydrogen by the anion of the metalating agent.



The operation of the coördination step of this mechanism would be expected to aid the reaction by increasing the polarization of the carbon–metal bond of the metalating agent and by enhancing the inductive effect of the electron-attracting substituents. In addition, the initial coördination might aid the reaction by tending to counteract the expected decrease in acidity of the *o*- and *p*-hydrogens associated with the resonance of unshared electron pairs on the substituent groups with the aromatic ring. It should be noted that the formulation of the reaction mechanism as a nucleophilic attack on hydrogen obviates any necessity for the operation of the time-variable tautomeric effect (electromeric effect) which plays an important part in determining the rate and orientation of the electrophilic nuclear substitution reaction.

This explanation is not completely satisfactory, however, since a number of apparently contradictory observations have been reported. For example, although 5-carbazolylbenzene is monometalated in an *o*-position and dimetalated in the two *o*-positions of the benzene ring,[9] triphenylamine,[10] triphenylarsine[11] and triphenylphosphine[12] are metalated in the *m*-position. Furthermore, while dibenzothiophene is metalated by butyllithium to give 4-lithodibenzothiophene,[13] phenylcalcium iodide effects metalation *meta* to the sulfur linkage.[14] In at least one case the rate of stirring of the reaction mixture was found to influence the course of the metalation reaction.[15] In addition, it should be noted that cumene is metalated by amylsodium in the *o*- and *p*-positions[16] and if the inductive effect alone determines the orientation in this metalation reaction the *m*-isomer would be the expected product of a nucleophilic attack by the anion of the metalating agent.

Experimental

Metalation of Benzotrifluoride.—To a solution of *n*-butyllithium prepared from *n*-butyl chloride (23 g., 0.25 mole), lithium metal (3.0 g., 0.43 gram atom) and 100 ml. of ether was added benzotrifluoride (25 g., 0.17 mole). The mixture was refluxed for six hours and then poured onto 500 g. of powdered Dry Ice. After the excess carbon dioxide had evaporated, water was added and the non-acidic material removed with ether. The aqueous residue was acidified and extracted with ether. Evaporation of the ether extract gave 15.5 g. (48%) of a mixture of trifluoromethylbenzoic acids. The crude product was crystallized from petroleum ether (b. p. 70–90°) giving 10.5 g. of *o*-trifluoromethylbenzoic acid., m. p. 102–107°. One recrystallization from the same solvent raised the melting point to 108–109°. The amide was prepared in the usual way and crystallized from benzene–petroleum ether, m. p. 162–163°. Reported melting points are 108.5° for the acid and 161° for the amide.[17]

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(6) Gilman, Pacewitz and Baine, THIS JOURNAL, **62**, 1514 (1940).

(7) (a) Wittig and Merkle, *Ber.*, **75B**, 1491 (1942); (b) Wittig, Pieper and Fuhrmann, *ibid.*, **73B**, 1193 (1940); (c) Wittig and Fuhrmann, *ibid.*, **73B**, 1197 (1940); (d) Gilman and Stuckwisch, THIS JOURNAL, **67**, 877 (1945).

(8) See Refs. 2 and 7c for somewhat different viewpoints.

(9) Gilman and Stuckwisch, THIS JOURNAL, **65**, 1729 (1943).

(10) Gilman and Brown, *ibid.*, **62**, 3208 (1940).

(11) Gilman and Stuckwisch, *ibid.*, **63**, 3532 (1941).

(12) Gilman and Brown, *ibid.*, **67**, 824 (1945).

(13) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(14) Gilman, Jacoby and Pacewitz, *ibid.*, **3**, 120 (1938).

(15) Morton and Fallwell, THIS JOURNAL, **60**, 1924 (1938).

(16) Morton, Massengale and Brown, *ibid.*, **67**, 1620 (1945).

(17) De Brouwer, *Bull. soc. chim. Belg.*, **39**, 298 (1930).

The mother liquors from the crystallization of the *o*-acid were evaporated to dryness and attempts were made to separate the components by fractional crystallization. Only a small quantity (0.22 g.) of the pure *m*-isomer was obtained, m. p. 103–104.5° (lit.[18] m. p. 103°), which was identified by conversion to isophthalic acid (methyl ester, m. p. 62–63°). The balance of the solid crystallization residues (4.1 g.) was analyzed by hydrolysis with hot 80% sulfuric acid and separation of the resulting phthalic acids by the method of Smith.[19] From 1.08 g. of the crystallization residue there was obtained 0.36 g. (38%) of phthalic acid, 0.56 g. (48%) of isophthalic acid and 0.02 g. (2%) of terephthalic acid. On this basis the composition of the original mixture of trifluoromethylbenzoic acids was *ortho*, 83%; *meta*, 16%; and *para*, <1%.

Competitive Metalation Reaction. Anisole and Benzotrifluoride.—To an ethereal solution of *n*-butyllithium (0.1 mole) was added rapidly a mixture of anisole (10.8 g., 0.1 mole) and benzotrifluoride (14.8 g., 01. mole). The resulting mixture was refluxed for two hours and then carbonated. After the non-acidic materials had been extracted with ether, acidification gave 6.0 g. (40%) of crude acid, m. p. 90–98°. The product was recrystallized from benzene-petroleum ether giving 5.9 g. of pure *o*-anisic acid, m. p. 100–102° (mixed melting points with *o*- and *m*-trifluoromethylbenzoic acids <85°).

Summary

Benzotrifluoride is metalated by *n*-butyllithium less readily than anisole but more readily than benzene. Carbonation of the metalation products of benzotrifluoride gives *o*- and *m*-trifluoromethylbenzoic acids in a ratio of about five to one.

CAMBRIDGE 38, MASS. RECEIVED MARCH 27, 1946

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[18] Swarts, *J. chim. phys.*, **17**, 32 (1919).

[19] Smith, THIS JOURNAL, **43**, 1920 (1921).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DAVIDSON COLLEGE]

The Effect of KCl, NaCl and Na_2SO_4 on the Aqueous Solubility of Acetanilide

BY THOMAS S. LOGAN

Because of its rather low solubility in water, and the convenience and accuracy with which this solubility can be determined,[1] acetanilide is particularly well suited for the study of salting out phenomena. The desirability of comprehensive studies in this field has been pointed out by various investigators.[2] This paper reports measurements of the solubility of acetanilide in solutions of potassium chloride, sodium chloride and sodium sulfate at ionic strengths from 0.05 to 4 and at temperatures from 0 to 60°.

Experimental

The solubility of acetanilide was determined by the method previously described.[1] The potassium chloride, sodium chloride and sodium sulfate used in making up the solutions were C. P. salts. They were dried at 130° from two to three hours before use. Check experiments showed that their presence in solution had no effect on the determination of acetanilide.

A solution was prepared by putting into a dry solubility flask a weighed portion of salt. To this was added acetanilide in excess of that necessary for saturation. The flask was closed with a rubber stopper and weighed. Approximately the required quantity of hot water was then pipetted into the flask. It was stoppered and weighed again. The flask was shaken as it cooled. At a few degrees above the temperature of the determination the stopper was quickly removed and replaced by a stopper containing the tubes for withdrawing the solution. The flask was then put into the thermostat. A few experiments were run where equilibrium was approached from the low temperature side. The results were concordant with the others. Two samples of the solution were withdrawn for acetanilide analysis. These duplicate analyses showed an averaged error of ±0.16% from their means. An error of ±0.5%, or more, was obtained in 5% of the analyses. The largest error was ±0.6%.

The concentrations of the salt solutions reported are those secured by direct weighing, as described above. As a check, a number of chloride analyses were run on solution samples withdrawn from the flasks. These were taken at the same time that samples for acetanilide analysis were withdrawn. The results gave an average error of ±0.5% in comparison with the listed values of the ionic strength. The estimated maximum error in solubility resulting from this deviation in ionic strength is shown in Table I.

TABLE I

Ionic strength	Error, ±%
1, or less	0.2
2, or less	.5
3, or less	.7
4, or less	.9

Weight corrections to vacuum were applied where appropriate. For the salt solutions the densities were taken as those listed in the "International Critical Tables" for the salt solutions in water.

The thermostat was regulated to ±0.05° at temperatures of 40° and lower. The regulation was ±0.10 at the two higher temperatures. The estimated effect of this variation on the solubility was ±0.2% at the lower and ±0.4% at the higher temperatures.

Results

The results have been evaluated on a basis of the Randall and Failey modification[3] of the well-known Setschenow equation

$$\log S_0/S = k\mu$$

where S_0 and S are the solubilities of the acetanilide in pure water and the salt solution, respectively, μ is the ionic strength, and k is the salting out constant.

Table II records the solubility, S_0, of acetanilide in pure water at the temperatures studied. S_0 is given as grams of acetanilide per 100 g. of water. Except for the values at 15 and 32.6°, these data were calculated from those of the

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[1] Logan, THIS JOURNAL, **67**, 1182 (1945).

[2] (a) Glasstone and Pound, *J. Chem. Soc.*, **127**, 2660 (1925); (b) P. M. Gross, *Chem. Rev.*, **13**, 91 (1933); (c) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corporation, New York, N. Y., p. 400; (d) Akerlof, THIS JOURNAL, **57**, 1196 (1935).

[3] Randall and Failey, *Chem. Rev.*, **4**, 271 (1927).