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The Acidifying Effects of Chlorine and Bromine : Little Difference

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Abstract : Lithium diisopropylamide deprotonates *ortho*- and *para*-bromochlorobenzene randomly at the two halogen adjacent positions. Obviously for steric reasons, the bulkier base lithium 2,2,6,6-tetramethylpiperidide favors the attack in the vicinity of the chlorine rather than the bromine atom to the extent of 2 : 1. - At -75 °C, both 2-bromo-3-chlorophenyllithium and 3-bromo-2-chlorophenyllithium isomerize to give 2-bromo-6-chlorophenyllithium. The latter species can be directly generated from 1-bromo-3-chlorobenzene.

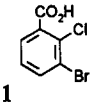
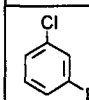
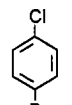
Fluorobenzene undergoes *ortho*-lithiation more *rapidly* than chlorobenzene when treated with *sec*-butyllithium in tetrahydrofuran at -100 °C (k_{rel} 8) and more *completely* when treated, at -75 °C, with lithium 2,2,6,6-tetramethylpiperidide (61% and 91% *vs.* 21% and 43% using one and, respectively two equivalents of the base). Obviously, the smallest halogen enhances the proton mobility ("kinetic acidity") and the proton availability ("thermodynamic acidity") more strongly than the next heavier halogen does. Will this gradation be repeated when we move further down the periodic table ? In other words, does the acidifying effect of chlorine significantly exceed that of bromine, say by one order of magnitude ?

Relative basicities of aryllithium species seem to parallel those of the corresponding pyridines, the latter being isoelectronic with the experimentally inaccessible "naked" carbanions [1]. As far as the proton affinities are concerned in both the gaseous [2] and the aqueous [3] phase, 2-chloropyridine is only little ahead of 2-bromopyridine ($\Delta pK < 1$ kcal/mol) whereas the difference between 2-fluoropyridine and 2-chloropyridine is about 5 times greater ($\Delta pK > 4$ kcal/mol). Therefore, one would not expect to encounter much of discrimination between halogens in the metalation of bromochlorobenzenes.

This conclusion is, however, at variance with a recent report according to which lithium diisopropylamide ("LIDA") promotes the hydrogen/metal exchange not at *both* available halogen-adjacent sites of 1-bromo-2-chlorobenzene but exclusively at the chlorine-neighboring position. 3-Bromo-2-chlorobenzoic acid was claimed to have been isolated as the sole product in 55% yield [4]. We immediately suspected the structure assignment to be mistaken. If so, this error would by no means diminish the value of the otherwise remarkable and meritorious work, but should be corrected for reasons of mechanistic importance.

We have hence embarked on a detailed investigation of the deprotonation of 1-bromo-2-chlorobenzene, varying the base, metalation temperature and exposure times (Table). For completeness, the two isomers 1-bromo-3-chloro- and 1-bromo-4-chlorobenzene, were included in the study (Table).

Table. Bromochlorobenzoic acids **1** - **5** obtained after consecutive treatment of bromochlorobenzenes with one equivalent of lithium diisopropylamide (LIDA) or lithium 2,2,6,6-tetramethylpiperidide (LITMP) in tetrahydrofuran, carbon dioxide and acid : product compositions and yields as a function of the temperature and metalation time. [a]

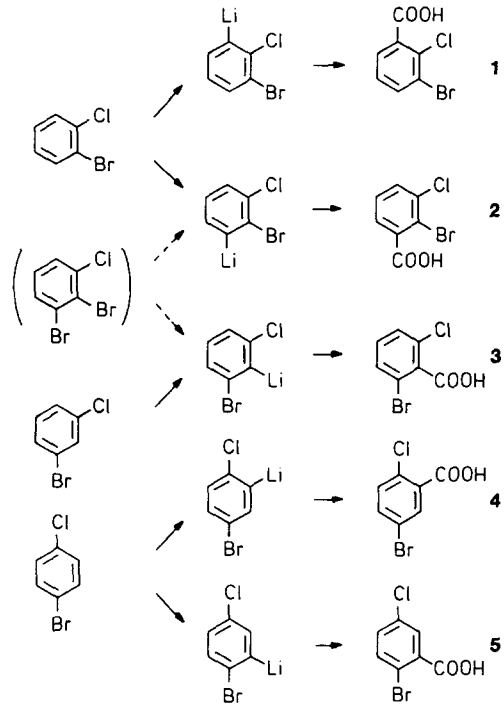
substrate	base, temper., time	 **1**	 **2**	 **3**	 **4**	 **5**
	LIDA -75 °C 0.5 h	13%	3%	15%	-	-
	LIDA -75 °C 2 h	2%	0%	38%	-	-
	LITMP -75 °C 2 h	35%	0%	17%	-	-
	LITMP -100 °C 2 h	4%	2%	0%	-	-
	LITMP [b] -100 °C 2 h	10%	5%	0%	-	-
	LITMP -75 °C 2 h	-	-	94%	-	-
	LIDA -75 °C 2 h	-	-	-	23%	20%
	LIDA -100 °C 2 h	-	-	-	24%	17%
	LITMP -75 °C 0.7 h	-	-	-	56%	23%
	LITMP -75 °C 2 h	-	-	-	52%	17%
	LITMP [b] -100 °C 2 h	-	-	-	29%	4%

a) Products quantified by gas chromatography (30 m, DB-1701, 220 °C; 30 m, DB-FFAP, 220 °C).
b) Exceptionally two equivalents of the base were used.

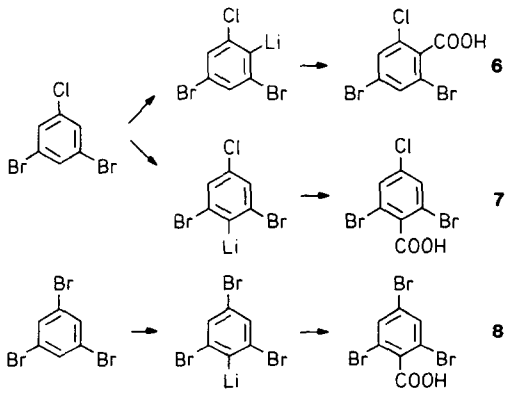
At - 100 °C, 1-bromo-2-chlorobenzene is attacked in the approximate ratio 2 : 1 at the positions adjacent to the lighter and the heavier halogen, respectively. The intermediates can be trapped with carbon dioxide to afford 3-bromo-2-chlorobenzoic acid (**1**) and 2-bromo-3-chlorobenzoic acid (**2**). The yields are poor, since LITMP reacts only very slowly and LIDA not at all under these conditions. At -75 °C, the 2-bromo-3-chlorophenyllithium component is quantitatively converted into the thermodynamically more stable 2-bromo-6-chlorophenyllithium, 1,2-dibromo-3-chlorobenzene acting as the presumed turntable for this new example of a halogen migration ("dance") [5, 6]. The same precursor to 2-bromo-6-chlorobenzoic acid (**3**) can be generated, without any isomeric contamination, from 1-bromo-3-chlorobenzene. At -75 °C in the presence of lithium diisopropylamide, 2-bromo-6-chlorophenyllithium is formed at the expense of not only 2-bromo-3-chlorophenyllithium but also 3-bromo-2-chlorophenyllithium. The latter isomerization can be readily explained if reversibility of the haloarene lithiation is assumed.

5-Bromo-2-chlorophenyllithium and 2-bromo-5-chlorophenyllithium, simultaneously derived from 1-bromo-4-chlorobenzene by *ortho*-lithiation and trapped as the acids **4** and **5**, decompose already at -75 °C, the former slowly, the latter rapidly. The two organometallic intermediates are produced approximately in 1 : 1 and

2 : 1 ratios depending on whether LIDA or LITMP is employed as a base. This means, the bulky reagent shows a moderate preference for the vicinity of a chlorine rather than of a more voluminous bromine atom.



Chlorine and bromine exhibit similar acidifying effects also in intermolecular as in intramolecular competition experiments. 1-Bromo-3-chlorobenzene undergoes LIDA-promoted deprotonation at the 2-position only slightly more rapidly than 1,3-dibromobenzene does (k_{Cl}/k_{Br} 1.2). 1,3-Dibromo-5-chlorobenzene and 1,3,5-tribromobenzene react again at almost identical rates (k_{Cl}/k_{Br} 1.1), the former affording, upon carboxylation and neutralization, acids **6** (66%) and 7 (22%), the latter acid **8** (59%).



Procedures and Products

2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and then dropwise, in the course of 5 min, the haloarene (25 mmol) were added to a solution of butyllithium (25 mmol) in hexane (17 mL) and

tetrahydrofuran (50 mL) cooled to -75 °C. After 2 h at this temperature, the mixture was poured on an excess of freshly crushed dry ice. The solvent were evaporated and the residue dissolved in water (50 mL). The aqueous layer was washed with diethyl ether (2 × 20 mL) and acidified with concentrated hydrochloric acid (to pH 1). Extraction with dichloromethane (3 × 20 mL) and crystallization from hexane or toluene afforded a colorless product. - *3-Bromo-2-chlorobenzoic acid* (**1**) : from 1-bromo-2-chlorobenzene; mp 163 - 165 °C (lit. [7] mp 165 °C); 50%. - *2-Bromo-3-chlorobenzoic acid* (**2**) : using again 1-bromo-2-chlorobenzene as the substrate but treating it with two equiv. of LIDA (at -100 °C) rather than LITMP (at -75 °C); isolated by sublimation of the residue left behind upon evaporation of the mother liquors obtained after repetitive removal of isomer **1** by fractional crystallization from hexane; mp 146 - 148 °C (lit. [4] mp 146 - 147 °C); 5%. - *2-Bromo-6-chlorobenzoic acid* (**3**) : from 1-bromo-3-chlorobenzene; mp 141 - 143 °C (lit. [8] mp 144 - 146 °C); 94%. - *5-Bromo-2-chlorobenzoic acid* (**4**) : from 1-bromo-4-chlorobenzene; mp 154 - 156 °C (lit. [9] mp 155 - 156 °C); 52%. - *2-Bromo-5-chlorobenzoic acid* (**5**) : again from 1-bromo-4-chlorobenzene but employing LIDA rather than LITMP as the base; isolated by sublimation of the residue left behind upon evaporation of the mother liquors obtained after repetitive removal of isomer **4** by fractional crystallization from hexane; mp 148 - 149 °C (lit. [10] mp 148 - 149 °C); 20%. - *2-Chloro-4,6-dibromobenzoic acid* (**6**) : from 1-chloro-3,5-dibromobenzene [11] using LIDA as the base : isolated by sublimation of the residue left behind upon evaporation of the mother liquors obtained after repetitive removal of isomer **6** by fractional crystallization from toluene; mp 170 - 172 °C; 77%. - ^{1}H-NMR : δ 7.85 (1 H, d, *J* 1.6), 7.73 (1 H, d, *J* 1.7). - Analysis : calc. for $C_7H_3Br_2ClO_2$ (314.37) C 26.74, H 0.96; found C 26.57, H 1.09%. - *4-Chloro-2,6-dibromobenzoic acid* (7) : from 1-chloro-3,5-dibromobenzene [11] using LIDA as the base and after recrystallization from toluene; mp 171 - 173 °C; 22%. - ^{1}H-NMR : δ 7.74 (2 H, s). - Analysis : calc. for $C_7H_3Br_2ClO_2$ (314.37) C 26.74, H 0.96; found C 26.88, H 0.88%. - *2,4,6-Tribromobenzoic acid* (**8**) : from 1,3,5-tribromobenzene as described above; mp 188 - 190 °C (lit. [12] mp 194 °C); 59%.

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