

The Acidity of Chloro-Substituted Benzenes: A Comparison of Gas Phase, Ab Initio, and Kinetic Data

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Abstract: The deprotonation energies of benzene, chlorobenzene, all di-, tri-, tetrachlorobenzenes, and pentachlorobenzene have been determined in the gas phase using a Fourier transform ion cyclotron resonance mass spectrometer. The values measured differ only slightly, though significantly, from the corresponding data for oligofluorobenzenes. The heavier halogen acidifies *ortho*-positions slightly less and *meta*-positions slightly more than fluorine does. More-

over, the contributions of three or more chloro substituents are not perfectly additive. In fact the accumulation attenuates the contributions somewhat. Quantum chemical calculations at the MP2/6-311+G* level reproduce the gas-

Keywords: gas-phase reactions • metalation • quantum chemical calculations • relative rate measurements • substituent effects

phase acidities fairly well, but reveal special effects when extended to experimentally not observable benzenides carrying the halogens at anion-remote positions. Competition experiments have been performed to assess the relative reactivity of nine oligochlorobenzenes towards *sec*-butyllithium in tetrahydrofuran at -100°C . An almost exact linear correlation between logarithmic rates and gas-phase acidities has been found.

Introduction

The Brønsted equation,^[1] the oldest and still one of the most prominent linear free energy relationships, correlates the rates of acid/base driven reactions with the acidity of the catalyst. For example, the stronger the base employed to generate the crucial carbanionic intermediate, the faster a given hydrocarbon will undergo hydrogen/deuterium exchange. A similar situation is encountered when a hydrocarbon is submitted to a stoichiometric hydrogen/metal interconversion and the resulting organometallic species are subsequently derivatized by electrophilic trapping. The main difference lies in the irreversibility of the organometal-promoted deprotonation. This crucial step thus becomes the only rate limiting one. Whatever such details, one expects the rate to reflect, to some extent at least, the acidity gradient covered by the conversion of a stronger base, that is the reagent, to a weaker base, that is the metalated substrate. The problem is that no $\text{p}K_{\text{a}}$ values can be measured for common hydrocarbons under aqueous standard state conditions, not

even by resorting to the extrapolation of the H_{c} function.^[2] Therefore, proton affinities of carbanions measured in the gas phase must be considered as the only available^[3-5] data which are thermodynamically meaningful.

Results and Discussion

Gas-phase studies: In the continuation of previous work featuring fluoroarenes^[6] and (trifluoromethyl)arenes^[7] we have determined the gas-phase acidity of chlorobenzene,^[8,9] all di-, tri- and tetrachlorobenzenes, and pentachlorobenzene by collision-mediated hydrocarbon/carbanion equilibration using a Fourier transform ion cyclotron resonance instrument (see Table 1). The values collected differ strikingly little from those reported for the fluoro analogues.^[6] However, characteristic divergences become apparent when one looks into the details.

In the fluoro series, the experimental gas-phase acidities can be reproduced with reasonable accuracy if one starts with the parent benzene and subtracts deprotonation increments of 12, 6, and 4 kcal mol^{-1} from the free energy of the parent benzene for each *ortho*, *meta*, and *para* halogen substituent, respectively (average deviation 1.3, maximum deviation 3.1 kcal mol^{-1}).^[6] An even better fit can be achieved with increments of 12.5, 6.5, and 4.5 kcal mol^{-1} (average deviation 0.7, maximum deviation 2.5 kcal mol^{-1}). In other words, fluorine substituent effects are additive. This has already

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been suggested by Maksić et al.^[10] with respect to acidity values for 1,2-, 1,3-, and 1,4-difluorobenzenes obtained from ab initio calculations.

As previously described for the oligofluorobenzene series,^[6] the gas-phase acidities of all mono-, di-, tri-, tetra-, and pentachlorobenzenes were determined by Fourier transform ion cyclotron resonance spectrometry. The free energies measured for the deprotonation ΔG_g° were converted into enthalpies ΔH_g° in the usual straightforward way (Table 1).

Table 1. Acidity of zero-, mono-, di-, tri-, tetra- and pentachlorobenzenes in the gas phase: experimental free energies (ΔG_g°) and enthalpies (ΔH_g°) of deprotonation and proton affinities estimated on the basis of a simple set of increments (ΔH_{incr}),^[a] deviations from the experimental data being given in parentheses (Δ_g).^[b]

CH-acid	ΔG_g°	ΔH_g°	ΔH_{incr}	(Δ_g)
benzene	392.9	401.7	398.1	(−3.6)
chlorobenzene ^[c]	378.6	386.6	386.6	(±0.0)
1,2-dichlorobenzene	368.7	377.1	379.1	(+2.0)
1,3-dichlorobenzene	366.3	374.0	375.1	(+1.1)
1,4-dichlorobenzene	368.8	377.0	379.1	(+2.1)
1,2,3-trichlorobenzene	366.8	374.9	374.6	(−0.3)
1,2,4-trichlorobenzene	362.6	370.3	367.6	(−2.7)
1,3,5-trichlorobenzene	360.8	369.2	370.6	(+1.4)
1,2,3,4-tetrachlorobenzene	360.1	368.3	367.1	(−1.2)
1,2,3,5-tetrachlorobenzene	355.4	363.3	363.1	(−0.2)
1,2,4,5-tetrachlorobenzene	353.7	361.8	360.1	(−1.7)
pentachlorobenzene	347.4	355.0	355.6	(+0.6)

[a] See text for details. [b] All numbers represent energies given in kcal mol^{−1}. [c] Reference compound for the increment-based estimations of deprotonation enthalpies.

To probe the additivity of the contribution of individual substituents, we have attributed tentatively a carbanion stabilizing effect of 11.5, 7.5, and 4.5 kcal mol^{−1}, respectively, to any chlorine atom occupying an *ortho*, *meta*, or *para* position relative to the negatively charged center. The agreement between the experimental deprotonation enthalpies (ΔH_g°) and the enthalpies based on this single set of increments (ΔH_{incr}) is quite satisfactory at first sight (average deviation 1.4, maximum deviation 3.6 kcal mol^{−1}). Upon closer scrutiny one recognizes unacceptable discrepancies. Almost all major deviations ($\Delta = \Delta H_{\text{incr}} - \Delta H_g^\circ$) hit the early members of the structural family: benzene, 1,2-dichlorobenzene, and 1,4-dichlorobenzene (3.6, 2.0, and 2.1 kcal mol^{−1}, respectively). This suggests an attenuation mechanism which takes effect when more than two chlorine substituents are present in the same substrate. This issue will be examined more explicitly in the following Section dealing with ab initio calculations.

Gas-phase deprotonation studies are only moderately accurate. Standard error deviations generally fall in the range of 3–4 kcal mol^{−1}. Major sources of uncertainty are the precise assessment of the deprotonation energy of the reference acid and the pressures of the equilibrating components.^[7] Additional complications may be encountered with haloarenes as they can lose hydrogen halide by β -elimination, thus generating a 1,2-dehydroarene, even if this is an endothermic process.^[11–13] In particular, we have doubts about one value. According to all available evidence, 2,3,5-trichloro-

benzenide should be less basic than 2,4,6-trichlorobenzenide. In fact, we suspect that the true gas-phase acidity of 1,2,4-trichlorobenzene exceeds the experimentally established value by some 2.0 kcal mol^{−1} ($\Delta G^\circ \approx 360.6$, $\Delta H^\circ \approx 368.3$). We therefore sought support from theoretical calculations for this assumption.

ab initio Calculations: There was a second reason for involving quantum chemistry in our CH-acidity studies. Whatever the details of an acid/base equilibration experiment performed in the gas phase, it would only monitor the thermodynamically most stable carbanion, that is, the one generated by proton abstraction from the most acidic haloarene position (say, from the 2- rather than the 5-position of 1,3-dichlorobenzene). This restriction can be principally overcome by resorting to the silane cleavage method,^[14] as demonstrated with fluoro-, chloro-, and bromobenzene.^[15, 16] However, this approach has its pitfalls and may especially fail in the case of fairly acidic polyhalobenzenes. To bridge the gap, we have computed the deprotonation enthalpies of benzene, chlorobenzene, all di-, tri-, tetrachlorobenzenes, and pentachlorobenzene at the MP2/6-311+G*//RHF/6-311+G*+ZPE level (Table 2). Previously ab initio deprotonation enthalpies have already been reported for the *ortho*, *meta*, and *para* positions of chlorobenzene.^[12, 17, 18]

All calculated enthalpies (ΔH_{MP2}) were augmented by 1.4 kcal mol^{−1} (thus converting them into $\Delta H_{\text{MP2}}^{\text{corr}}$) to make the computed heat of deprotonation at the *ortho* position of chlorobenzene coincide with the experimental gas-phase acidity (ΔH_g°) and thus to facilitate the comparison. The ab initio procedure passed two crucial tests. Chlorobenzene was found to be less acidic than fluorobenzene, albeit only marginally (by 0.2 kcal mol^{−1}), in perfect accordance with the kinetic data.^[19, 20] Smaller basis sets^[18] tend to invert this order. Moreover, 1,2,4-trichlorobenzene ranked lower than its 1,3,5-isomer in the acidity scale (i.e., 2,3,5-trichlorobenzenide is perceived as less basic than the 2,4,6-isomer), again in line with experimental evidence (see also the following Section). Finally, the overall good agreement between gas-phase and MP2 acidities (as shown in Table 2), lends confidence in the mathematical approach employed. Nevertheless, some doubts remain. The computationally assessed acidities of tri- and tetrachlorobenzenes exceed the experimental values on an average by 2.8 and 3.5 kcal mol^{−1}, respectively. This conspicuous discrepancy either points to a systematic error in the gas-phase measurement or, more probable, reveals a weakness of the theoretical model to account for the attenuation of substituent effects upon chlorine accumulation. If such a computational artifact exists, it should vanish at higher levels of sophistication.

One fundamental conclusion appears to be already irrefutable. The acidity of polychlorobenzenes cannot be derived by a mere addition of individual effects. Again using increments as a probe, we notice a poor fit between the MP2 data ($\Delta H_{\text{MP2}}^{\text{corr}}$) and the parameter-based estimate as long as a single (“linear”) set of increments is used. It does not really matter what set of parameters is exactly chosen, for example the same one which was already used to estimate gas-phase basicities (*ortho* − 11.5, *meta* − 7.5, and *para* − 4.5 kcal mol^{−1};

Table 2. Acidity of zero-, mono-, di-, tri-, tetra- and pentachlorobenzenes as evaluated by ab initio calculations in comparison with experimental and parametrized deprotonation enthalpies.^[a,b]

Benzenide ion	ΔH_g°	ΔH_{MP2}	ΔH_{MP2}^{corr}	(Δ°)	ΔH_{incr}^I	(Δ^I)	ΔH_{incr}^{II}	(Δ^{II})
unsubstituted	401.7	399.0	400.4	(+1.3)	398.1	(2.3)	400.6	(+0.2)
2-Cl ^[c]	386.6	385.2	386.6	[0.0]	[386.6]	[0.0]	[386.6]	[0.0]
3-Cl	–	387.1	388.5	–	390.6	(2.1)	388.6	(+0.1)
4-Cl	–	389.7	391.1	–	393.6	(2.5)	391.6	(+0.5)
2,3-Cl ₂	377.1	376.3	377.7	(–0.6)	379.1	(1.4)	376.4	(–1.3)
2,4-Cl ₂	–	377.0	378.4	–	382.1	(3.7)	379.4	(+1.0)
2,5-Cl ₂	377.0	374.6	376.0	(+1.0)	379.1	(3.1)	376.4	(+0.4)
2,6-Cl ₂	374.0	371.9	373.3	(+0.7)	375.1	(1.8)	374.4	(+1.1)
3,4-Cl ₂	–	380.9	382.3	–	386.1	(3.8)	381.4	(–0.9)
3,5-Cl ₂	–	376.1	377.5	–	383.1	(5.6)	378.4	(+0.9)
2,3,4-Cl ₃	374.9	370.9	372.3	(+2.6)	374.6	(2.3)	370.7	(–1.6)
2,3,5-Cl ₃	–	366.3	367.7	–	371.6	(3.9)	367.7	(±0.0)
2,3,6-Cl ₃	370.3	364.2	365.6	(+4.7)	367.6	(2.0)	365.7	(+0.1)
2,4,5-Cl ₃	–	369.0	370.4	–	374.6	(4.2)	370.7	(+0.3)
2,4,6-Cl ₃	369.2	364.7	366.1	(+3.1)	370.6	(4.5)	368.7	(+2.6)
3,4,5-Cl ₃	–	372.4	373.8	–	378.6	(4.8)	372.7	(–1.1)
2,3,4,5-Cl ₄	368.3	362.9	364.3	(+4.0)	367.1	(2.8)	363.2	(–1.1)
2,3,4,6-Cl ₄	363.3	359.2	360.6	(+2.7)	363.1	(2.5)	361.2	(+0.6)
2,3,5,6-Cl ₄	361.8	356.5	357.9	(+3.9)	360.1	(2.2)	358.2	(+0.3)
Cl ₅	355.0	353.4	354.8	(+0.2)	355.6	(0.8)	354.7	(–0.1)

[a] All energies in kcal mol^{–1}. [b] ΔH_g° = gas phase deprotonation enthalpies; ΔH_{MP2} and ΔH_{MP2}^{corr} = uncorrected and corrected ab initio deprotonation enthalpies; $\Delta^\circ = \Delta H_g^\circ - \Delta H_{MP2}^{corr}$; $\Delta^I = \Delta H_{MP2}^{corr} - \Delta H_{incr}^I$; $\Delta^{II} = \Delta H_{MP2}^{corr} - \Delta H_{incr}^{II}$; ΔH_{incr}^I and ΔH_{incr}^{II} = deprotonation enthalpies obtained using the linear and graduated set of increments (see text). [c] Reference compound (see text).

now ΔH_{incr}^I : average deviation 3.0, maximum deviation 5.6 kcal mol^{–1}) or a similar one. A satisfactory agreement (ΔH_{incr}^{II} : average deviation 0.7, maximum deviation 2.6 kcal mol^{–1}) with the computational results (ΔH_{MP2}^{corr}) was only achieved with a gradative set of increments which allows for an attenuation with an increasing degree of substitution. Maximum values of increments of –14.0, –12.0, and –9.0 kcal mol^{–1} were attributed to an *ortho*-, *meta*-, and *para*-positioned chloro substituent at the Cl₀ → Cl₁ (benzenide → chlorobenzenides) transition. These numbers were progressively diminished by 1.8, 1.5, 1.2, and 1.0 kcal mol^{–1} upon each introduction of an additional chlorine atom. Thus, increments of –12.2, –10.2, and –7.2 were used at the Cl₁ → Cl₂ transition, of –10.7, –8.7, and –5.7 at the Cl₂ → Cl₃ transition, of –9.5, –7.5, and –4.5 at the Cl₃ → Cl₄ transition and finally of –8.5, –6.5, and –3.5 at the Cl₄ → Cl₅ transition.

Hydrogen/metal interconversion rates: The ultimate and decisive step was to correlate the acidity with reactivity. To this end, the metalation of ten chloro-substituted benzenes was studied in tetrahydrofuran at –100 °C using *sec*-butyllithium (“LIS”) as the reagent. Three of these substrates (1,2,3-trichlorobenzene and 1,2,3,4- and 1,2,3,5-tetrachlorobenzene) underwent concomitant hydrogen/metal and halogen/metal exchange. This may or may not compromise the accuracy of the numbers listed. Pentachlorobenzene had to be withdrawn from the series since it reacted in an uncontrolled way leading to an inseparable mixture of products. The relative hydrogen/metal interconversion rates k_{LIS}^{rel} were determined in competition experiments and are all projected

on chlorobenzene as the reference compound (Table 3). The experimental ratios were corrected statistically by dividing them by the number of equivalent exchange sites (e.g., 6 for benzene and 2 for chlorobenzene). The resulting “factorized” rates (k_{LIS}^f) were converted into differential free energies of activation ($\Delta\Delta G_{LIS}^{*,f}$, Table 3).

Table 3. Metalation of zero-, mono-, di-, tri-, tetra- and pentachloro substituted benzenes with *sec*-butyllithium in tetrahydrofuran at –100 °C: relative rates^[a] before (k_{LIS}^{rel}) and after (k_{LIS}^f) statistical correction^[b] the corresponding free energies^[c] of activation ($\Delta\Delta G_{LIS}^{*,f}$), the differential free energies^[c] of deprotonation in the gas phase^[d] ($\Delta\Delta G_g^\circ$), the same after statistical correction (ref. [21]) for equivalent sites ($\Delta\Delta G_g^{*,f}$)^[b] and the carbanion character (“c.c.[‡]”) of the transition state.^[e]

CH-acid	k_{LIS}^{rel}	k_{LIS}^f	$(\Delta\Delta G_{LIS}^{*,f})$	$\Delta\Delta G_g^\circ$	$\Delta\Delta G_g^{*,f}$	c.c. [‡]
C ₆ H ₆ ^[f]	5.0×10^{-4}	8.3×10^{-5}	+3.23	+14.3	+14.8	0.22
C ₆ H ₅ Cl	2.0×10^0	1.0×10^0	0.00	0.0	0.0	–
1,2-C ₆ H ₄ Cl ₂	1.0×10^2	6.0×10^1	–1.35	–9.9	–9.9	0.14
1,3-C ₆ H ₄ Cl ₂	1.5×10^2	1.4×10^2	–1.72	–12.3	?12.6	0.14
1,4-C ₆ H ₄ Cl ₂	1.9×10^2	4.8×10^1	–1.33	–9.9	–9.6	0.14
1,2,3-C ₆ H ₃ Cl ₃	[g]	–	–	–11.8	–11.8	–
1,2,4-C ₆ H ₃ Cl ₃	1.4×10^3	1.4×10^3	–2.51	–18.0	–18.3	0.14
1,3,5-C ₆ H ₃ Cl ₃	9.5×10^2	3.2×10^2	–1.98	–17.8	–17.6	0.11
1,2,3,4-C ₆ H ₂ Cl ₄	7.8×10^2	3.9×10^2	–2.05	–18.5	–18.5	0.11
1,2,3,5-C ₆ H ₂ Cl ₄	4.2×10^3	2.1×10^3	–2.63	–23.2	–23.2	0.11
1,2,4,5-C ₆ H ₂ Cl ₄	1.0×10^4	5.0×10^3	–2.93	–24.9	–24.9	0.12
C ₆ HCl ₅	[g]	–	–	–31.2	–31.5	–

[a] Best averages from Table 6; reference: chlorobenzene. [b] Substrate concentrations divided by the number of equivalent acidic positions (e.g., benzene: 6, chlorobenzene: 2). [c] All energies are given in kcal mol^{–1}. [d] Relative to chlorobenzene; for absolute values, see Table 1. [e] c.c.[‡] = $\Delta\Delta G_{LIS}^{*,f}/\Delta\Delta G_g^{*,f}$. [f] At –75 °C; for details see ref. [22]. [g] Determination not possible due to extensive side reactions.

A comparison between the substituent effects of the free activation energies ($\Delta\Delta G_{LIS}^{*,f}$) and the gas-phase basicity of chloro-substituted benzenide ions ($\Delta\Delta G_g^{*,f}$) unveils an amazingly good linear correlation. The $\Delta\Delta G_{LIS}^{*,f}/\Delta\Delta G_g^{*,f}$ ratios cluster around 0.13, with one exception (see below). These ratios monitor the carbanion character (“c.c.[‡]”) of the proton-losing aromatic center at the transition state of the metalation reaction. Since organolithium compounds are believed to retain about 40% of the electron excess found in the counterion free (“naked”) carbanions,^[22] this means that at the transition state approximately one third of the fractional charge has been transferred from the *sec*-butyllithium reagent to the emerging di- or trichlorophenyllithium species.

As a closer look reveals (Table 3), the transition state carbanion character is not constant within the entire series but follows a distinct trend. It attains a maximum value of 0.22 with benzene to diminish through 0.14 (1,2- and 1,4-dichlorobenzene) to less than 0.12 (1,3,5-tri- and 1,2,4,5-tetrachlorobenzene). In part this is an illustration of the Polanyi–Bell–Marcus treatment of reaction profiles^[23–27] according to which, within the same family of reactions, the most exoenergetic process should have the earliest transition state. However, this does not explain the large difference between the pairs benzene/chlorobenzene (c.c.[‡] 0.22) and chlorobenzene/1,2-dichlorobenzene (c.c.[‡] 0.14). This discrepancy calls for

another explanation. Obviously the presence of heterosubstituents, regardless of how many, in the vicinity of the reaction site causes a profound alteration of the transition state structure and energetics.

Experimental Section

For working routine and abbreviations, see recent publications from this laboratory.^[28–30] The ¹H NMR spectra were recorded at 400 MHz; the samples were dissolved in deuteriochloroform. All chloro-substituted benzenes studied have been purchased (from Fluka and Aldrich, both CH-9741 Buchs) except for 1,2,3,5-tetrachlorobenzene which was prepared according to a literature procedure.^[31]

Gas-phase acidities: The acid/base equilibration experiments were performed in a homemade Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with a 1.4 T electromagnet and a cubic inch cell. The instrument and its operation have been described previously.^[7, 32, 33]

In general, it took 3–4 s to establish an equilibrium between the two CH acids, the chlorinated aromatic substrate (HA_{Cl_n}), the reference acid (HA_{ref}), and the corresponding carbanions by crossover proton transfer. The relative peak intensities of the two anions in the equilibrium composition provided the ion-abundance ratio $A_{Cl_n}^- / A_{ref}^-$. To calculate the equilibrium constant *K* one needed also to know the relative gas-phase concentrations of the neutral components, that is the chloro-substituted substrate (H–A_{Cl_n}) and the reference acid (H–A_{ref}). These ratios resulted from the partial pressures as read by the ionization-gauge manometer after the appropriate correction for relative manometer sensitivities *R_x* (Table 4; relative to nitrogen *R_x* = 1.00). As almost no experimental values *R_x* are available from the literature,^[34] the required parameters were derived from the relationship $R_x = 0.36 \alpha + 0.3$.^[34] The polarizabilities α were taken from the literature^[35] whenever possible. As the polarizabilities α are unknown for all tri-, tetra-, and pentachlorobenzenes, the *R_x*[calcd] values were estimated to equal those of the dichlorobenzenes (5.39). Similarly, the unknown *R_x*[calcd] values of 1,3-difluorobenzene, 1,2,3-, 1,2,4-trifluorobenzene, and 1,2,3,5-tetrafluorobenzene were assumed to coincide with those of their isomers.

Table 4. Calculated and experimental polarizabilities α ^[35] and manometer sensitivities *R_x*^[34] (relative to N₂).^[a]

Substrate	α [calcd]	α [exptl]	<i>R_x</i> [calcd.]	<i>R_x</i> [exptl]
C ₆ H ₅ Cl	12.25	12.25	4.71	4.88
1,2-C ₆ H ₄ Cl ₂	14.15	14.17	5.39	–
1,3-C ₆ H ₄ Cl ₂	14.15	14.23	5.39	–
1,4-C ₆ H ₄ Cl ₂	14.15	14.20	5.39	–
1,2,3-C ₆ H ₃ Cl ₃	–	–	5.39 ^[b]	–
1,2,4-C ₆ H ₃ Cl ₃	–	–	5.39 ^[b]	–
1,3,5-C ₆ H ₃ Cl ₃	–	–	5.39 ^[b]	–
1,2,3,4-C ₆ H ₂ Cl ₄	–	–	5.39 ^[b]	–
1,2,3,5-C ₆ H ₂ Cl ₄	–	–	5.39 ^[b]	–
1,2,4,5-C ₆ H ₂ Cl ₄	–	–	5.39 ^[b]	–
C ₆ H ₅ Cl ₅	–	–	3.89 ^[b]	–
C ₆ H ₅ F	10.13	9.86	3.95	–
1,2-C ₆ H ₄ F ₂	9.89	9.80	3.89	–
1,3-C ₆ H ₄ F ₂	–	–	3.89 ^[b]	–
1,4-C ₆ H ₄ F ₂	9.98	9.80	3.89	–
1,2,3-C ₆ H ₃ F ₃	–	–	3.88 ^[b]	–
1,2,4-C ₆ H ₃ F ₃	–	–	3.88 ^[b]	–
1,3,5-C ₆ H ₃ F ₃	9.94	9.74	3.88	–
1,2,3,4-C ₆ H ₂ F ₄	9.97	9.69	3.89	–
1,2,3,5-C ₆ H ₂ F ₄	–	–	3.89 ^[b]	–
1,2,4,5-C ₆ H ₂ F ₄	9.97	9.69	3.89	–
C ₆ HF ₅	10.05	9.63	3.92	–

[a] See text. [b] Estimated.

The temperature at the ion-trapping plate opposite to the filament was estimated as 330 K (57 °C). The free deprotonation energies (ΔG_g°) of the chloro-substituted benzenes then followed from the relative concentrations of ions and neutrals and the known gas-phase acidities of the reference acids (Table 5). They were converted into deprotonation enthalpies (ΔH_g° , Table 5) in the usual way^[31] by taking into account the entropy change due to proton detachment and small possible changes in the rotational symmetry. Sources and probable magnitudes of errors have been previously discussed.^[7]

Table 5. Acid/base equilibrations performed between benzene, chlorobenzene or oligochlorobenzenes and reference compounds in the gas phase: deprotonation free energies (ΔG_g°) and enthalpies (ΔH_g°) [kcal mol^{–1}].

Benzene derivative	Reference acid	(ΔG_{ref}°) ^[a]	ΔG_g°	ΔH_g°
C ₆ H ₆ ^[b]	–	–	392.9	401.7
C ₆ H ₅ Cl	C ₆ H ₅ F	(378.8) ^[c]	378.6	386.6
1,2-C ₆ H ₄ Cl ₂	1,2-C ₆ H ₄ F ₂	(369.7) ^[d]	368.7	377.1
1,3-C ₆ H ₄ Cl ₂	1,3-C ₆ H ₄ F ₂	(366.4)	366.3	374.0
1,4-C ₆ H ₄ Cl ₂	1,4-C ₆ H ₄ F ₂	(372.4)	368.8	377.0
1,2,3-C ₆ H ₃ Cl ₃	1,2,3-C ₆ H ₃ F ₃	(367.6)	366.8	374.9
1,2,4-C ₆ H ₃ Cl ₃	1,2,4-C ₆ H ₃ F ₃	(362.8)	362.6	370.3
1,3,5-C ₆ H ₃ Cl ₃	1,3,5-C ₆ H ₃ F ₃	(361.6)	360.8	369.2
1,2,3,4-C ₆ H ₂ Cl ₄	1,2,3,4-C ₆ H ₂ F ₄	(361.9)	360.1	368.3
1,2,3,5-C ₆ H ₂ Cl ₄	1,2,3,5-C ₆ H ₂ F ₄	(355.6)	355.4	363.3
1,2,4,5-C ₆ H ₂ Cl ₄	1,2,4,5-C ₆ H ₂ F ₄	(353.5)	353.7	361.8
C ₆ HCl ₅	C ₆ HF ₅	(349.2)	347.4	355.0

[a] All reference data are taken from ref. [6] unless stated otherwise. [b] G. E. Davico, V. M. Bierbaum, C. H. DePuy, G. B. Ellison, R. R. Squires, *J. Am. Chem. Soc.* **1995**, *117*, 2590–2599. [c] Ref. [8]. [d] S. G. Lias, J. E. Bartmess, J. F. Liebmann, J. L. Holmes, R. D. Levin, W. G. Mallard, *J. Phys. Chem. Ref. Data Suppl.* **1988**, *17*, 1–861 [*Chem. Abstr.* **1989**, *111*, 13265a].

Computational work: The GAMESS^[36] program was employed to perform the calculations with the MP2/G-311+G**/RHF/6-311+G* basis set. As indicated by this notation, the standard 6-311 set was supplemented with polarization functions of d-type symmetry^[37] at the carbanionic center as well as at each of the two neighboring carbon centers and a diffuse sp orbital^[38, 39] was included at the carbanionic center. The temperature was corrected to 298 K and zero-point energies were multiplied by the known empirical factor of 0.89.^[40] Two 266 MHz iMac computers with a 64 Mb RAM and a 6 Gb hard-disk capacity served as the hardware equipment.

Rate measurement: The reactivities of the various chloro-substituted benzenes towards *sec*-butyllithium were compared by competition experiments among themselves and including fluorobenzene and 1-fluoronaphthalene (Table 6). Rate ratios k_B/k_A were evaluated using the standard formula.^[41, 42] Whenever possible, redundant data were collected. For example, the metalation rates of all three dichlorobenzenes relative to chlorobenzene were determined (though indirectly, using 1-fluoronaphthalene as a “relay compound”). In addition, the three isomers were compared with each other in direct competition. The k_{rel}^B/k_{rel}^A ratios (as listed in Table 3), are best approximation obtained by averaging all six experimental rate ratios ($k^{1,2}/k^{Cl}$, $k^{1,3}/k^{Cl}$, $k^{1,4}/k^{Cl}$, $k^{1,2}/k^{1,3}$, $k^{1,2}/k^{1,4}$, $k^{1,3}/k^{1,4}$).

General competition protocol: A commercial solution of *sec*-butyllithium (0.10 mol) was transferred in a 0.25 L Schlenk vessel. The solvent was removed and residual volatiles were completely evaporated under reduced pressure ($\leq 10^{-5}$ Torr) for 45 min at 25 °C (water bath). The reagent was dissolved in precooled (–100 °C) tetrahydrofuran (0.10 L) and the solution was stored at –75 °C. Stock solutions of substrates A_H and B_H (5.0 mL each) and the internal standard (tridecane or *tert*-butylbenzene, 1.0 mL), 1.0 M each in tetrahydrofuran, were mixed. A few drops of this mixture were saved for later gas chromatographic analysis before the rest was cooled to –100 °C and added in one portion to a –100 °C cold 1.0 M solution of *sec*-

Table 6. Relative reactivities of substrates A and B towards *sec*-butyllithium in tetrahydrofuran at -100°C as revealed by competition experiments.^[a]

A	B ^[b]	[A ^o]	[B ^o]	[A ⁱ]	[B ⁱ]	k^B/k^A
C ₆ H ₅ Cl	C ₆ H ₅ F	4.98	4.99	3.78	1.24	4.9
C ₆ H ₅ Cl	1-C ₁₀ H ₇ F	4.99	5.00	4.01	0.48	10.6
1,2-C ₆ H ₄ Cl ₂	C ₆ H ₅ F	4.99	5.01	0.89	4.38	0.077
1,2-C ₆ H ₄ Cl ₂	1-C ₁₀ H ₇ F	4.98	4.99	1.25	3.67	0.22
1,2-C ₆ H ₄ Cl ₂	1,3-C ₆ H ₄ Cl ₂	5.02	5.03	2.52	1.74	1.5
1,2-C ₆ H ₄ Cl ₂	1,4-C ₆ H ₄ Cl ₂	4.99	5.01	3.77	2.68	2.2
1,2-C ₆ H ₄ Cl ₂	1,2,4-C ₆ H ₃ Cl ₃	5.02	5.01	4.24	0.52	14
1,2-C ₆ H ₄ Cl ₂	1,3,5-C ₆ H ₃ Cl ₃	4.98	5.01	3.99	1.02	7.2
1,3-C ₆ H ₄ Cl ₂	C ₆ H ₅ F	5.04	5.01	0.48	4.24	0.071
1,3-C ₆ H ₄ Cl ₂	1-C ₁₀ H ₇ F	4.98	4.98	0.97	3.75	0.18
1,3-C ₆ H ₄ Cl ₂	1,4-C ₆ H ₄ Cl ₂	5.02	5.01	2.66	2.47	1.1
1,3-C ₆ H ₄ Cl ₂	1,2,4-C ₆ H ₃ Cl ₃	5.02	5.06	4.13	0.70	10
1,3-C ₆ H ₄ Cl ₂	1,3,5-C ₆ H ₃ Cl ₃	5.00	5.01	4.25	1.41	7.8
1,4-C ₆ H ₄ Cl ₂	C ₆ H ₅ F	5.01	5.01	0.56	4.45	0.053
1,4-C ₆ H ₄ Cl ₂	1-C ₁₀ H ₇ F	4.99	5.00	0.38	3.80	0.11
1,4-C ₆ H ₄ Cl ₂	1,2,4-C ₆ H ₃ Cl ₃	5.00	4.99	4.05	1.05	7.5
1,4-C ₆ H ₄ Cl ₂	1,3,5-C ₆ H ₃ Cl ₃	5.00	5.00	3.51	0.91	4.8
1,2,4-C ₆ H ₃ Cl ₃	1,3,5-C ₆ H ₃ Cl ₃	5.03	5.00	2.69	2.39	0.83
1,2,4-C ₆ H ₃ Cl ₃	1,2,3,5-C ₆ H ₂ Cl ₂	2.00	2.00	3.27	1.61	3.0 ^[d]
1,2,4-C ₆ H ₃ Cl ₃	1,2,4,5-C ₆ H ₂ Cl ₄	4.99	4.96	4.03	1.01	7.4
1,3,5-C ₆ H ₃ Cl ₃	1,2,4,5-C ₆ H ₂ Cl ₄	5.00	5.02	4.62	2.57	8.5

[a] [A^o] or [B^o] and [Aⁱ] or [Bⁱ] = amount [mmol] of substrate before (°) and after (i) the reaction. [b] Fluorobenzene and 1-fluoronaphthalene serve as “internal standards” (see text). [c] Corrected for a 1:1 competition between hydrogen/metal exchange (at the 5-position) and chlorine/metal exchange (at the 2-position). [d] Corrected for a 91:5.5:3.5 competition between hydrogen/metal exchange (at the 4-position) and chlorine/metal exchange (at the 2- and 1-positions).

butyllithium in tetrahydrofuran (5.0 mL) which had been transferred from the storage vessel by means of a nitrogen-purged pipet. After 45 min at -100°C , the reaction mixture was poured on an excess of freshly crushed dry ice. After all carbon dioxide had evaporated, a given amount of a second “internal standard” (benzoic acid) and pentanes (25 mL) were added. The organic layer was extracted with a 1.0 M aqueous solution (3×10 mL) of sodium hydroxide and washed with brine (2×10 mL) before being examined by gas chromatography. The peak areas of substrates A and B relative to that of the neutral standard, before and after the treatment with *sec*-butyllithium, were listed and used to calculate rate ratios (k^B/k^A). The combined aqueous layers were acidified (to pH ≈ 2) and extracted with diethyl ether (3×25 mL). The organic phase was treated with diazomethane in diethyl ether until the yellow color persisted. The concentrations of the A_H and B_H derived esters were determined by comparison of the their peak areas in the gas chromatograms with that of the methyl ester of the alkali-soluble “internal standard”. Unequal detector sensitivities for the various esters were corrected by calibration factors. In each case it was ascertained that the consumption of substrates A_H and B_H was counterbalanced by the formation of esters in corresponding quantities.

Conditions of gas chromatographic analysis: As a rule, two columns of different polarity were used to probe the concentrations of substrates and products. Different conditions had to be employed for the oligochlorobenzene substrates (2 m, 5% C-20M, $65 \rightarrow 200^{\circ}\text{C}$; 2 m, 5% Ap-L, $75 \rightarrow 200^{\circ}\text{C}$; heating rate $10^{\circ}\text{C min}^{-1}$) and methyl ester products (2 m, 5% C-20M, 200°C ; 20 m, DB-1701, $120 \rightarrow 160^{\circ}\text{C}$).

Authentic materials for comparison: 2-Chloro-,^[43] 2,3-dichloro,^[44] 2,6-dichloro,^[44] 2,5-dichloro-,^[44] 2,3,4-trichloro-,^[45] 2,3,6-trichloro-,^[45] 2,4,6-trichloro-,^[46] 2,3,4,5-tetrachloro-,^[47] 2,3,4,6-tetrachloro-,^[48] 2,3,5,6-tetrachloro-,^[49] and penta-chloro-,^[50] benzoic acid have all been reported in the literature. The corresponding methyl esters are also known.^[47, 51–58] Thus all products could be identified unambiguously by comparison of their gas chromatographic retention time with those of authentic samples.

Acknowledgements

The authors are indebted to the *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung* (grants 20-49'307-96 and 20-55-303-98), Bern (Switzerland), for financial support.

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Received: December 22, 2000 [F2958]