

Bis- and Oligo(trifluoromethyl)benzenes: Hydrogen/Metal Exchange Rates and Gas-Phase Acidities

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Abstract: The proton mobilities (kinetic acidities) of bis- and tris(trifluoromethyl)benzene are dictated to a large extent by steric factors; the trifluoromethyl group is a fairly bulky substituent that can seriously impede the approach of the metalating reagent. Most satisfactory results in terms of yields and selectivities have been achieved with lithium 2,2,6,6-tetramethylpiperidide or

with methyllithium in the presence of potassium *tert*-butoxide, a slim version of the standard superbases. The rates of deprotonation under irreversible conditions do not parallel the thermodynamic

(equilibrium) acidities. Substituent effects on the deprotonation energies in the gas phase appear to be additive: each trifluoromethyl group lowers it by 13 kcal mol⁻¹ when located *ortho* with respect to the carbanion, and by 10 kcal mol⁻¹ when located in a *meta* or *para* position.

Keywords: acidity • fluorine • kinetics • lithiation • substituent effects

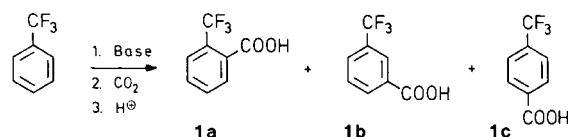
Introduction

Our efforts to metalate 1,2,4-tris(trifluoromethyl)benzene have led to unexpected observations.^[1] In order to gain further insight, we have embarked on a systematic investigation of the kinetic and thermodynamic acidities of all bis- and tris(trifluoromethyl)benzenes. For comparison, (trifluoromethyl)benzene (benzotrifluoride, α,α,α -trifluorotoluene) and 1,2,4,5-tetrakis(trifluoromethyl)benzene were also included in the study.

Results and Discussion

Preparative runs and products: The metalation of (trifluoromethyl)benzene was first accomplished with butyllithium in refluxing diethyl ether to afford 24%, 9% and 0.2% of 2-, 3-,

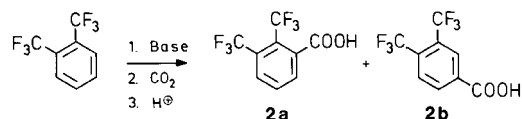
and 4-(trifluoromethyl)benzoic acid (**1a**, **1b** and **1c**), respectively.^[2] A repetition of this work with modern analytical equipment confirmed the data.^[3] By the use of *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA)-activated *sec*-butyllithium (in tetrahydrofuran at -75°C) as a more energetic base (LIS-PMDTA), we were able to improve the yields, but could not secure product homogeneity (47% **1a** contaminated with 25% **1b** and 6% **1c**). Selectivity, in the sense of clean *ortho*-metalation, was only achieved with butyllithium in the presence of potassium *tert*-butoxide (LIC-KOR)(**1a**: 94% by gas chromatography,^[4] 67% crystallized).^[5] As we have found in the meantime, another superbasic mixed-metal reagent, potassium *tert*-butoxide activated methyllithium ("LIM-KOR"), gave an even superior result (83% of analytically pure acid **1a**).



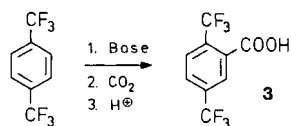
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The regioselectivity was lost again when we turned to 1,2-bis(trifluoromethyl)benzene as the next substrate. With LIS-PMDTA in tetrahydrofuran at -75°C , a 1:1 mixture (71%) of 2,3- and 3,4-bis(trifluoromethyl)benzoic acid (**2a** and **2b**) was obtained. Too weak to cope with (trifluoromethyl)benzene, the amide base, lithium 2,2,6,6-tetramethylpiperidide (LITMP), performed the deprotonation this time efficacious-

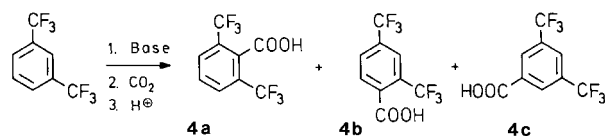
ly in tetrahydrofuran at -75°C , but gave a 2:1 mixture (80%) of the acids **2a** and **2b**. Even the superbasic LIM-KOR reagent (in diethyl ether at -75°C) was not regioselectively perfect; it gave a 9:1 mixture of **2a** and **2b**. Moreover, the yield was poor (8%).



With 1,4-bis(trifluoromethyl)benzene, any structural ambiguity is precluded. The only remaining question is how fast and how complete this substrate undergoes the hydrogen/metal exchange. As it turned out, the acid **3** was formed almost quantitatively, independent of whether LITMP or LIM-KOR (both in tetrahydrofuran at -75°C) was used.



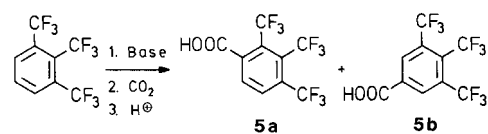
The *meta* isomer 1,3-bis(trifluoromethyl)benzene already has an established reputation as a capricious substrate.^[4, 6] It reacts with the superbasic mixture (LIC-KOR) of butyllithium (LIC) and potassium *tert*-butoxide (KOR) exclusively at the 2-position: 78% of acid **4a** after carboxylation, but with *tert*-butyllithium in tetrahydropyran at -20°C with equal ease at the 4- and 5-position (39 and 42% of acids **4b** and **4c**, respectively).^[4] Lithiation at the 4-position prevails with LIS-PMDTA in tetrahydrofuran at -75°C (after 10 h of metalation time: 56% of **4b** and 8% of **4c**; after 2 h: 38% of **4b** and 14% of **4c**). When employed in excess (2.0 equiv) and in



Abstract in German: Die Protonbeweglichkeiten (kinetischen Aciditäten) von Bis- und Tris(trifluoromethyl)benzolen werden in hohem Maße von sterischen Faktoren beherrscht. Die Trifluoromethyl-Gruppe erweist sich somit als ein ziemlich sperriger Substituent, der die Annäherung eines Metallierungsreagenzes offenbar erheblich behindern kann. Die besten Ergebnisse im Hinblick auf Ausbeuten und Selektivitäten wurden mit Lithium-2,2,6,6-tetramethylpiperidid oder mit Methylithium in Gegenwart von Kalium-*tert*-butylalkoholat erzielt (wobei das letztgenannte Gemisch als schlanke Spielart der üblichen Superbase aufzufassen ist). Die Deprotonierungsgeschwindigkeiten unter irreversiblen Bedingungen ändern sich nicht gleichlaufend mit den thermodynamischen (unter Gleichgewichtsbedingungen bestimmten) Aciditäten. Der Substituenteneinfluss auf die Deprotonierungsenergien in der Gasphase scheint sich additiv zu verhalten, wobei jede Trifluormethyl-Gruppe eine Verminderung um 13 kcal mol^{-1} bewirkt, wenn sie in einer ortho-Stellung bezüglich des carbanionischen Zentrums untergebracht ist, und um 10 kcal mol^{-1} , wenn sie eine meta- oder para-Stellung besetzt.

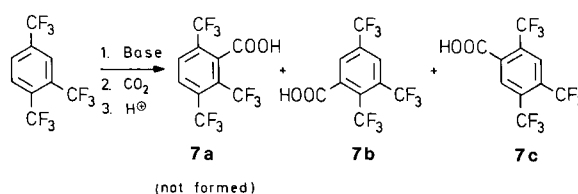
diethyl ether at -25°C , LITMP again produced a mixture of regioisomers (39% of **4b** and 14% of **4c**). However, in the presence of 10% lithium azetide, a slim base added to catalyze acid–base equilibration, and in glycol dimethyl ether as the solvent, LITMP generated only the 2-lithio species (44% of acid **4a**). Neat deprotonation at the 2-position also occurred with either LITMP or methylithium, both in the presence of potassium *tert*-butoxide in tetrahydrofuran (94% and 92% of acid **4a**).

All attempts to submit 1,2,3-tris(trifluoromethyl)benzene to a controlled hydrogen/metal exchange failed. Most of the material decomposed, presumably in a process triggered by a single-electron transfer. Only trace amounts (<3%) of acids could be identified and the assignment (structures **5a** and **5b**) remains speculative.



In contrast, the isomeric 1,3,5-tris(trifluoromethyl)benzene reacted smoothly with LIM-KOR in tetrahydrofuran at -75°C or LITMP (2.0 equiv) in diethyl ether at -25°C . The only possible product, acid **6**, was isolated in high yield (74% and 94%, respectively). In tetrahydrofuran there was an abundant formation of tar, even at -75°C .

Extensive decomposition also occurred when 1,2,4-tris(trifluoromethyl)benzene was treated with LIS, LIM-KOR, or LIC-KOR. However, metalation with LITMP made the acids **7b** and **7c** accessible in excellent yields (94% and 92%). The ratios varied between 1:25 or 1:8, depending on whether diethyl ether (at -25°C ; 2.0 equiv base) or tetrahydrofuran (at -75°C) were used as the solvent. The isomer **7a**, in which the carboxyl group is flanked by two trifluoromethyl moieties, was not detected at all.



The findings reported so far are surprising in more than one respect. Evidently, there are two clearly distinguishable structural features that can compromise metalation. In 1,3-bis(trifluoromethyl)benzene and 1,2,4-tris(trifluoromethyl)benzene the attack of the base at the position flanked by two acidifying, but bulky substituents is impeded and only potassium-containing mixed-metal reagents are capable of overcoming this obstacle. In addition, a buttressing effect^[7] must be operating in 1,2-bis(trifluoromethyl)benzene and 1,2,3-tris(trifluoromethyl)benzene that retards or prevents any reaction by not allowing the substituent to step back and to make way for the reagent.

Competition experiments and relative rates: The reactions reported in the preceding section were preparation-oriented. All efforts were made to elaborate protocols that would allow the substitution of bis- and tris(trifluoromethyl)benzenes in a rational way by performing site-selective metalation/electrophilic trapping sequences. Moreover, the identity of the products, their purity, and yields had to be established.

Nevertheless, the kinetic dimension did not pass unnoticed. The rates of metalation appeared to be dictated by steric rather than electronic factors; the activation provided by the electronegativity of a given trifluoromethyl moiety was often outweighed by its bulkiness. For example, 1,3-bis- and 1,2,4-tris(trifluoromethyl)benzene, let alone the 1,2,3-isomer, were found to be far less reactive than expected on the basis of the rate increase when going from benzene to (trifluoromethyl)benzene and 1,4-bis(trifluoromethyl)benzene.

In order to quantify the differences in reactivity, we have carried out competition experiments to probe the affinity of a lithiation reagent added in substoichiometric quantities, for

either of two simultaneously present substrates. The data (summarized in Table 1) do indeed give an idea of to what extent steric hindrance can affect deprotonation rates and site selectivities.

A simultaneous comparison of the kinetic and thermodynamic acidities of the various members of the fluoroarene and

Table 2. Gas-phase acidity of benzene^[7,8] and several trifluoromethyl-substituted congeners: free energies of deprotonation [kcal mol⁻¹], absolute numbers (ΔG_g°), and relative to (trifluoromethyl)benzene ($\Delta\Delta G_g^\circ$), and relative dissociation constants [ΔpK_g] at 330 K.

CF ₃ substituents	ΔG_g°	$\Delta\Delta G_g^\circ$	ΔpK_g
zero	391	+13	+9.6
mono	378	0	0
1,2-bis	369	-10	-6.4
1,3-bis	365	-13	-8.7
1,4-bis	367	-12	-7.6
1,2,3-tris	357	-22	-14.3
1,2,4-tris	355	-23	-15.1
1,3,5-tris	354	-24	-15.9
1,2,4,5-tetrakis	341	-38	-25.0

Table 1. Relative lithiation rates^[a] of benzene, (trifluoromethyl)benzene, 1,2-, 1,4-, and 1,3-bis(trifluoromethyl)benzene, as well as 1,2,3-, 1,3,5-, and 1,2,4-tris(trifluoromethyl)benzene with a variety of bases.^[b]

Substrate	Site	LIM-KOR (THF, -75 °C)	LIS (THF, -75 °C)	LITMP (THF, -75 °C)	LITMP (DEE, -25 °C)
	x	-	2×10^{-4}	$3 \times 10^{-4[d]}$	-
	x	1×10^0	1×10^0	1×10^0	1×10^0
	x	-	3×10^1	4×10^1	5×10^1
	y	-	3×10^1	2×10^1	2×10^1
	x	3×10^2	1×10^2	3×10^2	1×10^2
	y	2×10^4	[d]	[d]	[d]
	y	[d]	2×10^2	7×10^2	3×10^2
	z	[d]	7×10^2	8×10^0	1×10^2
	x	-	-	[e]	[e]
	x	3×10^4	-	5×10^2	6×10^2
	y	-	-	[d]	[d]
	x	-	-	8×10^3	2×10^3
	y	-	-	1×10^3	5×10^2
	z	-	-	-	-

[a] The numbers indicated are statistically corrected for equivalent positions in the substrate. The rate ratios were determined as described in the Experimental Section, and the dashes indicate that the experiment was not executed. [b] LIM-KOR = methyllithium in the presence of potassium *tert*-butoxide; LIS = *sec*-butyllithium; LITMP = lithium 2,2,6,6-tetramethylpiperidide; DEE = diethyl ether. [c] The competition experiment was performed at +25 °C and gave a k_{rel} of 3×10^{-3} . The selectivity is estimated to increase by one power of ten (at least) when the temperature is lowered to -75 °C. [d] Below the threshold of detection. [e] Extensive decomposition; no straightforward reaction products were isolated.

(trifluoromethyl)arene families is most revealing. (Trifluoromethyl)benzene is, at least in the gas phase (see Table 2), slightly more acidic than fluorobenzene.^[10] On the other hand, strong organometallic or amide bases deprotonate fluorobenzene roughly ten times faster than (trifluoromethyl)benzene. The relative inertness of the latter substrate may be attributed to the steric hindrance exerted by the fairly bulky trifluoromethyl substituent. 1,4-Bis(trifluoromethyl)benzene underwent the hydrogen/metal exchange (metalation) considerably faster than 1,4-difluorobenzene^[10]. This time, steric effects were outweighed by the particularly long-ranging acidifying effect of the trifluoromethyl group. A second trifluoromethyl group at the *ortho* position, with respect to the metalation site, still appreciably accelerated the LIMKOR-promoted metalation, as demonstrated by a comparison between (trifluoromethyl)benzene ($k_{\text{rel}} = 1 \times 10^0$), 1,3-bis(trifluoromethyl)benzene ($k_{\text{rel}} = 2 \times 10^4$), and 1,3,5-tris(trifluoromethyl)benzene ($k_{\text{rel}} = 3 \times 10^4$). However, a cumulation of trifluoromethyl groups did not necessarily enhance the metalation rate when lithium 2,2,6,6-tetramethylpiperidide (LITMP) or other lithium bases were employed. In fact, proton abstraction from the doubly activated position flanked by two trifluoromethyl groups only occurred with 1,3,5-tris(trifluoromethyl)benzene, whereas in 1,3-bis(trifluoromethyl)benzene and 1,2,4-tris(trifluoromethyl)benzene the more readily accessible positions were attacked. No reaction at all was observed with 1,2,3-tris(trifluoromethyl)benzene; apparently a consequence of a pronounced buttressing effect.

The compiled data is highly approximate. In extreme cases, the error may almost reach a power of ten. The reason for this inaccuracy is clear: competition kinetics provide reliable data only when the individual reactivities of the rivaling components do not differ by more than a factor of 20. The substrate couples

examined in the framework of the present study often considerably exceeded this threshold value.

There was another point of concern. Did the organolithium species generated with LITMP really originate from irreversible deprotonation processes or did they merely reflect equilibrium states? The reversibility of LITMP-promoted lithiations has been demonstrated with a variety of dihaloarene substrates.^[7] In the present case, however, such artefacts can be ruled out. The proportions of 2,4-bis- and 3,5-bis(trifluoromethyl)phenyllithium in the mixtures obtained (see above) did not vary with time, although the latter component must be significantly more basic than the former, and both of them, without doubt, much more basic than 2,6-bis(trifluoromethyl)phenyllithium.

Gas-phase studies and equilibrium acidities: The determination of the relative stabilities of all possible trifluoromethylated aryllithium species can be envisaged by equilibrating them pairwise together with bromo- or iodo-substituted counterparts. The equilibrium establishing halogen/metal permutation is known to be a fast process in tetrahydrofuran, even at -75°C . However, the same problems in the accuracy will be encountered whenever the basicities of two competing organolithium species differ by significantly more than one $\text{p}K$ unit.

Such limitations can be easily overcome if the gas-phase acidities are measured, since the gap between two strongly diverging acids can always be bridged by reference compounds that fit in between the extremes (bracketing method). Therefore, we have determined the gas-phase acidities of (trifluoromethyl)benzene, of all the three bis- and tris(trifluoromethyl)benzenes, and of one tetra(trifluoromethyl)benzene, in a low-pressure mass spectrometer (see Table 2).

As the data unequivocally reveal, steric effects play only a minor role, if any, in the gas phase. The acidity steeply increases with each extra trifluoromethyl substituent. As in the previously investigated family of fluoroarenes,^[10] cumulated substituent effects appear to be additive. In contrast to the fluoroarene series,^[10] the distance dependence of substituent effects is much more attenuated with trifluoromethyl arenes. The experimental gas-phase deprotonation energies can be reproduced with amazingly good agreement if a charge-stabilizing effect of 13, 10, and 10 kcal mol^{-1} is attributed to each trifluoromethyl group located at the *ortho*, *meta* and *para* position of a phenyl anion, respectively.

Experimental Section

General: For laboratory routine and abbreviations, see related publications.^[1, 11] The ^1H NMR and ^{19}F NMR spectra were recorded at 400 and 376 MHz, respectively, unless stated otherwise.

Starting materials (trifluoromethylated arenes): (trifluoromethyl)benzene, 1,3- and 1,4-bis(trifluoromethyl)benzene, and 1,3,5-tris(trifluoromethyl)benzene are commercially available. 1,2-Bis(trifluoromethyl)benzene,^[12] 1,2,3-tris(trifluoromethyl)benzene,^[13] and 1,2,4,5-tetrakis(trifluoromethyl)benzene^[14] were prepared according to published procedures.

1,2,4-Tris(trifluoromethyl)benzene:^[15] At -10°C , a 1 L stainless steel autoclave was filled with trimellitic anhydride (1,2,4-benzenetricarboxylic anhydride; 0.26 kg, 1.4 mol) and anhydrous hydrogen fluoride (0.30 L, 0.30 kg, 15 mol). The autoclave was cooled to -75°C , evacuated

(2 mm Hg), and sulfur tetrafluoride (1.10 L, 0.58 kg, 5.4 mol) then condensed into it. The autoclave was placed in a rocking muffle furnace, heated to 180°C , and shaken for 10 h. When cooled to 25°C , gaseous products (in particular, thionyl fluoride and unconsumed sulfur tetrafluoride and hydrogen fluoride) were evaporated and the liquid residue was dissolved in diethyl ether (0.20 L). The organic phase was washed with a 10% aqueous solution of potassium hydroxide (3×50 mL) and dried. Distillation afforded a colorless liquid. Yield: 0.35 kg (89%); b.p. $140-142^{\circ}\text{C}$; ^1H NMR (200 MHz): $\delta = 8.12$ (1H, s), 8.0 (2H, m); ^{19}F NMR (188 MHz): $\delta = 64.0$ (s, 3F), 60 (m, 6F).

Preparative reactions and products: As a rule, three different lithiation protocols were tested. Not all reactions were performed, but only the best results are reported under the product headings below. As an exception, all data collected with 1,3-bis(trifluoromethyl)benzene are listed at the end of this Section (Table 3).

Method A with LIM-KOR/THF: At -75°C , a suspension of potassium *tert*-butoxide (2.8 g, 25 mmol) in a mixture of tetrahydrofuran (50 mL) and diethyl ether (20 mL), which contained methylithium (25 mmol), was vigorously stirred until homogeneity was achieved. The trifluoromethylated substrate (25 mmol) was added and the clear solution was kept at -75°C for 2 h. The mixture was poured onto an excess of freshly crushed dry ice, evaporated to dryness, and the residue dissolved in aqueous sodium hydroxide (50 mL, 2M). The aqueous layer was washed with diethyl ether (2×10 mL), acidified with concentrated hydrochloric acid to pH 1, and then extracted with dichloromethane (3×20 mL). Crystallization or sublimation gave an analytically pure product.

Method B with LITMP/THF: Alternatively, lithium 2,2,6,6-tetramethylpiperidide was prepared at -75°C by the rapid addition of 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) in precooled tetrahydrofuran (25 mL) to butyllithium (25 mmol), from which the commercial solvent (hexane) had already been removed. Then the substrate (25 mmol) was treated with this mixture at -75°C for 2 h before the reaction was stopped by carboxylation.

Method C with LITMP/DEE: When lithium 2,2,6,6-tetramethylpiperidide was applied in diethyl ether, it was generated in the same way as described above, but was employed in a twofold excess (50 mmol in 25 mL of the solvent). The lithiation time was still 2 h, but the temperature was raised to -25°C .

2-(Trifluoromethyl)benzoic acid (1a) was prepared from (trifluoromethyl)benzene and LIM-KOR. Yield: 83%; m.p. $110-112^{\circ}\text{C}$ (literature value:^[4] m.p. $110-113^{\circ}\text{C}$). The 3- and 4-isomers (**1b** and **1c**), obtained with LIS-PMDTA, were identified by gas chromatography.

2,3-Bis(trifluoromethyl)benzoic acid (2a) was prepared from 1,2-bis(trifluoromethyl)benzene and LITMP in tetrahydrofuran. Recrystallized twice from hexane. Yield: 44%; m.p. $111-113^{\circ}\text{C}$ (literature value:^[14] m.p. $110-112^{\circ}\text{C}$). The 3,4-isomer **2b**^[16] was enriched in the mother liquors and was identified by ^1H NMR spectroscopy.

2,5-Bis(trifluoromethyl)benzoic acid (3) was prepared from 1,4-bis(trifluoromethyl)benzene with LIM-KOR (85%) or LITMP (93%) in tetrahydrofuran. M.p. $78-80^{\circ}\text{C}$ (literature value:^[17] m.p. $78-80^{\circ}\text{C}$).

2,6-Bis(trifluoromethyl)benzoic acid (4a) was prepared from 1,3-bis(trifluoromethyl)benzene with either LITMP or methylithium in tetrahydrofuran at -75°C in the presence of one molar equivalent of potassium *tert*-butoxide. Yield: 92%; m.p. $133-135^{\circ}\text{C}$ (literature value:^[4] m.p. $133-135^{\circ}\text{C}$).

2-Iodo-1,3-bis(trifluoromethyl)benzene was prepared analogously with either LIDA-KOR (lithium diisopropylamide activated with potassium *tert*-butoxide)^[18] or LIC-KOR as the base and iodine as the electrophile in tetrahydrofuran at -75°C for 2 h. Yellowish crystals. Yield: 78%; m.p. $71-73^{\circ}\text{C}$; ^1H NMR: $\delta = 7.9$ (2H, d, $J = 8.1$), 7.71 (1H, t, $J = 8.1$); anal. calcd for $\text{C}_8\text{H}_3\text{F}_6\text{I}$ (340.01): C 28.26, H 0.89; found C 28.07, H 0.97.

2,4-Bis(trifluoromethyl)benzoic acid (4b) was prepared from 1,3-bis(trifluoromethyl)benzene with LITMP in tetrahydrofuran. Yield: 94%; m.p. $109-111^{\circ}\text{C}$ (literature value:^[4] m.p. $109-111^{\circ}\text{C}$).

2,4,6-Tris(trifluoromethyl)benzoic acid (6) was prepared from 1,3,5-tris(trifluoromethyl)benzene and LITMP (2.0 equiv) in diethyl ether. Yield: 94%; m.p. $118-120^{\circ}\text{C}$ (literature value:^[19] m.p. $118-120^{\circ}\text{C}$).

2,4,5-Tris(trifluoromethyl)benzoic acid (7c) was prepared from 1,2,4-tris(trifluoromethyl)benzene with LITMP in tetrahydrofuran. Yield: 92%

(crude), 71% (pure); m.p. 132–133 °C (recrystallized twice from toluene; literature value:^[1] m.p. 132–133 °C); ¹H NMR: δ = 10.12 (s, broad), 8.36 (1H, s), 8.23 (1H, s); ¹⁹F NMR: δ = –60.3 (q, J = 7.6), –60.4 (q, J = 7.6), –60.6 (s). If the reaction was carried out in diethyl ether at –25 °C, 2,3,5-tris(trifluoromethyl)benzoic acid (**7b**) was formed in considerable amounts as a by-product and was identified in the mother liquors (after crystallization of **7c**) spectroscopically. ¹H NMR: δ = 8.24 (1H, s), 8.16 (1H, s); ¹⁹F NMR: δ = –55.7 (q, J = 15.3), –59.3 (q, J = 15.3), –64.1 (s).

Table 3. Lithiation of 1,3-bis(trifluoromethyl)benzene and subsequent carboxylation to **4a**, **4b**, and **4c**: total yield of acids and product distribution.

Reagent ^[a]	Solvent ^[b]	Time [h] ^[c] Temp. [°C]	Σ 4 [%]	Ratio a:b:c
LIC-KOR ^[d]	THF	3, –75	78	100:0:0
LIS-PMDTA ^[d]	THF	10 h, –75	56	0:87:13
LIT ^[d]	THP	1, –20	39	0:48:52
LIS-PMDTA	THF	2, –75	52	0:73:27
LITMP ^[d]	DEE	2, –25	53	0:73:27
LITMP	THF	2, –75	94	0:99:1
LITMP-LIAZE ^[e]	EGE	2, –25	44	100:0:0
LITMP-KOR	THF	2, –75	94	100:0:0
LIM-KOR	THF	2, –75	92	100:0:0

[a] LIM = methyllithium; LIC = butyllithium; LIS = *sec*-butyllithium; LIT = *tert*-butyllithium; LITMP = lithium 2,2,6,6-tetramethylpiperidide; LIAZE = lithium azetide; PMDTA = *N,N,N',N',N''*-pentamethyldiethylenetriamine; KOR = potassium *tert*-butoxide. [b] THF = tetrahydrofuran, THP = tetrahydropyran, EGE = (mono)ethylene glycol dimethyl ether (1,2-dimethoxyethane). [c] Duration of the exposure of the substrate to the action of the base (before carboxylation). [d] When in DEE, 2.0 molar equivalents. [e] Used in stoichiometric and catalytic amounts (LITMP and LIAZE: 1.0 and 0.10 equiv, respectively).

Competition kinetics: Two trifluoromethylated arenes (10 mmol each) and decane (approximately 1 mL, 5 mmol) were dissolved in tetrahydrofuran or diethyl ether (10 mL) and the concentrations of the two substrates were determined by comparing the peak areas in the gas chromatograms with that of the internal standard decane [2 m, 5% C-20M, 30 °C (8 min) → 220 °C; 2 m, 5% Ap-L, 30 °C (10 min) → 215 °C]. The base (LIM-KOR or LIS or LITMP, 10 mmol in each case), dissolved in tetrahydrofuran or diethyl ether, was added to this mixture. After 2 h at –75 °C (or –25 °C, see Tables 1 and 3), the reaction mixture was poured onto freshly crushed dry ice, diluted with 10% aqueous sodium hydroxide (10 mL), and extracted with diethyl ether (3 × 10 mL). The organic phase was analyzed by gas chromatography (see above) for residual substrate concentrations. The rate ratios were calculated by applying the standard logarithmic formula.^[20, 21]

Gas-phase acidity measurements: The 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. Details of the instrument and experimental procedures have been described previously.^[22, 23]

Table 5. Mono-, bis-, tris-, and tetrakis(trifluoromethyl)benzenes: free energies (ΔG_g°) and enthalpies (ΔH_g°) of gas-phase deprotonation [in kcal mol^{–1}], as determined by means of reference acids at 330 K.

Reference acid	ΔG_g° (H-A _{ref}) ^[a]	(Trifluoromethyl)arene	ΔG_g° (H-A _{(CF₃)_n)^[b]}	ΔH_g° (H-A _{(CF₃)_n)^[b]}
C ₆ H ₅ F	379.1	C ₆ H ₅ CF ₃	378.1 ^[c]	386.2 ^[d]
(H ₃ C) ₂ CHOH	368.8	1,2-C ₆ H ₄ (CF ₃) ₂	368.5	376.7
H ₃ CCN	365.2	1,3-C ₆ H ₄ (CF ₃) ₂	365.0	372.6
H ₇ C ₃ OH	369.5	1,4-C ₆ H ₄ (CF ₃) ₂	366.6	375.2
4-FC ₆ H ₄ NH ₂	357.1	1,2,3-C ₆ H ₃ (CF ₃) ₃	356.6	364.7
4-FC ₆ H ₄ NH ₂	357.1	1,2,4-C ₆ H ₃ (CF ₃) ₃	355.4	363.0
3-FC ₆ H ₄ NH ₂	354.0	1,3,5-C ₆ H ₃ (CF ₃) ₃	354.2	362.6
H ₃ CCOOH	341.5	1,2,4,5-C ₆ H ₂ (CF ₃) ₄	341.4	349.7

[a] Standard error: ± 2.0 kcal mol^{–1}, except for fluorobenzene^[7] (± 5.0 kcal mol^{–1}). [b] Standard errors: ± 2.8–3.1 kcal mol^{–1}, except for (trifluoromethyl)benzene^[8] (± 6.1 kcal mol^{–1}). [c] Ref. [7]: 379.1 (± 5.0) kcal mol^{–1}. [d] Ref. [8]: 387.1 (± 2.0) kcal mol^{–1}.

The ICR cell contained NH₃ at a pressure of 4.0 × 10^{–7} mbar (as indicated by an ion-gauge manometer), the trifluoromethyl-bearing arene under investigation (H-A_{(CF₃)_n), and the reference acid (H-A_{ref}) at partial pressures of between 1.0 and 3.0 × 10^{–7} mbar; the total pressure was between 8.0 and 9.0 × 10^{–7} mbar. The primary ions, NH₂⁺, were generated from NH₃ at 4.0–4.5 eV by dissociative electron capture during an ionization time interval of 175 ms. The anions A_{(CF₃)_n}[–] and A_{ref}[–] were generated by NH₂⁺-mediated proton abstraction from the appropriate conjugate acids during a subsequent reaction time interval of usually 1.0 s. Subsequently, these anions were isolated by ejection of all the other ions from the FT-ICR cell by applying suitable radiofrequency pulses to the excitation plates of the cell. Then a variable reaction time of between 1.0 and 4.0 s followed, after which a mass spectrum was acquired of all the ions formed after this time interval.}

The proton transfer from H-A_{(CF₃)_n to A_{ref}[–] and from H-A_{ref} to A_{(CF₃)_n}[–] was studied by monitoring the reactions of the mass-selected anions as a function of the reaction time until the equilibrium was achieved, in general 3 to 4 s. Relative acidities [kcal mol^{–1}] were calculated as $\Delta\Delta G_g^\circ = -RT \cdot \ln K$, where R is the gas constant, T the absolute temperature, and K the proton-transfer equilibrium constant ($K = [A_{(CF_3)_n}^-][H-A_{ref}]/[A_{ref}^-][H-A_{(CF_3)_n}]$). The required equilibrium ion-abundance ratios ($[A_{(CF_3)_n}^-]/[A_{ref}^-]$) were taken directly from the peak intensities in the reaction mixture.}

The ratios of the concentration of the neutrals ($[H-A_{ref}]/[H-A_{(CF_3)_n}]$) are equal to the partial pressure ratios, which were calculated from the partial

Table 4. Calculated and experimental polarizabilities $\alpha^{[23]}$ and relative ion-gauge manometer sensitivities R_x .^[22]

Compound	Calcd	α Exptl	Calcd	R_x Exptl
C ₆ H ₅ F	10.01	9.86	3.85	–
C ₆ H ₅ CF ₃	11.47	–	4.43	–
C ₆ H ₄ (CF ₃) ₂	13.18	–	5.04	–
C ₆ H ₃ (CF ₃) ₃	15.08	–	5.73	–
C ₆ H ₂ (CF ₃) ₄	17.06	–	6.44	–
H ₃ CCN	4.42	–	1.89	1.99
H ₇ C ₃ OH	6.95	6.77	2.80	2.60
(H ₃ C) ₂ CHOH	6.95	–	2.80	2.86
<i>p</i> -FC ₆ H ₄ NH ₂	11.15	11.51	4.44	–
<i>m</i> -FC ₆ H ₄ NH ₂	11.15	–	4.44	–
H ₃ CCOOH	5.26	5.15	2.19	1.54

pressures read by the ionization-gauge manometer and corrected for the ion-gauge sensitivities R_x (Table 4) relative to N₂ ($R_x = 1.00$). For all reference acids employed, with the exception of fluorobenzene and *m*- and *p*-fluoroaniline, experimental values for R_x are available from the literature.^[24] The relative sensitivities R_x of all other acids followed from the relationship $R_x = 0.36\alpha + 0.3$.^[24] The polarizabilities α were calculated^[25] if experimental values^[25] were unavailable.

The relative acidities, $\Delta\Delta G_g^\circ$, were converted into the free energies of gas-phase deprotonation ΔG_g° (listed in Table 5) by correlating them with the established free deprotonation energies of the reference acids employed

(Table 5). The deprotonation enthalpies ΔH_g° (Table 5) were calculated in the usual way^[26] by adding to the free energies, ΔG_g° , a term $T\Delta_g^\circ$, which comprises the effect of the entropy change due to proton detachment ($7.7 \text{ kcal mol}^{-1}$) and due to the change in rotational symmetry (calculated as the logarithmic ratio of the symmetry numbers of external rotations of $\text{H-A}_{(\text{CF}_3)_n}$ and $\text{A}_{(\text{CF}_3)_n}^-$, multiplied by RT).

The range of error of the partial pressures read from the ionization-gauge manometer is $\pm 20\%$ due to instabilities during the measurement. In the case of compounds for which experimental R_x values are known with an accuracy of $\pm 8\%$ (Table 4), the overall uncertainty of the pressure determination should be less than 30% . If R_x has to be computed, the accuracy of the pressure determination depends on the validity of the equation $R_x = 0.36\alpha + 0.3$. In most cases this approximation worked well with deviations of less than 20% , but in a few cases errors up to 40% were observed.^[24] Unfortunately, there is no experimental data available for halogenated aromatic compounds, except chlorobenzene, for which the deviation is 2.7% .^[24]

However, since the limits of error are between 10 and 30% for many aromatic hydrocarbons, as well as for polyfluoroalkanes and polychloroalkanes,^[24] it can be assumed that the uncertainty in the determination of the partial pressure lies between -50% and $+200\%$ for all the (trifluoromethyl)arenes investigated. By taking into account the $\pm 10\%$ uncertainty^[22, 23] in the determination of the ion abundances, the limits of error for the equilibrium constant K should not exceed -80% and $+500\%$.

A further source of error is the temperature in the instrument. The calculation of the relative free deprotonation energies $\Delta\Delta G_g^\circ$ was based on 330 K , the ordinary temperature of the ion-trapping plate situated opposite the filament. However, the real temperature may lie between 300 and 330 K , since the temperature of the inlet system is about 25°C . This uncertainty adds to the inaccuracy with which the equilibrium constant K has been assessed and it increases the error from approximately 1.0 to approximately $1.1 \text{ kcal mol}^{-1}$.

The error estimate reported for the free deprotonation energies ΔG_g° of the reference acids (in general, $2.0 \text{ kcal mol}^{-1}$) has to be combined with the inaccuracy of the determination of the relative gas-phase acidities $\Delta\Delta G_g^\circ$. Thus, the total standard deviation of the ΔG_g° values, as specified above for the (trifluoromethyl)arenes, should average $3.0 \text{ kcal mol}^{-1}$.

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