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Rate enhancing and rate retarding effects of methoxy substituents on arene metalation

Raimondo Maggi and Manfred Schlosser *

Institut de Chimie organique de l'Université (BCh), CH-1015 Lausanne, Switzerland

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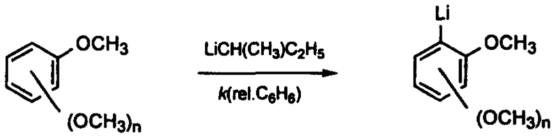
Abstract

Competition experiments have been performed to determine the rates, relative to benzene, with which anisole, the three dimethoxybenzenes and the three trimethoxybenzenes are deprotonated by *sec*-butyllithium. Only the first substituent (anisole relative to benzene) has a strong effect (k^{f}_{rel} 2800); the second one accelerates moderately at best (1,3-dimethoxybenzene relative to anisole: k^{f}_{rel} 12). Methoxy groups being located *para* with respect to the metalation site or occupying a vicinal position to another methoxy substituent diminish the reactivity by up to two powers of ten (relative to anisole). These surprising findings are without precedence. © 1999 Elsevier Science Ltd. All rights reserved.

Even if recognized as such only in hindsight, the *ortho*-lithiation[1–3] of anisole represents a landmark event which has profoundly altered the course of preparative organic chemistry. The regioselective functionalization of sterically less accessible aromatic positions, so far a dream, came into realistic reach. The methods and tools steadily evolved from the rough to the subtle. Neighboring group-assisted electrophilic substitutions are nowadays commonplace.[4–6] Further progress in this area will largely depend on our ability to make substituent effects on the rates of hydrogen/metal exchange processes predictable, at least in a semi-quantitative sense.

In continuation of our systematic assessment of kinetic CH-acidities,[7–9] we have measured the relative rates with which mono-, di- and tri(methoxy)benzene undergo deprotonation when treated with *sec*-butyllithium in tetrahydrofuran at –75°C (Scheme 1). Scheme 2 indicates the relative rates found in a series of competition experiments.[10,11] Table 1 lists the factorized relative rates (partial rate factors k^{f}_{rel}) obtained by statistical correction.



Scheme 1.

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* Corresponding author. Fax: ++41 21 692 39 65.

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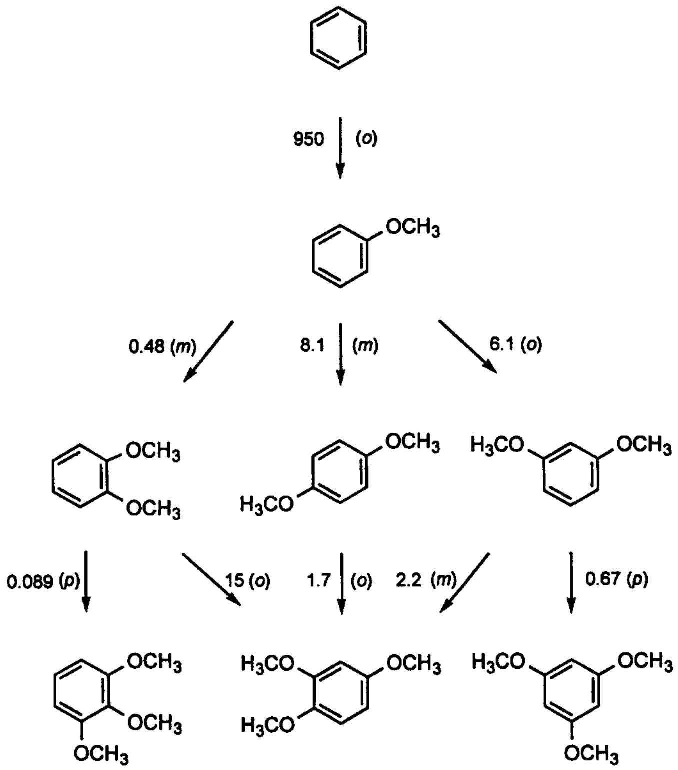

Scheme 2. Pairwise reaction of methoxy-substituted benzenes with *sec*-butyllithium in tetrahydrofuran at –75°C: rates of the higher substituted substrate relative to the reference compound (the position of the extra substituent with respect to the site of deprotonation is specified in parentheses)

Table 1

Reaction of methoxy-substituted benzenes with *sec*-butyllithium in tetrahydrofuran at –75°C: partial rate factors (k) obtained after division of relative rates (k, determined in competition experiments; see Scheme 2) by the number of equivalent exchange-active positions

Position of OCH_3 groups	substrate	k^{f}_{rel}
0	benzene	$3.6 \cdot 10^{-4}$
1	anisole	$\equiv 1.0 \cdot 10^{0}$
1,2	catechol dimethyl ether	$4.8 \cdot 10^{-1}$
1,3	resorcinol dimethyl ether	$1.2 \cdot 10^{+1}$
1,4	hydroquinone dimethyl ether	$4.1 \cdot 10^{0}$
1,2,3	pyrogallol trimethyl ether	$2.1 \cdot 10^{-2}$
1,2,4	hydroxyhydroquinone trimethyl ether	$1.8 \cdot 10^{+1}$
1,3,5	phloroglucin trimethyl ether	$2.7 \cdot 10^{0}$

The data reveal three noteworthy features. Two of them are unprecedented.

(i) Whereas the per-site reactivity of anisole is almost 3000 times higher than that of benzene, the partial rate factors of anisole and resorcinol dimethyl ether (1,3-dimethoxybenzene) differ by just a factor of 12. This kind of attenuation of substituent assistance was already previously encountered with fluoroarenes. The introduction of the first halogen atom *ortho* to a given deprotonation site accelerated the reaction with *sec*-butyllithium by almost five powers of ten (k^{f}_{rel} [C_6H_5F/C_6H_6]=0.5×10^5), while the second halogen caused an increase of less than three powers of ten (k^{f}_{rel} [1,3-$C_6H_4F_2/C_6H_5F$]=0.8×10^3).[7]

(ii) The immediate vicinity of two methoxy groups weakens their metalation-promoting effect. The singly activated anisole undergoes *ortho*-lithiation twice as fast as catechol dimethyl ether (1,2-dimethoxybenzene) and 50 times as fast as pyrogallol trimethyl ether (1,2,3-trimethoxybenzene). To minimize steric repulsion, the most favorable conformations of a *vic*-dimethoxyarene will orient the methyl groups so that they point away from the neighbor substituent. Thus, they oblige the two sets of oxygen-borne lone pairs to face each other. The latter become hence less available for the coordination of the metal of the reagent.

(iii) The partial rate factor of phloroglucin trimethyl ether (1,3,5-trimethoxybenzene) is almost five times smaller than that of resorcinol dimethyl ether (1,3-dimethoxybenzene). In other words, the additional alkoxy substituent *para* to the deprotonation site retards the metalation reaction. Though unexpected, this result is well understandable on the basis of our counterpolarization model. The heteroatom attracts electrons inductively by polarization of the σ-bond skeleton while its lone pairs simultaneously push the π-electron cloud of the aromatic sextet away.[12] As a consequence, charge density accumulates at the *para*-position without being any more overcompensated by the inductive effect, which levels off with the cube root, if not a higher power, of the distance.

Working procedure: At −75°C, *sec*-butyllithium (5.0 mmol) in hexanes (2.9 mL) was added to a solution containing the two selected methoxyarenes (about 5.0 mmol each) and the 'internal standard' dodecane in tetrahydrofuran (10 mL). After 2 h at −75°C, the mixture was poured onto an excess of freshly crushed dry ice. Water (10 mL) was added and the aqueous phase extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (2×5 mL) and analyzed by gas chromatography (2 m, 5% Carbowax 20M, 95°C, and 2 m, 5% Apiezon L, 115°C for the competition of anisole with 1,2-, 1,3- and 1,4-dimethoxybenzene, and the same columns at 125 and 140°C, respectively, for the competition of 1,2-dimethoxybenzene with 1,2,3- and 1,2,4-trimethoxybenzene, of 1,3-dimethoxybenzene with 1,2,4- and 1,3,5-trimethoxybenzene and of 1,4-dimethoxybenzene with 1,2,4-trimethoxybenzene). As a control, the aqueous alkaline layer was acidified. The aromatic carboxylic acids were taken up in diethyl ether to be identified and quantified by gas chromatography.

Acknowledgements

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