The effect of topologically controlled coulombic interactions on the regioselectivity of the reductive cleavage of alkyl phenyl ethers

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The importance of electrostatic effects in the chemical evolution of charged intermediates of the radical anion type is demonstrated. Thus, the regioselectivity of the electron transfer-induced reductive cleavage of alkyl 2,6-diphenylphenyl ethers and alkyl 2,6-dimethoxyphenyl ethers is completely reversed when a positive charge is placed in a controlled manner near the alkyl ether bond.

Alkali metals are known to induce cleavage of the C–O bonds of aryl alkyl ethers under aprotic conditions in various solvents.[1] Cleavage of the alkyl–oxygen bond with formation of phenols (dealkylation) is most often observed; cleavage of the phenyl–oxygen bond (dealkoxylation) is achieved only in particular cases,[2] especially in the presence of potassium and in solvents of low[3] or very low[4] polarity.

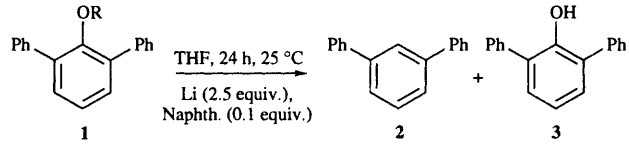
Recently, Herold and co-workers[5] suggested that the position of the counterion (together with the relative orientation of the alkyl ether bond with respect to the benzene ring plane) is a main factor governing the regioselectivity of the radical anion fragmentation. Thus, they proposed that dealkylation occurred when the countercation is close to the oxygen atom, but that dealkoxylation is the main process when the countercation moves to a position over the aromatic ring.

The 'Topologically Controlled Coulombic Interactions (TCCI) Effect' has been recently introduced and used by some of us[6] to achieve the previously unknown reductive cleavage of nitrophenyl (and other electron-poor) alkyl ethers. This effect involves altering the normal behaviour of a negatively charged intermediate by specifically placing a positive charge in its structure [*i.e.* through the use of ω-(*N*-methylpiperidinium)-alkyl chains].

We wish to report here the first observation of how the use of aryl alkyl ethers bearing a TCCI alkyl chain of variable length completely alters the 'normal' regioselectivity of the reductive cleavage of aryl alkyl ethers. Alkyl 2,6-diphenylphenyl ethers (Scheme 1) and alkyl 2,6-dimethoxyphenyl ethers (Scheme 2) were selected due to the fact that in both cases the central alkoxy group is practically perpendicular to the plane of the phenyl ring, and hence the conformational effects will remain constant.

Results and discussion

In Scheme 1, the reductive cleavage (lithium naphthalenide, homogeneous conditions) of alkyl 2,6-diphenylphenyl ethers, **1**, in THF is described. Major formation of *m*-terphenyl, **2**, (dealkoxylation) was observed for 2,6-diphenylanisole, **1a**. The corresponding reactions with ethers bearing a longer alkyl chain gave an even higher regioselectivity, dealkoxylation being in all cases the main process observed. This was also the case when a 4-(*N*-methylpiperidinium)butyl chain was used. However, when γ-(*N*-methylpiperidinium)propyl and β-(*N*-methylpiperidinium)ethyl chains were used (substrates **1e** and **1f**) a continuous regioselectivity change was observed, dealkylation now being the main (exclusive in the case of substrate **1f**) product observed. In these cases, the fraction of the reaction crudes soluble in water showed polymerization and the presence of a complex mixture, precluding further investigation of the fate of the *N*-methylpiperidinium alkyl moiety after fragmentation.



1 **2** **3**

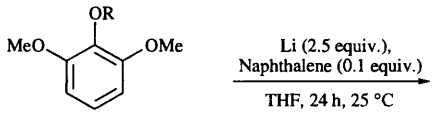
		Yield (%)	
a	R = Me	70	30
b	R = $(CH_2)_8CH_3$	95	5
c	R = $(CH_2)_2$–$N(C_5H_{10})$	72	28
d	R = $(CH_2)_4$–$N(C_5H_{10})$ +| Me BF_4^-	95	5
e	R = $(CH_2)_3$–$N(C_5H_{10})$ +| Me BF_4^-	20	80
f	R = $(CH_2)_2$–$N(C_5H_{10})$ +| Me BF_4^-	0	100

$N(C_5H_{10})$ = piperidino

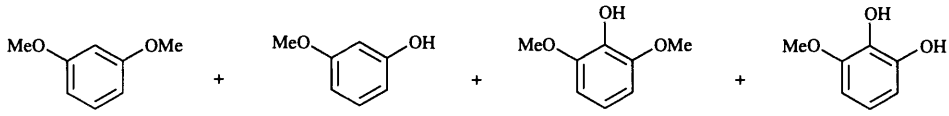
Scheme 1

In Scheme 2, the corresponding reactions of alkyl 2,6-dimethoxyphenyl ethers **4** are described. In these cases the reaction mixtures were more complex due to the fact that dealkoxylation can be followed by dealkylation (product **6**), and dealkylation can occur on the central (product **7**) or on two (product **8**) alkoxy group(s). In any case, and for the sake of simplicity, we will consider total dealkoxylation (**5** + **6**) and total dealkylation (**7** + **8**). The reactions of 'normal' 2-alkoxy-1,3-dimethoxybenzenes (**4a**, **4c**) with lithium naphthalenide as reducing agent under homogeneous conditions led in all cases to selective dealkoxylation. Here again when the β-(*N*-methylpiperidinium)ethyl chain was used (substrate **4f**), the regioselectivity of the process was inverted, dealkylation being the major process observed.

The TCCI effect just described was investigated with the help of electrochemical techniques. Thus, preparative electrolysis of *N*-methyl-*N*-[2-(2,6-diphenylphenoxy)ethylpiperidinium tetrafluoroborate, **1e**, (TCCI alkyl chain) in DMF using an applied potential of −2.6 V (*vs.* SCE), tetrabutylammonium tetrafluorate as supporting electrolyte, glassy carbon as working electrode and under a nitrogen atmosphere, led to 2,6-



4



5 6 7 8

		Yield (%)			
		Dealkoxylation		Dealkylation	
a	R = Me	63	35	—	—
c	R = $(CH_2)_2$–$N(C_5H_{10})$	73	26	—	—
f	R = $(CH_2)_2$–$N^+(Me)(C_5H_{10})$ BF_4^-	30	—	47	23

$N(C_5H_{10})$ = piperidino

Scheme 2

diphenylphenol, **3**, in 88% yield (2.1 F mol^{-1}). In cyclic voltammetry at a low sweep rate (0.1 V s^{-1}), substrate **1e** shows an irreversible (2 electrons) reduction wave (E_{pc} = −2.49 V *vs.* SCE) that changes to a slightly reversible wave at a faster sweep rate. From a study of the variation of the cyclic voltammograms with sweep rate, the radical anion limiting lifetime was calculated ($\tau \approx 1$ ms.). The nature of the chemical reaction that follows the electrochemical step, *i.e.*, unimolecular cleavage of the radical anion or bimolecular reaction (elimination)[7] due to the basicity of the radical anion, was studied. Thus, the reduction peak potential for substrate **1e** was measured as a function of sweep rate and concentration to determine the molecular order for the disappearance of the radical anion. At relatively low scan rates, *i.e.* 0.1–2.0 V s^{-1}, the peak potential (E_{pc}) shifted in the positive direction with decreasing scan rate (v) so that $dE_p/d \log v = -29$ mV. The peak potential was independent of concentration over a concentration range of 1.01–7.08 mmol dm^{-3}. These data are consistent with a first-order chemical reaction following electron transfer in a sequential type mechanism.[8] Thus, the cyclic voltammetry data indicate that cleavage of the radical anion of substrate **1e** (TCCI effect) is first-order, with a rate constant greater than 10^3 s^{-1}. It is likely that this mechanism is also operating in the reactions described in Schemes 1 and 2, where, however, the possible action of a second base (the naphthalene radical anion), in addition to the radical anion of the substrate, must be taken into consideration. This possibility can be reasonably ruled out, however, since there is no reason to expect a higher basicity of the former (E° of naphthalene = −2.54 V *vs.* SCE in acetonitrile)[9] than of the latter in THF, and NMR analysis of the reaction crudes (Schemes 1 and 2) showed no evidence of the presence of ethylenic protons. An alternative Grob type cleavage mechanism that would lead to ethene and *N*-methylpiperidine from the radical anion of substrate **1f** can also be ruled out since this would only operate in a substrate with a two-methylene unit linker. In Scheme 1 a continuous change (see, for instance, the behaviour of substrate **1e**) in regioselectivity on increasing the linker length is described.

Our results lead to the conclusion that, all other factors being equal, the distribution of electron density plays a crucial role in determining the evolution of charged intermediates. Indeed, the reactions described herein involve radical anions as intermediates,[10] and for both types of substrate the regioselectivity of the breaking step is completely reversed when a positive charge is included in the structure in a topologically controlled manner in such a way as to unbalance the system with respect to the 'normal' situation [case of β-(*N*-methylpiperidinium)ethyl chain]. These results confirm earlier suggestions, based on theoretical calculations,[5] about the importance of the counterion position on the final outcome of the cleavage reaction.

Experimental

^1H (300 MHz) and ^{13}C (75 MHz) spectra were recorded on a Varian VXR 300s spectrometer for solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J* values are given in Hz. Flash chromatography was performed on silica gel (ICN Silica 32-63, 60 Å). Elemental analyses were performed in the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Synthesis of starting materials and reaction products

m-Terphenyl **2**, 2,6-diphenylphenol **3**, 1,2,3-trimethoxybenzene **4**, 1,3-dimethoxybenzene **5**, 3-methoxyphenol **6**, 2,6-dimethoxyphenol **7** and 3-methoxycatechol **8** were purchased from Aldrich. 2,6-Diphenylanisole **1a** was prepared according to a literature method.[11] 2,6-Diphenylphenyl hexyl ether **1b** was prepared by the reaction of the sodium salt of **3** (prepared by treatment of **3** with excess NaH in THF) with 1-bromohexane (Aldrich) in THF under reflux for 72 h and purified by flash chromatography, with EtOAc–hexane 1:9 as eluent: pale viscous oil (Found: C, 87.4; H, 8.05. $C_{24}H_{26}O$ requires C, 87.2; H, 7.95%). The *N*-methylpiperidinium tetrafluoroborates **1d–f** and **4f** were prepared by the method described in ref. 6(*b*) through the corresponding amines, such as **1c** and **4c**, as white crystalline solids, and purified by recrystallisation from Me_2CO–Et_2O. Characterisation was carried out by ^1H and ^{13}C NMR spectroscopy. Physical constants and analytical data of a typical substrate {the *N*-[-2-(2,6-diphenylphenoxy)ehtyl]-*N*-methylpiperidinium tetrafluoroborate **1f**} were as follows: mp 204 °C (Found: C, 67.85; H, 6.4; N, 3.15. $C_{26}H_{30}NO{\cdot}BF_4$ requires: C, 68.0; H, 6.6; N, 3.05%); δ_H 1.52–1.76 (6 H, m, CH_2), 2.76 (3 H, s, CH_3), 3.10–3.22 (2 H, m. CH_2), 3.24–3.60 (6 H, m, CH_2), 7.26–7.55 (13 H, m, aromatic); δ_C 19.95, 20.29, 47.66, 61.66, 62.59, 66.01, 125.42, 127.85, 128.54, 129.31, 130.51, 135.76, 138.05 and 152.00.

General procedure for the reductive cleavage of compounds 1a–f and 4a,c,f

Lithium metal [50 mg, atom, 1.15 g of a 30% dispersion in mineral oil (Aldrich),† 2.5 equiv.] was placed under argon in a

† Lithium metal tends to accumulate in the upper layer of commercially available dispersions; drawing a sample without homogenising the dispersion with a spatula can lead to stoichiometric errors.

two-necked flask equipped with reflux condenser and magnetic stirrer, washed with anhydrous THF (3×10 cm^3), and suspended in anhydrous THF (30 cm^3). Naphthalene (26 mg, 2 mmol) was added without solvent and the mixture was stirred until a dark green colour appeared. To this suspension, cooled to 25 °C if necessary, was added the appropriate substrate **1a–f** and **4a,c,f** (20 mmol) at once without solvent, and the mixture was stirred at 25 °C for 24 h. Analysis of the reaction mixture by TLC and ^{1}H NMR spectroscopy showed complete conversion of the starting material. The mixture was cooled to 0 °C and quenched by slow, dropwise addition of H_2O (10 cm^3) (**CAUTION!**). After 1 h stirring at room temperature the mixture was acidified with conc. HCl, cooled and extracted with Et_2O (3×30 cm^3); the organic layer was then separated, dried ($CaCl_2$) and the solvent evaporated. The ratio between the reaction products (Schemes 1 and 2) was determined on the crude reaction mixture by ^{1}H NMR spectroscopy: this ratio was confirmed and the yields determined by separation of the reaction products by flash chromatography, with mixtures of hexane and EtOAc as eluant. In the case of the 2,6-dimethoxy-substituted substrates **4a,c,f** the phenolic products **6**, **7** and **8** could also be separated from the neutral **5** by treatment of the mixture with aqueous NaOH; this was impossible for the 2,6-diphenyl-substituted substrates **1a–f**, since the 2,6-diphenylphenol **3** is insoluble in NaOH solutions. In the case of the *N*-methylpiperidinium tetrafluoroborates **1d–f** and **4f** the aqueous layer remaining after Et_2O extraction was evaporated to dryness to afford an intractable, sticky residue; any attempt to purify this mixture failed. The ^{1}H NMR spectrum in CD_3OD showed a very complex pattern, with no low-field signals and very broad signals suggesting polymerisation.

Acknowledgements

Financial support from 'Ministerio de Educación y Ciencia' of Spain through projects DGICYT PB93-0895 and 'Accion Integrada Hispano-Italiana' 89-A 1994; from MURST (40% and 60% Funds) of Italy; and from 'Generalitat de Catalunya' through the project GRQ93-2070 and a grant for F. C., is gratefully acknowledged.

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Paper 6/05459E
Received 1*st July* 1996
Accepted 7*th August* 1996