Electron-transfer-induced reductive dealkoxylation of alkyl aryl ethers. III. Reductive cleavage of methoxy-substituted *N*,*N*-dimethylanilines (*N*,*N*-dimethylanisidines)

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Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday
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Abstract
The reactivity of the three isomeric methoxy-substituted *N*,*N*-dimethylanilines (*N*,*N*-dimethylanisidines) and of *N*,*N*-dimethyl-2,6-dimethoxyaniline in the reduction with alkali metals in aprotic solvents was investigated. *N*,*N*-Dimethyl-*p*-methoxyaniline was found to be unreactive, while the other substrates underwent exclusive cleavage of carbon-oxygen bond(s), with the following order of reactivity: 2,6-dimethoxy > *o*-methoxy > *m*-methoxy > *p*-methoxy. Both the relative reactivity and the regioselectivity of cleavage (demethoxylation *vs.* demethylation) was found to parallel closely that of the corresponding di- and trimethoxy-substituted substrates. These results suggest that intermediates with different electron distribution or even different intermediates are involved in the reductive cleavage of aryl-oxygen and aryl-nitrogen bonds.

Keywords: Electron-transfer, reduction, bond cleavage, alkali metals, aromatic ethers

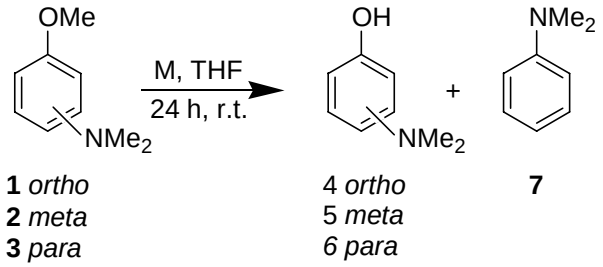
Introduction

Recently we have reported that phenyl- and diphenyl-substituted *N*,*N*-dimethylanilines easily undergo reductive cleavage of the dimethylamino group by treatment with Li metal in tetrahydrofuran (THF).[1] In view of our active interest in the mechanism of cleavage of the carbon-oxygen bonds in anisole[2] and substituted anisoles[3-8] under electron transfer reductive conditions, we felt it worthy to study the reactivity of aromatic substrates bearing both the dimethylamino and the methoxy group in order to check the relative ease of cleavage of the two groups.

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We could anticipate that we would encounter some difficulties in performing electron-transfer reduction of such electron-rich molecules.[9] Indeed, the ability of methoxy-substituted *N*,*N*-dimethylanilines to behave as electron donors[10] and readily form the corresponding radical cations or charge-transfer complexes under chemical,[11] photochemical,[12] and electrochemical conditions[13] is well known. On the contrary, there are no available data on the electrochemical reduction of *N*,*N*-dimethylanisidines and only two literature reports[14,15] on their ability to behave as electron acceptors towards alkali metals. Reduction of the *meta*- and *para*-isomers with lithium metal and *t*-butyl alcohol in liquid ammonia afforded the corresponding 1,3-cyclohexadienyl derivative as the only reaction product (92% yield for the *meta*; yield not reported for the *para*);[14] under similar reaction conditions, the *ortho*-isomer gave the 1,4-cyclohexadienyl derivative (62% yield) together with minor amounts of products derived from loss of the methoxy group (*N*,*N*-dimethylaniline and a tetrahydro-derivative thereof) or of the dimethylamino group (1-methoxy-1,4-cyclohexadiene).[14] In a similar reaction, using a large excess of lithium metal and methanol instead of *t*-butyl alcohol as a proton source, reduction of the *para*-isomer led to complete conversion of the substrate and isolation of a mixture containing the corresponding 1,3- and 1,4-cyclohedienyl derivatives, with the former predominant.[15]

We wish to report the results obtained in the reduction of the three isomeric *N*,*N*-dimethylanisidines **1**-**3** with alkali metals, namely lithium, sodium and potassium, in THF and in 2,2,4-trimethylpentane (isooctane) (Scheme 1). To get an additional comparison with the results obtained in the reductive cleavage of substituted anisoles, particularly of 1,2,3-trimethoxybenzene and its derivatives,[6-8] we have also investigated the reductive cleavage of *N*,*N*-dimethyl-2,6-dimethoxyaniline **8** (*vide infra*) in order to check the effect of two *ortho*-methoxy groups on the ease of cleavage of the aromatic carbon-nitrogen bond.



Scheme 1. Reductive cleavage of isomeric *N*,*N*-dimethylanisidines **1**-**3**.

Results

The reactions were carried out by vigorous stirring of a *ca*. 0.1 M solution of the substrate with 2 equivalents of metal in anhydrous, freshly distilled solvents at room temperature under Ar. For the purpose of comparison with the data previously obtained in the reduction of variously substituted anisoles[2-8] and *N*,*N*-dimethylanilines,[1] the reactions were quenched after 24 h, even if

this corresponded, in some cases, to a very low conversion yield. Quenching was performed by adding H_2O, after standard workup, the significant products were first identified by ^1H NMR and then separated by flash chromatography. No attempts were made to detect methanol and methane, the likely by-products of these reductions.[2,3] Quite clean reaction mixtures were obtained in all cases; neither products of partial reduction of the aromatic ring nor biaryl derivatives were detected.

In preliminary tests, **1** was found to be the most reactive among the three isomers; consequently, its reduction was studied in more detail under various reaction conditions. Exclusive cleavage of the carbon-oxygen bonds was observed in all cases, with formation of variable amounts of demethylation products (*N*,*N*-dimethylaminophenols **4** and **5**) and of demethoxylation product (*N*,*N*-dimethylaniline **7**).[16] No evidence for the formation of products of carbon-nitrogen bond cleavage was obtained. Selected results are reported in the Table.

Table. Reductive cleavage of compounds **1**-**3** with alkali metals

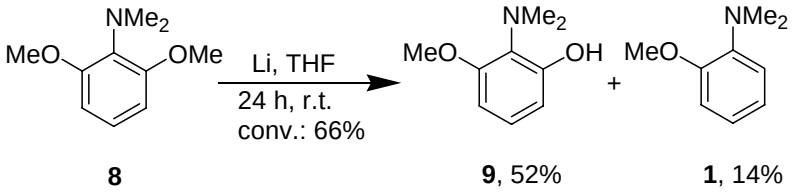
Entry	Compound	Conversion Metal	Product Ratio (%)	Aminophenol	**7**
1	**1**	Li	8	**4** (28)	(72)
2	**1**	Li[b]	36	**4** (27)	(73)
3	**1**	Li[c]	37	**4** (38)	(62)
4	**1**	Li[d]	42	**4** (13)	(87)
5	**1**	Li[e]	*ca*. 3	[f]	[f]
6	**1**	Li[b,e]	12	**4** (16)	(84)
7	**1**	Na	0		
8	**1**	Na[b]	7	**4** (44)	(56)
9	**1**	K	5	**4** (42)	(58)
10	**1**	K[b]	30	**4** (40)	(60)
11	**1**	K[e]	33	**4** (10)	(90)
12	**1**	K[b,e]	53	**4** (15)	(85)
13	**2**	Li	17	**5** (100)	(0)
14	**2**	Na	0		
15	**2**	K	0		
16	**3**	Li	0		
17	**3**	K	0		

[a] Reactions were run in THF, unless otherwise stated. [b] In the presence of naphthalene (0.1 equiv). [c] In the presence of 12-crown-4 (2.0 equiv). [d] In the presence of tetrabutylammonium tetrafluoborate (2.0 equiv). [e] Reaction run in isooctane. [f] Owing to the very low conversion yield, a reliable value of the products ratio could not be obtained.

In the case of anisidine **1**, a poor reactivity was observed in the reactions carried out with Li or K alone in THF (entries 1 and 9) or with Li in isooctane (entry 5), even in the presence of

naphthalene (entry 6); no reaction occurred with Na alone (entry 7). Higher conversion yields were obtained in all cases in the presence of naphthalene (entries 2, 6, 8, 10, and 12), by raising the polarity of the medium or adding a crown ether in the case of Li (entries 3 and 4), or by using isooctane instead of THF in the case of K (entries 11 and 12). Reduction of anisidine **2** with Li in THF led to a very low conversion (entry 13), with exclusive formation of *N*,*N*-dimethyl-*m*-aminophenol **5**. No reactivity was observed using Na or K as reducing agents (Table, entries 14 and 15) or using isooctane as a solvent (not reported in the Table). Anisidine **3** resulted completely unreactive towards the alkali metals reduction, and was recovered unchanged under any reaction conditions.

In the hope of obtaining evidence of cleavage of a carbon-nitrogen bond, the reactivity of *N*,*N*-dimethyl-2,6-dimethoxyaniline **8** was next studied. Amine **8** was chosen as an analog of 1,2,3-trimethoxybenzene, which in our previous work[3,7,8] had been found to be the most reactive substrate, giving almost exclusive cleavage of the central methoxy group under all conditions. Amine **8** was allowed to react with Li powder in THF, *i.e.*, under the conditions that led to exclusive cleavage of the dimethylamino group in the reduction of phenyl-substituted *N*,*N*-dimethylanilines.[1] Even with this substrate, however, exclusive cleavage of carbon-oxygen bonds was observed. The results are reported in Scheme 2.



Scheme 2. Reductive cleavage of *N*,*N*-dimethyl-2,6-dimethoxyaniline.

Discussion

Our results clearly indicate that in aromatic substrates bearing both the methoxy and the dimethylamino group reductive cleavage of the latter does not occur, and only cleavage of carbon-oxygen bonds is observed, though to a minor extent than that of di- and trimethoxy-substituted aromatic substrates. Apart from the general low reactivity of substrates **1**-**3** and **8**, to be likely imputed to their very negative reduction potentials,[9,17,18] the results obtained in this work indicate rather similar behaviors of anisidines **1**-**3** and **8** and of methoxy-substituted anisoles, both in the relative reactivity and in the regioselectivity of cleavage. As regards the relative reactivity, the following order can be drawn for anisidines: **8** > **1** > **2** >> **3**; this order parallels quite well that found for anisoles (2,6-dimethoxy > *o*-methoxy ≥ *m*-methoxy > *p*-methoxy).[3] As to regioselectivity, in THF at room temperature both *o*-dimethoxybenzene and *N*,*N*-dimethyl-*o*-anisidine give preferential cleavage of the aryl-oxygen bond, whereas the

corresponding *meta*-isomers give exclusive cleavage of the methyl-oxygen bond. A substantial difference can instead be seen in the behavior of 1,2,3-trimethoxybenzene and amine **8**: the former gives almost exclusive demethoxylation at the 2-position (see above), whereas in the latter the 2-position is unreactive and preferential demethylation of a methoxy group in the 1- or 6-position is observed.

Taken as a whole, our findings confirm the prediction made by Smith[17] and reported as such by Zweig[18] "that a given carbon-nitrogen bond of amino-substituted aromatics should be cleaved reductively with greater difficulty than its carbon-oxygen analogue." We have been dealing with a related problem in previous work on the generation of α-amino-substituted benzylic carbanions by the reductive cleavage of *N*-substituted 2-aryl-1,3-oxazolidines[19] and α-*N*,*N*-dialkylamino-substituted benzyl alkyl ethers.[20] We found that these substrates, by treatment with alkali metals in various aprotic solvents (THF, isooctane, etc.), readily undergo cleavage of the benzylic carbon-oxygen bond, with no evidence of cleavage of carbon-nitrogen bonds. On the other hand, to the best of our knowledge, no specific studies have been carried out so far on the relative ease of reductive cleavage of aryl-nitrogen and aryl-oxygen bonds.

A simple rationalization of the results obtained, based on the analogy of behaviour of substrates **1**-**3** and **8** and the various methoxy-substituted compounds previously investigated,[2-4,7] would be to suggest that fragmentation occurs at the level of the radical anion. The observation that when a carbon-oxygen bond is present no cleavage of a carbon-nitrogen bond occurs could then be related with the different leaving group abilities of MeO^- and Me_2N^-. As regards the cleavage of radical anions, however, things may not be so straightforward.[5,21,22] Indeed, many factors are involved in the behaviour of such intermediates, such as the distribution of charge and/or spin, the type and topology of their ion pairs with the alkali metal cations, the relative strengths of the scissile bonds, etc. However, the discussion of these important points is beyond the scope of the present work. We can only suggest that the cleavage of the two different bonds is mainly related to different electron distribution in the intermediate undergoing fragmentation, or even to the intervention of different intermediates.

Experimental Section

General Procedures. Boiling points are uncorrected. ^{1}H-NMR (300 MHz) spectra were measured on a Varian VXR spectrometer for samples in $CDCl_3$ solution with tetramethylsilane as internal standard. Flash chromatography was performed on silica gel 60 (ICN Silica 32-63 μ). Elemental analyses were performed in the Micro analytical Laboratory of the Dipartimento di Chimica, Università di Sassari. THF and isooctane were dried over Na and distilled from Na/K alloy under nitrogen immediately prior to use. All products and reagents were of the highest commercial quality from freshly opened containers and were used without further purification.

Synthesis of starting materials. Methoxy-substituted *N,N*-dimethylanilines were prepared in very good yields according to a known procedure involving reaction of the corresponding primary amines with aqueous HCHO and $NaBH_4$ under acidic conditions.[23] *N,N*-Dimethyl-*o*-methoxyaniline **1**, *N,N*-dimethyl-*m*-methoxyaniline **2**, and *N,N*-dimethyl-*p*-methoxyaniline **3** are already known.[23] *N,N*-Dimethyl-2,6-dimethoxyaniline **8** was purified and characterized as follows.

***N,N*-Dimethyl-2,6-dimethoxyaniline (8).** Purified by flash chromatography (hexane/EtOAc/Et_3N = 3:7:0.5); pale yellow oil, bp 125 °C/1 mmHg; ^{1}H NMR δ 2.82 (6H, s, 2 CH_3N), 3.84 (6H, s, 2 CH_3O), 6.54 (2H, d, *J* = 8.4, ArH), 7.04 (1H, t, *J* = 8.4, ArH); Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.26; H, 8.36; N, 7.73. Found C, 66.09; H, 8.51; N, 7.67.

General procedure for the reductive cleavage of compounds 1-3 and 8 with alkali metals Suspensions of alkali metals (6 mg atom, 2 equiv) in anhydrous THF (25 mL) were prepared under Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer as follows. Lithium metal [30% dispersion in mineral oil (Aldrich)] was washed with THF (3 x 10 mL) and suspended in THF; freshly cut potassium metal (Aldrich) was vigorously stirred in THF at a temperature above its melting point and then cooled to room temperature without stirring; freshly cut sodium metal (Aldrich) was used as such. To these suspensions, was added at once the appropriate substrate (3 mmol) dissolved in THF (5 mL); the mixture was then stirred at room temperature under Ar for 24 h. The mixture was cooled to 0 ^{0}C and quenched by slow, drop wise addition of H_2O (10 mL) (**CAUTION!**). After 1 h stirring at room temperature the mixture was extracted with Et_2O (3 x 30 mL); the organic layer was dried (Na_2SO_4) and the solvent evaporated. The ratio between the reaction products (Table and Scheme 2) was determined on the crude reaction mixture by ^{1}H NMR spectroscopy; this ratio was confirmed and the yields determined by separation of starting material and reaction products by flash chromatography, with mixtures of hexane and EtOAc containing Et_3N (2% v/v) as eluent.

The two isomeric *N,N*-dimethylaminophenols **4** and **5** and *N,N*-dimethylaniline **7** were identified by comparison of their physical constants and ^{1}H-NMR spectra with those of commercial samples (Aldrich). *N,N*-Dimethyl-2-methoxy-6-hydroxyaniline **9**, isolated from the reaction mixture of the reduction of **8** with Li metal, was purified and characterized as follows.

***N,N*-Dimethyl-2-methoxy-6-hydroxyaniline (9).** Purified by flash chromatography (hexane/EtOAc/Et_3N = 3:7:0.5), pale yellow oil, bp 140 °C/1 mmHg, ^{1}H-NMR δ 2.75 (6H, s, 2 CH_3N), 3.82 (3H, s, CH_3O), 6.38 (1H, d, *J* = 7.8 Hz, ArH), 6.54-6.60 (1H, m, ArH), 7.02 (1H, t, *J* = 7.8 Hz, ArH). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.63; H, 7.85; N, 8.38. Found C, 64.38; H, 8.07; N, 8.45.

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