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The reduction of substituted benzylamines by means of electrochemically generated solvated electrons in LiCl + methylamine *

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Abstract

Methoxy-substituted and N-methylated benzylamines were reduced to their 1,4-dihydro derivatives using the electrochemical Benkeser reduction. N,N-dimethyl-veratrylamine decomposed during the reduction. The differences in current efficiencies can be explained by differences in the stabilization of the radical anions and by differences in protonation rates. Rotating ring disk electrode (RRDE) experiments showed that in the reduction of benzylamines, the first protonation can be achieved either intramolecularly or intermolecularly.

1. Introduction

Several substituted benzenes can be reduced chemically and/or electrochemically to their 1,4-dihydro derivatives. The electrochemical reduction of several substituted aromatic amines is described here. The investigation was initiated by the question as to whether galanthamine (Fig. 1(A)) could be electrochemically reduced to its 1,4-dihydro derivative without affecting the functional groups present. The reduction of N,N-dimethyl-veratrylamine (Fig. 1(B)) served as a model. The electrochemical aromatic reduction described by Benkeser and Kaiser [1] (Fig. 2) was used for the reduction. The reaction is carried out in LiCl + methylamine. Either a divided or an undivided cell can be used, with each leading to different products. When benzene is reduced in a divided cell, the product is cyclohexene. In an undivided cell, the product is 1,4-cyclohexadiene. Because little is known about the influence of the presence and position of the functional groups on the overall reaction rate and on the product, the influence of the position of the methoxy group relative to various amine groups was studied. An undivided cell was used, which gave the most olefinic substituted 1,4-cyclohexadiene derivative as the major product.

2. Experimental

2.1. Reagents

Benzylamine (99%, Janssen Chimica), N-methylbenzylamine (98%, Alfa), 1-phenyl-3-aminopropane (98%, Janssen Chimica), p-methoxy-benzylamine (98%, Janssen Chimica), m-methoxy-benzylamine (Janssen Chimica) and veratrylamine (95%, Janssen Chimica) were used as received for the organic reduction reactions. Methylamine (Ucar) was distilled over lithium before use. N,N-dimethyl-benzylamine, N,N-dimethyl-p-methoxy-benzylamine and N,N-dimethyl-m-methoxy-benzylamine were synthesized by standard methods [2] and purified by distillation. For the rotating ring-disk electrode (RRDE) experiments, benzylamine was distilled twice before use. Lithium chloride (Janssen Chimica) and lithium bromide were dried at 150°C for 24 h before use. The purification of hexamethylphosphoramide (HMPA) is described in detail in ref. 3.

2.2. Reaction cell and measuring devices for the electrochemical studies

The cell and measuring devices are described in detail in ref. 3. The electrochemical cell is shown in Fig. 3. The glassy carbon–glassy carbon (C<sub>e</sub>–C<sub>e</sub>) RRDE used had dimensions r<sub>1</sub> = 0.350 cm, r<sub>2</sub> = 0.464 cm and r<sub>3</sub> = 0.599 cm, with N<sub>t</sub> = 0.358.
2.3. Reaction cell and measuring devices for the electro-organic reactions

The reduction cell of volume 125 cm$^3$ is shown in Fig. 4. Pt electrodes (both of cross-section 3.2 cm$^2$) served as the cathode and the anode. An Ag wire was used as the quasi-reversible reference electrode. The reaction temperature was measured using a Pt-Rh thermocouple and controlled by means of a Huber Variostat. Solvated electrons were generated potentiostatically at $-2.7$ V using a Wenking POS 73 potentiostat. This corresponded to a current density of approximately 300 mA cm$^{-2}$. The charge passed was recorded using a Wenking EVI 80 voltage integrator.

2.4. Electro-organic reaction procedure

The aromatic substrate (10 mmol) was added to 100 ml of a solution of 1 M LiCl chloride in methylamine. Current was passed through until all the substrate was reduced, as shown by $^1$H NMR. During the reaction argon gas was bubbled through the solution. The reaction temperature was $-15^\circ$C. The methylamine was allowed to evaporate. Water (100 ml) was added and the aqueous layer was extracted with ether ($2 \times 30$ ml). The combined organic layers were washed with water ($2 \times 50$ ml) and with a concentrated sodium chloride solution (25 ml), dried over magnesium sulfate and filtered. The ether was distilled off in a vacuum. The product was purified by distillation or column chromatography (aluminium oxide, chloroform).

2.5. Analysis

The following techniques were used in the analysis.

$^1$H NMR: Varian EM 360A.

$^{13}$C NMR: Bruker AM-400. For $^{13}$C NMR spectral data of several methoxy-substituted benzylamines see ref. 4.

Gas chromatography–mass spectroscopy (GCMS): HP 5790 A series gas chromatograph coupled to an HP 5970 A series mass selective detector (both from Hewlett Packard).

Mass spectroscopy (MS): electron impact spectrum, 70 eV; mass scale, 30–300. For mass spectra of benzylamine and benzylamine derivatives, see refs. 5 and 6.

Gas chromatography (GC): oven temperature, 100$^\circ$C; inlet helium pressure, 1.5 bar; column, OV-1, 25 m, with inner diameter 0.2 mm; film thickness, 0.33 $\mu$m (Hewlett Packard Ultra Performance); injection splitless; injection volume, 1 $\mu$l; dichloromethane solvent.

The following reduction products were obtained.

1) 2,5-Dihydro-benzylamine. $^1$H NMR $\delta$(CDCl$_3$, TMS): 1.5(s, 2H); 2.67(m, 4H); 3.2(s(b), 2H); 5.53(s(b), 1H); 5.67(s(b), 1H). $[M - 1] = 108.15$. 

Fig. 3. The electrochemical cell: (A) cross-section; (B) top view.
(2) 2,5-Dihydro-N-methyl-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 1.22(s, 1H); 2.47(s, 3H); 2.77(m, 4H); 3.13(s(b), 2H); 5.67(s(b), 1H); 5.77(s(b), 2H). [M – 1] = 122.10 (m/e 91.05 = 100%). BP, 37°C (0.2 Torr).

(3) 2,5-Dihydro-N,N-dimethyl-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 2.18(s, 6H); 2.62–2.87(m, 6H); 5.58(s(b), 1H); 5.73(s(b), 1H). [M] = 137.10 (m/e 91.05 = 100%).

(4) 2,5-Dihydro-4-methoxy-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 1.6(s, 2H); 2.7(m, 4H); 3.3(s(b), 3H); 3.5(s, 3H); 4.6(s(b), 1H); 5.48(s(b), 1H). [M – 1] = 138.10 (m/e 122 = 100%).

(5) 2,5-Dihydro-4-methoxy-N,N-dimethyl-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 2.18(s, 6H); 2.77(m, 6H); 3.48(s, 3H); 4.65(s(b), 1H); 5.52(s(b), 1H).

\[ ^{13}C \) NMR \( \delta(CDC_1,): 152.6(C=C); 133.6(C=C); 120.8(C==C); 90.6(C=C); 66.3(CH=O); 53.8(CH); 45.3(N-CH); 30.1(CH); 28.1(CH). [M] = 167.05 (m/e 122 = 100%).

(6) 2,5-Dihydro-3-methoxy-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 1.85(s, 2H); 2.67(m, 4H); 3.12(s(b), 2H); 3.43(s, 3H); 4.57(s(b), 1H); 5.53(s(b), 1H). [M] = 139.10 (m/e 122 = 100%).

(7) 2,5-Dihydro-3-methoxy-N,N-dimethyl-benzylamine. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 2.17(s, 6H); 2.57–2.9(m, 6H); 3.47(s, 3H); 4.53(s(b), 1H); 5.57(s(b), 1H).

\[ [M] = 167.20 (m/e 121.15 = 100%).

(9) 1-(2,5-Dihydrobenzyl)-3-amino-propane. \( ^1H \) NMR \( \delta(CDCl_3, TMS): 1.08(s, 2H); 1.3–2.18(m, 4H); 2.53–2.83(m, 6H); 5.42(s(b), 1H); 5.67(s(b), 1H). \[ ^{13}C \) NMR \( \delta(CDC_1,): 135.2(C=C); 124.8(C=C); 119.0(C=C); 42.6(CH=O); 35.4; 32.0; 29.5(CH); 27.4(CH). BP 54–57°C (0.15 Torr).

3. Results and discussion

3.1. The electrochemical generation of solvated electrons in LiCl + methylamine

The electrochemical generation and oxidation of solvated electrons at a C_2–C_2 RRDE in methylamine was investigated using the electrochemical cell shown in Fig. 3. LiCl was used as the electrolyte. The cyclic voltamgram is shown in Fig. 5, and is in agreement with the results presented in the literature [7–10]. Solvated electrons are generated at −2.3 V vs. Ag wire. The electron goes from the electrode to a pre-existing solvent trap [11]. The reverse scan shows the oxidation current. Figure 6 shows the Tafel plot for the cathodic process. The experimental data fit a straight line with a slope of 55 mV per decade. The exchange current density was determined as 200 mA cm⁻² at [e⁻] = 10⁻³ M (α = 0.6). Solvated electrons gradually decompose in methylamine. An anodic current which could be attributed to the oxidation of any decomposition product of e⁻ was not observed. The decomposition rate of e⁻ is shown in Fig. 7 where 1/Nₚ is plotted against 1/ω.

3.2. The reduction of substituted aromatic amines

As noted earlier, Benkeser and Kaiser [1] found that benzene could be electrochemically reduced to cyclohexene or 1,4-cyclohexadiene in LiCl + methylamine using a divided or an undivided cell respectively (Fig. 2). It was suggested that in the divided cell the lithium
methylamide formed is capable of establishing the equilibrium shown in Fig. 8, resulting in the "thermo-
dynamic" product cyclohexene, while in the undivided
cell the lithium amide is neutralized by methylamine
hydrochloride formed at the anode, resulting in 1,4-
cyclohexadiene.

In this work we investigate the reduction of various
(methoxy-substituted) aromatic amines by electrochem-
ically generated $e^-_\text{red}$ in methylamine using LiCl or LiBr
as electrolyte. An undivided cell was used. The general
reduction reaction scheme for the substituted aromatic
amines is shown in Fig. 9. The reaction was stopped
when the starting material had disappeared. The yields
and current efficiencies obtained for the different aro-
matic amines are shown in Table 1.

Examination of these results allows several conclu-
sions to be drawn. All amines except $N,N$-dimethyl-
veratrylamine (reaction (8)) gave the most substituted
olefinic compound as the major product, as predicted
by Benkeser and Kaiser [1]. In the case of $N,N$-di-
methyl-veratrylamine, 1-methoxy-4-dimethylamino-
methyl-1,4-cyclohexadiene and 1-methoxy-5-dimethyl-
aminomethyl-1,4-cyclohexadiene were also formed (Fig.
10).

**TABLE 1. Reduction of substituted aromatic amines by electrochemically generated $e^-_\text{red}$ in LiCl + methylamine**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Yield/%</th>
<th>Current efficiency/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CH$_2$NH$_2$</td>
<td>CH$_2$NH$_2$</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>2 CH$_2$NHCH$_3$</td>
<td>CH$_2$NHCH$_3$</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>3 CH$_2$N(CH$_3$)$_2$</td>
<td>CH$_2$N(CH$_3$)$_2$</td>
<td>70</td>
<td>31</td>
</tr>
<tr>
<td>4 H$_2$CO CH$_2$NH$_2$</td>
<td>H$_2$CO CH$_2$NH$_2$</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>5 H$_2$CO CH$_2$N(CH$_3$)$_2$</td>
<td>H$_2$CO CH$_2$N(CH$_3$)$_2$</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>6 H$_2$CO CH$_3$NH$_2$</td>
<td>H$_2$CO CH$_3$NH$_2$</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>7 CH$_3$CO CH$_2$N(CH$_3$)$_2$</td>
<td>CH$_3$CO CH$_2$N(CH$_3$)$_2$</td>
<td>65</td>
<td>30</td>
</tr>
<tr>
<td>8 CH$_3$CO CH$_2$N(CH$_3$)$_2$</td>
<td>CH$_3$CO CH$_2$N(CH$_3$)$_2$</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>9 (CH$_3$)$_2$NH$_2$</td>
<td>(CH$_3$)$_2$NH$_2$</td>
<td>85</td>
<td>57</td>
</tr>
</tbody>
</table>
Because one of the reactants \( (e^-) \) is added gradually, standard kinetic measurements fail. In order to compare the different reduction reactions, the current efficiency (CE) was taken as an indication of the total reaction rate. It can be seen that the reduction of the primary amines occurs at a higher CE than the reduction of the dimethylated amines. The CE of the monomethylated amine (reaction (21)) is comparable with that of the primary amine (reaction (1)). The reduction of 1-phenyl-3-amino propane (reaction (9)) occurs at an even higher CE than the reduction of the primary benzylamines. The presence of the methoxy group at the para position results in a higher CE, while meta substitution has almost no effect. How can the effect of the methoxy group be explained and why do dimethylated amines react more slowly than the primary or monomethylated amines?

A reaction mechanism for the reduction of benzene is shown in Fig. 11. A reaction profile for an initial reversible electron addition, with equilibrium constant \( K_e \), followed by an irreversible protonation, with reaction constant \( k_2 \), in the reduction for substituted benzenes was proposed by Birch et al. [12]. These workers postulated that when a 'good' proton donor is present (e.g. ethanol \( (pK_a = 17) \)) the first protonation step is quite fast, so that the relative rates of different substituted benzenes are largely determined by \( K_e \). This equilibrium constant, which reflects the stabilization of the radical anion, is affected by both the inductive effect of the substituent(s) and solvation. For example, a methoxy group is known to stabilize the radical anion by a dominating inductive effect and therefore anisole is reduced about three times faster than benzene. When a proton donor with low acidity is used, such as methylvamine \( (pK_a = 27) \), the total reduction rate will also depend on the protonation step which will then be rate determining with the total reaction rate \( k \) given by:

\[
k = K_e k_2
\]

\[
e^- \quad \xrightarrow{K} \quad + \quad \text{CH}_3\text{NH}_2 \quad \text{CH}_3\text{NH}^- \quad \text{CH}_3\text{NH}^-
\]

\[
e^- \quad + \quad \text{CH}_3\text{NH}_2 \quad \xrightarrow{K} \quad \text{CH}_3\text{NH}^- \quad \text{CH}_3\text{NH}^-
\]

Fig. 11. Reaction mechanism for the electrochemical reduction of benzene.

In the case of the (electrochemical) Benkeser reduction, the solvent itself can act as a proton donor. In this case proton addition will probably be the rate-determining step.

With regard to the reduction of substituted aromatic amines, a p-methoxy substituent increases the reaction rate and \( N,N \)-dimethylation lowers the total reduction rate. Various resonance structures of the radical anion formed after electron addition in the case of p- and m-methoxy-substituted amines are shown in Fig. 12. Because of the inductive effect, the negative charge is best stabilized at the carbon atom bearing the methoxy group. In the case of the p-methoxy benzylamine this locates the radical at the tertiary carbon atom which is more favorable than the position at the secondary carbon atom. When the methoxy group is attached at the meta position, this cannot be accomplished. Therefore the p-methoxy-benzylamine radical anion is probably better stabilized and this may explain the higher CE obtained for the reduction of the p-methoxy aromatic amines.

The difference between the reduction rates of the \( N,N \)-dimethylated amines and those of the primary or monomethylated amines may be due in part to solvation inhibition because the methyl group is not solvated to the same extent as a proton in a polar medium like methylamine. Moreover, in view of the low acidity of this solvent, the total reduction rate will also depend on \( k_2 \). In the case of the reduction of the primary/secondary amines, it is possible that protonation is achieved by an intramolecular or intermolecular proton transfer from an amine proton to the ring. The proton of the aromatic amine will differ in acidity from the proton of the methylamine, and this may explain the differences in the reduction rates. In order to prove the assumption that the aromatic amine itself can serve as a proton donor, RRDE experiments were performed in HMPA. The interaction between the aromatic amine and \( e^- \), with and without the addition of a proton donor, can be studied in HMPA + LiBr solutions.
3.3. RRDE experiments

RRDE experiments were carried out to determine whether benzylamine itself can serve as proton donor, either intramolecularly or intermolecularly. The RRDE has great potential as a technique for studying (the kinetics of) homogeneous reactions in solution. For example, reaction rate constants can be obtained for the case of a reactant generated at the disk electrode and diffusing into the solution where it reacts with a substrate. When this reactant (and not the product) reacts in a diffusion-controlled manner at the ring electrode, the collection efficiency will decrease as a result of the chemical reaction in the bulk. Albery and Bruckenstein [13] have derived an expression which relates the measured collection efficiency \( N_m \) to the (pseudo) first-order reaction rate constant \( k_1 \):

\[
N/N_m = 1 + 1.28 (\nu/D)^{1/3} (k_1/\omega)
\]

where \( N_r \) is the theoretical collection efficiency, \( N_m \) is the measured collection efficiency, \( \nu \) is the kinematic viscosity, \( D \) is the diffusion coefficient and \( \omega \) is the rotation frequency.

This relation was used to study the reaction between the aromatic amines and \( e^- \). The aromatic amine was added gradually to a LiBr + HMPA solution in which solvated electrons were galvanostatically generated at the disk electrode of a C,C RRDE. The effect of the addition of benzylamine on the ring electrode current is shown in Fig. 13. It was shown earlier [13] that benzene only reacts with \( e^- \) in the presence of a proton donor. However, benzylamine will react with \( e^- \) without the addition of a proton donor. It is known that the reaction between benzene and \( e^- \) in HMPA + ethanol does not stop at the 1,4-cyclohexadiene stage, but that further reduction to cyclohexene and finally to cyclohexane takes place. It is likely that this is also the case when benzylamine is reduced in HMPA, even when the proton donor is not an alcohol but an amine.

As a result of the \( e^- \) generation a maximum of 3% of the aromatic amine is reduced during the experiment so that its concentration does not change sufficiently to affect the reduction process.

During the reduction several intermediates are formed which can be reduced at the ring electrode under the reaction conditions. If this occurs under diffusion control, the limiting current will be determined by the diffusion coefficients of the oxidized particles according to the Levich equation. Therefore the decrease in \( N_m \) is the result of the decrease in \( e^- \), corrected for the oxidation of the oxidizable intermediates. Since their concentration is low, and, moreover, their diffusion coefficients are much smaller than the diffusion coefficient of \( e^- \), their contribution was neglected in the determination of the reaction rate constants. In Fig. 14 the collection efficiency is plotted against the rotating frequency for an aromatic amine concentration of \( 1.13 \times 10^{-2} \) M. Figure 15 shows \( 1/N_m \) plotted against \( 1/\omega \). A (pseudo) first-order reaction
rate constant can be calculated, and is 1.2 s\(^{-1}\) for benzylamine and 1.5 s\(^{-1}\) for benzene.

**Nomenclature**

- \(D\) diffusion coefficient, cm\(^2\) s\(^{-1}\)
- \(e_-\) solvated electron
- \(E_R\) ring potential, V vs. Ag wire
- \(I_D\) disk current, mA
- \(j\) current density, mA cm\(^{-2}\)
- \(k\) total reaction rate
- \(k_1\) first-order reaction rate constant, s\(^{-1}\)
- \(k_2\) second-order reaction rate constant, M\(^{-1}\) s\(^{-1}\)
- \(K_e\) equilibrium constant
- \(N_m\) measured collection efficiency
- \(N_t\) theoretical collection efficiency
- \(r_1\) disk radius, cm
- \(r_2\) inner ring radius, cm
- \(r_3\) outer ring radius, cm
- \(T\) temperature, °C
- \(\alpha\) transfer coefficient
- \(\nu\) kinematic viscosity, cm\(^2\) s\(^{-1}\)
- \(\omega\) rotation frequency, rad s\(^{-1}\)

**References**