Enantioselective Cathodic Reduction of Some Prochiral Ketones in the Presence of (1*R*,2*S*)-(−)-*N*,*N*-Dimethylephedrinium Tetrafluoroborate at a Mercury Pool Cathode

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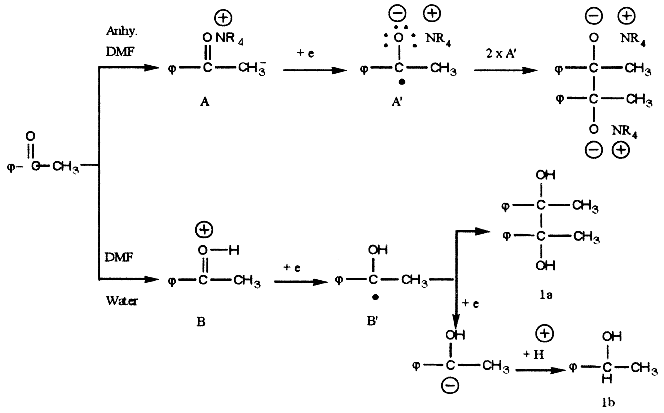
The enantioselective cathodic reduction of some prochiral ketones viz. acetophenone (I), propiophenone (II), butyrophenone (III), valerophenone (IV), isobutyrophenone (V), and pivalophenone (VI) has been accomplished at a mercury pool cathode in *N*,*N*-dimethylformamide (DMF)–water (90:10) using tetrabutylammonium fluoroborate (TBA·BF_4) as a supporting electrolyte in the presence of (1*R*,2*S*)-(−)-*N*,*N*-dimethylephedrinium tetrafluoroborate (DET). Cyclic voltammetric investigations have been carried out and a probable mechanism of the process has been presented.

Enantioselective synthesis using a chiral heterogeneous catalyst has been a fascinating area and has attracted tremendous interest.[1–4] A survey of the literature reveals that the variants applied in enantioselective electrosynthesis are: chirally modified electrodes,[5–7] the use of a chiral solvent,[8] a chiralsupporting electrolyte,[6] and cathodic reduction in the presence of optically active compounds,[2,3,6,9] crown ethers[10] etc. Our work is intended to explore the preparativescale enantioselective cathodic reduction of some prochiral ketones, I–VI, in DMF–H_2O (90:10) containing 0.1 M TBA·BF_4, at a mercury pool cathode using DET as a chiral auxillary. Pinacols (racemic/meso) viz **Ia–VIa** and corresponding alcohols viz. **Ib–VIb** were obtained, which were separated on a silicagel column (60–150 mesh) by eluting with benzene–ethyl acetate/distillation under reduced pressure, their optical purity (ee) was calculated, and their absolute configuration was determined.

Results and Discussion

A preliminary investigation on the cathodic reduction of acetophenone has shown that in the presence of anhydrous DMF (aprotic media), containing 0.1 M TBA·BF_4 and 10 mM of DET, pinacol **Ia** was obtained in 93% yield. However, if a proton source, e.g. water, was added to it, the formation of alcohol, ie. **Ib**, increased at the expense of **Ia**. In our experiments, we obtained compounds **Ia/Ib** in 75%/15%, 60%/33%, 45%/46%, and 30%/62% yields when the cathodic reduction of **I** was carried out at a mercury pool at a potential of −1.48 V vs Ag–AgCl in DMF:Water, i.e. 99:1, 95:5, 90:10, and 80:20, respectively. The ee of alcohol **Ib** was found to be 17%, 34%, 55%, and 35%, respectively. These results indicate that the DMF–Water (90:10) is suitable for our purpose. The above observations also suggest that the electron transfer from the cathode to ketone **I** is not direct, but occurs to a tetrabutylammonated ketone in an anhydrous DMF/protonated ketone in DMF–Water. In the former case, dimerization (of A′) is the main reaction, while in later case some radicals (B′) undergo dimerization to give pinacol **Ia**, and also some radical B′ undergoes one electron transfer followed by protonation to yield alcohol **Ib** (Scheme 1).

The reduction potential of ketones I–VI were determined by CV studies, and the preparativescale cathodic reduction was carried out at mercury pool at potentials of −1.48 V, −1.65 V, −1.72 V, −1.90 V, −2.00 V, and −2.10 V (Vs, Ag – AgCl in all cases), respectively, in DMF–Water (90:10) containing 0.1 M TBA·BF_4 and 10 mM DET. Pt foil was used as an anode in DMF–Water (90:10) containing 0.1 M TBA·BF_4. The charge was transferred corresponding to 2 F Mol^{-1}. The obtained products were pinacol **Ia–VIa** (racemic/meso) in 45%, 40%, 38%, 35%, 25%, and 18% yields, along with alcohols **Ib–VIb** in 46%, 54%, 52%, 54%, 60%, and 70% yields. The enantiomeric excess were assayed by comparing with known values of



Scheme 1.

the maximum rotation of each chiral alcohol[11] $[\alpha]_D^{20}$ −0.439° (neat, l = 0.01) for (*S*)-**Ib**[11a]; $[\alpha]_D^{20}$ −45.45° (c 5.15, chloroform) for (*S*)-**IIb**[11b]; $[\alpha]_D^{22}$ −45.2° (*c* 4.8, benzene) for (*S*)-**IIIb**[11a]; $[\alpha]_D^{22}$ −0.200° (neat, l = 0.01) for (*S*)-**IVb**[11a]; $[\alpha]_D^{25}$ −24.6° (neat) for *S*-**Vb**[11c]; $[\alpha]_D^{22}$ +25.9° (*c* 2.2, benzene) for (*R*)-**VIb**[11d]. The absolute configuration of alcohols **Ib–VIb** was found to be *S*.

Preliminary CV studies on the reduction of I at mercury film coated on a Pt wire (freshly prepared) in DMF containing 0.1 M TBA·BF_4 showed a reduction peak at E_p −1.52 V vs Ag/AgCl (i_p = 8.75 μA). Upon the addition of 10 mM DET, when CV was recorded two peaks appeared, viz E_{p_1} −1.14 V (peak current, i_{p_1} = 4.50 μA) and at E_{p_2} − 1.48 V (i_{p_2} = 13.25 μA). The first peak at E_{p_1} −1.14 disappeared in repeated scans, and was thus identified as being due to the adsorption of DE^+. The second peak i.e. E_{p_2} −1.48, due to the reduction of compound I, was slightly shifted anodically with an increase in i_{p_2}, indicating that the transfer of an electron from the cathode to a ketone becomes more facile upon the addition of DET. The effect of the concentration of DET on the cathodic reduction of I was then studied in DMF–Water (90:10) at a mercury pool at a potential of −1.48 V vs Ag–AgCl using 0.1 M TBA·BF_4 by passing charge corresponding to 2 F mol^{-1}. **Ia/Ib** was obtained in 50%/42%, 45%/46%, 48%/48%, and 46%/49% at DET concentrations 1 mM, 5 mM, 10 mM, and 20 mM, respectively. Compound **Ib** was found to have ee in 40%, 50%, 55%, 51%, and 45%, respectively, establishing that the inductor concentration, viz DET, does not significantly effect the yield of **Ia** and its optical yield and thus suggesting strong adsorption of DET on the surface of the cathode.[12]

Based on the above mentioned preliminary investigations, it appears that the DET is adsorbed on the surface of the cathode in a certain specific orientation, such that the H of –OH (of DE^+) remains towards the catholyte, and the oxygen of the protonated k-etone ($>C=O^+–H \longleftrightarrow >C^+–O–H$) forms a hydrogen bridge with H (of –OH) of the adsorbed DET. Upon electron transfer the intermediates (A′ and B′) are formed. Intermediate A′ (ion pair) undergoes dimerization exclusively in DMF to give racemic/meso **Ia**. The radical B′ either undergoes further electron transfer to give a carbanion (the electron is transferred to nearest p orbital as ketone (s) is in certain specific orientation towards cathode) or dimerization. The addition of a proton to carbanion in such a situation yields, the *S*-isomer selectively. The above preposition finds further support from an observation in the case of the reduction of ketone **VI**, where the corresponding alcohol **VIb** shows a loss of considerable enantioselectivity (5%), as the bulky group $–C(CH_3)_3$ appears to create a hinderance for a specific orientation on the surface of the cathode.

Detailed mechanistic studies of the process are being conducted and will be addressed later.

Experimental

Electrochemical studies were carried out on a Wenking potentiostat LB 72 M, a voltage scan generator VSG 72 and a Rikadenki X–Y recorder (model 101 T). The chiral auxillary viz. DET was synthesized by first refluxing (1*R*,2*S*) - ephedrine with methyl iodide (1:2) in alcohol for 10 h to give *N*,*N*-dimethylephedrinium bromide. The TBA·BF_4 and DET were prepared by reported methods,[13,14] and were dried under a vacuum and kept in a desiccator. DMF was dried by a reported method[15a] and kept over activated molecular sieves (4 Å) under nitrogen gas.

A typical preparativescale electroreduction of acetophenone has been described as under: 1.2 g acetophenone in 40 mL DMF + H_2O (90:10) containing 0.1 M TBA·BF_4 and 10 mM DET·BF_4 was taken as a catholyte. A porous diaphragm was used as a cell divider, and to it 20 mL DMF–H_2O (90:10) containing 0.1 M TBA·BF_4 was added, which served as an anolyte. A Hg pool (36 cm^2) was used as a cathode and Pt foil (9 cm^2) served as an anode. A charge corresponding to 2 F mol^{-1} was transferred at an applied potential of −1.48 V vs Ag –AgCl.

After electrolysis, the solvent was removed under pressure (50 °C, 35 mm). To it water (~30 mL) was added, and the organic product(s) were extracted with ether (3 × 30 mL). The combined ethereal layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed. Distillation of mass under reduced pressure, 79–83 °C at 3 mm Hg (reported[15b] 79 °C at 3 mm Hg), afforded 540 mg of pure **Ib** (yield 46%, mp 46–47 °C) $[\alpha]_D^{22}$ −0.240° (neat, l = 0.01) in 55% ee assigned by a comparison of the known rotation value, $[\alpha]_D^{20}$ −0.439° (neat, l = 0.01)[11a]. The remaining mass upon recrystallization afforded pinacol **Ia** (45%).

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