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Electrochemical Reduction of Methyl 2-Bromomethylbenzoate at Carbon Cathodes in Dimethylformamide Containing Water

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Cyclic voltammetry and controlled-potential electrolysis have been employed to examine the electrochemical reduction of methyl 2-bromomethylbenzoate at carbon cathodes in dimethylformamide (DMF) containing tetramethylammonium tetrafluoroborate (TMABF4). A cyclic voltammogram for the reduction of the substrate exhibits one irreversible cathodic wave with a peak potential of -1.45 V vs. SCE, which is due to the two-electron cleavage of the benzylic carbon-bromine bond. The corresponding reductive peak current also increases incrementally with the amount of water in DMF. Bulk electrolyses of methyl 2-bromomethylbenzoate have been carried out at -1.85 V vs. SCE with different concentrations of water in the solvent. The reduction process involves carbanion intermediates to afford various products including phthalide, which is generated via intramolecular cyclization that is affected by the presence of water. Detailed mechanism for the electrochemical reaction is proposed and further studied by isotope incorporation experiment.

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Many cyclic and bicyclic compounds have been synthesized by electrochemical means via either oxidation or reduction of various substrates. Organic halides, which often can be directly reduced to carbanion intermediates or catalytically reduced to radicals, are used regularly as the starting materials for those electrosyntheses. Peters and colleagues employed electrogenerated nickel(I) salen as the catalyst to reduce 6-halo-1-phenyl-1-hexyne¹ and 6-bromo-1-hexene² to the corresponding radicals, which would undergo intramolecular cyclization to form different cyclic products. It has been reported that other nickel macrocyclic complexes could also induce the similar electroreductive cyclization of unsaturated halides.³ Radical cyclization of bromo propargyloxy and allyloxy esters can be catalyzed by nickel(I) tetramethylcyclam electrogenerated at carbon cathodes in DMF to give several furofuran lignans in high yields.^{4,5} The same strategy has been applied to synthesize tetrahydrofuran derivatives from propargyl bromoethers.⁶ Moreover, the same type of reactions could be carried out with other nickel Schiff base catalysts7 or in environmental-friendly solvents.8-10 Olivero and co-workers also prepared functionalized indanes from ortho-halo-substituted ally ethers and esters via electrochemical cyclization by using nickel cyclam and its derivatives as the mediators.¹¹ Additionally, intramolecular cyclization involving radical intermediates may be achieved by electroreduction of organic halides with a few selected cobalt catalysts. Medeiros et al. utilized cobalt complexes containing a chiral salen derivative to catalyze the electrochemical reduction of unsaturated 2-bromophenyl ethers and α -bromoesters for the synthesis of some bicyclic compounds.^{7,12} Bromoacetals have been reduced by electrogenerated cobaloxime(I) species to form heterocyclic products.¹³ In general, electroactive metal complexes are usually required to obtain the radicals from organic halides via the homolytic cleavage of carbon-halogen bonds prior to intramolecular cyclization.

On the other hand, direct reduction of organic dihalides involving carbanion intermediates can also give rise to the formation of cyclic compounds. Electrochemical cyclization of allylic α,ω -dibromides has been accomplished for the synthesis of cycloalkadienes.¹⁴ Reduction of dimethyl α,α' -dibromoalkanedioates at platinum cathodes in DMF could produce dimethyl 1,2-cylcoalkanedicarboxylates in relatively high yields.¹⁵ More interestingly, electrolyses of *o*-trichloroacetylanilides in acetonitrile at selected cathodic potentials would lead to different bicyclic products, depending upon the substituents on the imine group.¹⁶ Nevertheless, electrochemical methods

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are limited for the synthesis of heterocyclic compounds by reducing organic halides directly to the intermediate carbanions.

Benzyl halides and their derivatives have been broadly used as the substrates for the electrochemical synthesis of many organic compounds including ketones,¹⁷ esters,¹⁸ and carboxylic acids^{19,20} via reduction followed by intermolecular coupling (e.g. with CO₂). Either benzylic radicals or anions can be directly generated at various cathodes in aprotic solvents, depending upon the applied potentials.^{21,22} Given a benzyl halide derivative with the appropriate structure and configuration, comparable electrochemical strategy involving intramolecular cyclization of carbanion intermediates could be employed to make bicyclic products. It appears that there is not much research has been done on this topic.

In this study, methyl 2-bromomethylbenzoate was electrolyzed at carbon cathodes in DMF without or with the addition of water, which acts as the proton donor. The substrate can be directly reduced at a potential of -1.85 V vs. SCE to form the corresponding benzylic anions, which lead to the generation of methyl *o*-toluate, phthalide, and a dimer (dimethyl 2,2'-(1,2-ethanediyl)bisbenzoate) as the major products. The yield of phthalide, which is a bicyclic compound that serves as the core chemical structure for a variety of dyes, fungicides, and natural oils, is considerably affected by the amount of water in DMF. The detailed reaction mechanism pertaining to the intramolecular cyclization of carbanion intermediates was proposed on the basis of cyclic voltammetry (CV) and controlled-potential electrolysis (CPE) data. Studies including isotope incorporation experiment were also carried out to further confirm the electrochemical mechanism.

Experimental

Reagents.— Each of the following chemicals was purchased and used as received: 2,2'-azobisisobutyronitrile (AIBN, Aldrich, 98%), *N*-bromosuccinimide (Alfa Aesar, 99%), methyl *o*-toluate (Alfa Aesar, 99%), phthalide (Aldrich, 98%), *n*-dodecane (Alfa Aesar, 99%), tetramethylammonium hydroxide (TMAOH, Alfa Aesar, 98%), H₂¹⁸O (Aldrich, 95 atom% ¹⁸O), potassium hydride (Acros Organics), methanol (Fisher, HPLC grade), chloroform (EM Science, ACS grade), and anhydrous diethyl ether (J.T. Baker, 99.9%). TMABF₄ (Aldrich, 97%), used as the supporting electrolyte, was stored in a vacuum oven at 60°C prior to use. Anhydrous DMF (Burdick & Jackson, 99.9%) was employed as solvent for the electrochemical experiments. All deaeration procedures were carried out with Praxair zero-grade argon.

Methyl 2-bromomethylbenzoate²³ and dimethyl 2,2'-(1,2ethanediyl)bisbenzoate²⁴ were synthesized according to the literature methods. Methyl 2-(methoxymethyl)benzoate was generated by reacting methyl 2-bromomethylbenzoate with methoxide, which was prepared by mixing methanol with sodium metal. The identity of each compound was confirmed with the aid of gas chromatography-mass spectrometry (GC-MS, 70 eV): (a) for methyl 2-bromomethylbenzoate, m/z 230 & 228, M⁺ (5%); 199 & 197, $[M - OCH_3]^+$ (7%); 171 & 169, $[M - COOCH_3]^+$ (2%); 149, [M- Br]⁺ (100%); 118, [M - Br - OCH₃]⁺ (17%); 105, C₆H₅CO⁺ (12%); 91, C₇H₇⁺ (28\%); 77, C₆H₅⁺ (7\%); (b) for dimethyl 2,2'-(1,2ethanediyl)bisbenzoate, m/z 298, M⁺ (0.2%); 266, [M - OCH₃ - H]⁺ (40%); 234, [M - 2OCH₃ - 2H]⁺ (100%); 207 [M - OCH₃ - H - $COOCH_3$]⁺ (18%); 178, [M - 2COOCH₃ - 2H]⁺ (29%); 149, [M - $CH_2C_6H_4COOCH_3$]⁺ (17%); 119, $C_7H_7CO^+$ (10%); 91, $C_7H_7^+$ (25%); 77, C₆H₅⁺ (4%); (c) for methyl 2-(methoxymethyl)benzoate, m/z 180, M⁺ (2%); 165, [M - CH₃]⁺ (29%); 149, [M - OCH₃]⁺ (12%); 133, $[M - CH_3 - OCH_3 - H]^+$ (100%); 119, $C_7H_7CO^+$ (7%); 105, C₆H₅CO⁺ (26%); 91, C₇H₇⁺ (16%); 77, C₆H₅⁺ (15%).

Cells, electrodes, and instrumentation.— Cells for CV^{25} and CPE^{26} have been described previously. For CV experiments, a 3-mmdiameter glassy carbon working electrode (CHI104, CH Instruments) was used and a platinum wire was employed as the auxiliary electrode. Customized 2.4 cm diameter × 0.4 cm thick reticulated vitreous carbon disks (Duocel RVC 100 PPI, Energy Research and Generation) were used as working cathodes for CPE; these disks were cleaned and handled according to the established procedures.²⁷ The reference electrode consists of a cadmium-saturated mercury amalgam in contact with DMF saturated with both cadmium chloride and sodium chloride^{28,29} and it has a potential of -0.76 V vs. SCE at 25°C. The potentials are quoted with respect to SCE in this paper. All CV and CPE experiments were carried out with a CH Instruments model 620B electrochemical analyzer.

Separation, identification, and quantitation of products.- Electrolysis products were characterized with the aid of an Agilent Technologies model 6890N gas chromatograph (GC) equipped with a flame ionization detector (FID) and a model 5973N mass-selective detector (MSD). The analytes were separated on Agilent Technologies 30 m \times 0.25 mm capillary columns (HP-1 for FID and HP-5MS for MSD) with a stationary phase of either 1% or 5% crosslinked phenylmethylsiloxane. Their identities were confirmed by comparing gas chromatographic retention times as well as mass spectra of suspected products with those of authentic compounds. Quantitation of the products was accomplished by means of GC using an internal standard method, which has been outlined elsewhere.³⁰ A known amount of *n*-dodecane was added as the electroinactive internal standard to each solution prior to electrolysis. Samples for gas chromatographic analysis were taken from the diethyl ether extracts of the electrolyzed solutions washed with brine.²⁷ The GC response factors were determined experimentally with respect to n-dodecane for all electrolysis products and the product yields reported in this paper represent the absolute percentage of starting material incorporated into a particular species.

Results and Discussion

Cyclic voltammetry.— Fig. 1A depicts the cyclic voltammogram for the reduction of methyl 2-bromomethylbenzoate recorded at a scan rate of 100 mV s⁻¹ with a glassy carbon electrode in DMF containing 0.050 M TMABF₄. One irreversible cathodic wave with a peak potential of -1.45 V, which corresponds to the two-electron reductive cleavage of the carbon–bromine bond, can be observed. This reduction peak potential is 0.35 V more positive than that for benzyl bromide (-1.80 V),²² likely due to the presence of electron withdrawing ester group at *ortho* position in the substrate, which would make it easier to break the benzylic carbon–bromine bond. With the addition of 100 mM of water to DMF, the cathodic peak current in-



Figure 1. Cyclic voltammograms recorded at a glassy carbon electrode (3-mm-diameter) at 100 mV s⁻¹ for 2.6 mM methyl 2-bromomethylbenzoate in DMF containing 0.050 M TMABF₄ with the addition of (A) 0 mM, (B) 100 mM, (C) 250 mM, (D) 500 mM, and (E) 1.0 M of water.

creases slightly while the peak potential shifts approximately 10 mV in the negative direction (Fig. 1B). This CV behavior is generally consistent with the electrochemical reduction of carbon-halogen bond as water can act as a proton donor to protonate the electrogenerated carbanions.³¹ The CV peak current keeps increasing incrementally with the amount of water in DMF (Fig. 1C–1E) but eventually levels off after approximately 500 mM of water are added.

Controlled-potential electrolyses.— Addition of the first electron to methyl 2-bromomethylbenzoate is expected to form the transient radical–anion of the starting material, which quickly decomposes to the radical and bromide. The subsequent second electron transfer would generate the carbanion intermediate. Overall, the electrochemical reduction of the substrate could be a two-electron process. Previous reports showed that benzyl radical is reduced to benzyl anion at -1.43 V vs. SCE in acetonitrile.^{21,32} In this study, controlled-potential electrolyses of methyl 2-bromomethylbenzoate were carried out at -1.85 V to ensure carbanions would be produced. Compiled in Table I are coulometric results and product yields for the direct reduction of the substrate at reticulated vitreous carbon cathodes in DMF containing 0.050 M TMABF₄ with the addition of various amounts of water. Each tabulated entry is the average of at least three identical experiments and the coulometric *n* values are reproducible to ± 0.03 .

Although high quality anhydrous DMF was used for the CV and CPE, it is believed that the solvent always contains residual

| Table I. Coulometric data and product distributions for CPE |
|---|
| (-1.85 V) of 10 mM methyl 2-bromomethylbenzoate at reticulated |
| vitreous carbon cathodes in DMF containing 0.050 M TMABF ₄ |
| with or without the addition of water. |

| Water added | | Product distribution (%) ^a | | | | | |
|-------------|------|---------------------------------------|----|----|---|----------------|-------|
| to DMF (mM) | n | 1 | 2 | 3 | 4 | 5 ^b | Total |
| 0 | 1.09 | 51 | 7 | 28 | 2 | 7 | 95 |
| 100 | 1.17 | 55 | 14 | 12 | 1 | 12 | 94 |
| 250 | 1.21 | 57 | 18 | 7 | 1 | 13 | 96 |
| 500 | 1.25 | 60 | 19 | 2 | 2 | 11 | 94 |

^a **1** = methyl *o*-toluate; **2** = phthalide; **3** = dimethyl 2,2'-(1,2ethanediyl)bisbenzoate; **4** = methyl 2-(methoxymethyl)benzoate; **5** = 1-methyl 1,2-benzenedicarboxylate (anion).

^b This product was determined by HPLC analyses according to the literature procedure.³⁴



Scheme 1. Proposed mechanism for the electrochemical reduction of methyl 2-bromomethylbenzoate.

water. Without further addition of water to DMF, the electrochemical reduction of 10 mM of methyl 2-bromomethylbenzoate affords methyl o-toluate, phthalide, and a dimer (dimethyl 2,2'-(1,2ethanediyl)bisbenzoate) as the major products in the yield of 51%, 7%, and 28%, respectively, with a coulometric *n* value of 1.09. Tiny amounts of methyl 2-(methoxymethyl)benzoate are also found in the electrolyzed solutions. With the addition of 100 mM of water, which could act as the proton donor, CPE of the starting material at -1.85 V causes slight increases in the *n* value and the yield of methyl *o*-toluate. However, a dramatic change in the product yields of phthalide and the dimer is also observed. The amount of phthalide is doubled to 14% and that of dimer decreases more than half to 12%. Comparable variations in the experimental results except for the formation of phthalide have been reported for the reduction of aromatic halides when carbanion intermediates are involved and proton donors are present.³³ The n values as well as the product yields of methyl o-toluate and phthalide continue to increase slightly with more water present in DMF whereas that of dimer decreases significantly.

The yield of phthalide, which is a bicyclic product, can be almost tripled when 500 mM of water are added to DMF. 1-Methyl 1,2-benzenedicarboxylate, which is an anion arising from reactions involving the incorporation of oxygen into the substrate,^{33,34} has also been found by HPLC in the electrolyzed solutions in this study. All the products from the electrolyses account for 94–96% of the starting material. Obviously, water plays an important role in the reduction of methyl 2-bromomethylbenzoate and the detailed mechanism is discussed below.

Mechanistic features.— On the basis of established mechanistic pictures^{21,33} and our current findings, we are able to propose a possible mechanism for the direct electrochemical reduction of methyl 2-bromomethylbenzoate, as shown in Scheme 1. At -1.85 V, the substrate undergoes an overall two-electron reductive cleavage of the carbon-bromine bond to form the corresponding benzylic carbanion intermediates, which can be subsequently protonated by residual water in DMF to afford methyl o-toluate (1). Alternatively, the electrogenerated carbanions can also take a S_N2 attack on the starting material to give the dimer (3). Hydroxide, which is a by-product from the formation of 1, can further react with the substrate to produce methyl 2-(hydroxylmethyl)benzoate (6). Not surprisingly, the hydroxyl group could attack the nearby carbonyl in 6 and the following addition-elimination reaction would lead to intramolecular cyclization to generate phthalide (2). Since not all of the starting materials are consumed electrochemically, the coulometric n values are much less than two.

Upon addition of extra water as the proton donor, more carbanions are protonated by H_2O instead of reacting with methyl 2bromomethylbenzoate. Consequently, the *n* value as well as the yield of methyl *o*-toluate increase, along with a significant decrease in the yield of dimer. Meanwhile, more hydroxide ions could be generated from the protonation reaction, giving rise to a higher yield of phthalide. Methyl 2-(methoxymethyl)benzoate (**4**), which is a minor product of the electrolyses, is likely formed by S_N2 reaction between the starting material and methoxide produced from intramolecular cyclization. Since usually the electrochemical cell is not perfectly sealed

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during electrolyses,^{33,34} it is not surprising that adventitious oxygen may leak into the system and oxidize the alcohol (6) to the corresponding carboxylate anion (5, 1-methyl 1,2-benzenedicarboxylate).

According to the proposed mechanistic pathways, water molecules are involved in the formation of phthalide. The esteric oxygen in phthalide should come from water instead of the substrate. To further confirm this step in the mechanism, H218O was employed for the CPE. The products were analyzed by GC-MS and as expected, ¹⁸O was found to be incorporated into phthalide. Scheme 1 also shows that the formation of phthalide is solely a chemical process, as long as hydroxide ions are present. To test this proposition, methyl 2bromomethylbenzoate was mixed with TMAOH in acetonitrile. Quantitative amounts of phthalide were obtained after several hours of refluxing, during which methyl 2-(hydroxylmethyl)benzoate (6) was also found by GC-MS in the reaction mixture. These experimental results demonstrate that the suggested sequence of mechanistic steps is legitimate. In addition, the similar approach may also work for intermolecular reactions. For example, the electrochemical reduction of benzyl bromide in the presence of ethyl acetate was carried out to give benzyl acetate as one of the products.

Conclusions

In summary, the electrochemical reduction of methyl 2bromomethylbenzoate at -1.85 V vs. SCE in DMF undergoes carbanion pathways. In the presence of water, intramolecular cyclization of the substrate intermediates can take place to generate phthalide, which is a bicyclic lactone. Moreover, the product yield of phthalide is considerably affected by the amount of water in DMF. The study shows that the direct reduction of selected organic halides involving carbanion intermediates could lead to the formation of cyclic products via the addition-elimination reaction at carbonyl group. The strategy could be potentially useful for the electrosyntheses of esters and heterocyclic compounds.

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