Regularities of anodic acetoxylation of 1,4-dimethoxybenzene in protic and aprotic media

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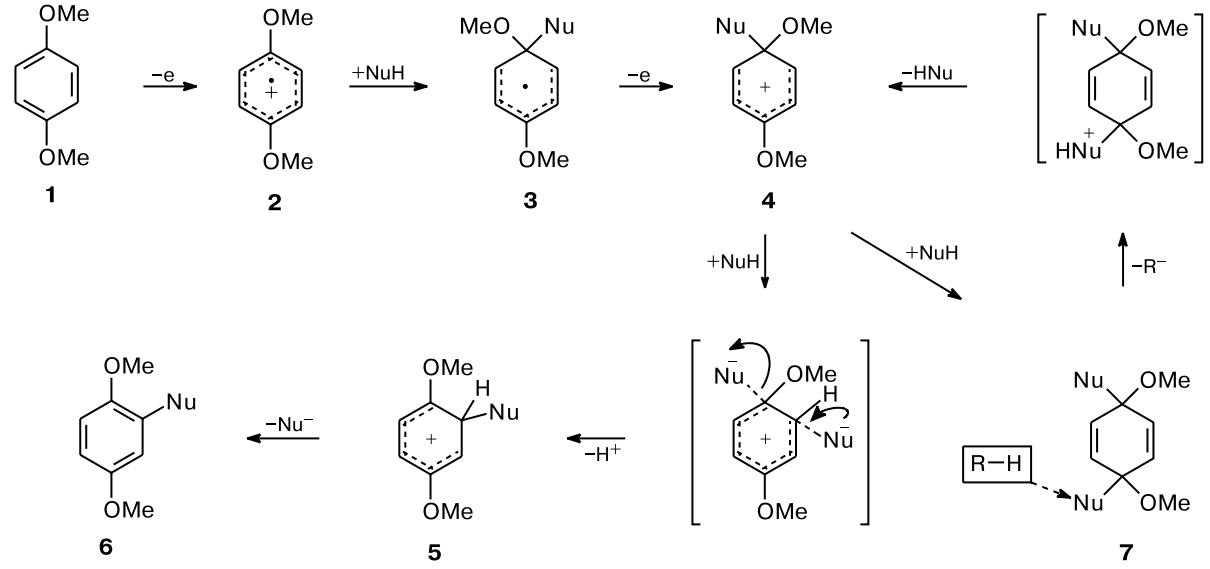
Electrochemical acetoxylation of 1,4-dimethoxybenzene during amperostatic electrolysis in an undivided cell at Pt electrodes in MeCN or MeOH solutions containing Et_4NOAc gives 2,5-dimethoxyphenyl acetate if AcOH or CH_2Cl_2 co-solvent has been added in a concentration of $\geq$50%. The reaction mechanism includes a nucleophilic attack of AcO^- ion on the *ipso*-position of 1,4-dimethoxybenzene radical cation. The process efficiency depends on factors that determine the stability and reactivity of the intermediate 1,4-dimethoxy-1-acetoxyarenonium cation.

Key words: anodic acetoxylation, 1,4-dimethoxybenzene, tetraethylammonium acetate, 1,4-dimethoxy-1-acetoxyarenonium cation, 2,5-dimethoxyphenyl acetate.

Recent studies[1—3] show the possibility of electrosynthesis of *N*-dimethoxyphenylazoles during amperostatic electrolysis of azole mixtures with 1,4-dimethoxybenzene (**1**) in undivided cell. The pattern of this process can be described by general Scheme 1 in which the nonionized form of azole (also nucleophilic) is designated by NuH.

The conclusion[3] that the transformation of product **7** into **6** taking place during electrolysis is determined by the competitive *ipso*- or *ortho*-interaction of the nucleophile with the intermediate arenonium cation **4** is of key importance. The *ortho*-interaction is accompanied by the irreversible rearrangement of the arenonium cation **4** into cation **5** proceeding by a *cine*-substitution mechanism; conversely, the *ipso*-interaction, resulting in product **7** is expected to be reversible. Only this condition does ensure transformation of products **7** into **6**, which proceeds through the **7** → **4** → **5** → **6** sequence. Especially important role belongs to the acidic component of the reaction mixture, RH, which catalyzes[3] the back reaction **7** → **4**

Scheme 1



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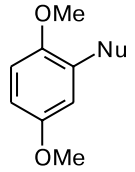
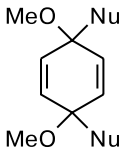
(see Scheme 1) due to the electrophilic assistance to elimination of the nucleophile from product **7**.

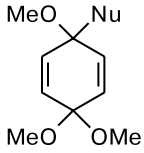
It should be emphasized that the formation of previously unknown *ipso*-bis-addition products **7a** and **8a**, together with the *ortho*-substitution products **6a** depends on the process conditions. Indeed, compounds **7a** were formed in the electrolysis in MeCN,[1,2] while **8a** were produced in MeOH,[3] where the azole and solvent molecules competed as nucleophiles.



6a—d



7a,c,d



8a,b

Nu = Az (azole residue, **a**), CN (**b**), OMe (**c**), OAc (**d**)

Previously,[4] it was shown that electrolysis of **1** in MeOH containing NaCN gives *ipso*-bis-addition products **7c**, together with compounds **6b** and **8b**. Meanwhile, electrolysis of **1** in MeOH containing no nucleophilic additives gives only product **7c**, while 1,2,4-trimethoxybenzene (a possible *ortho*-substitution product) is not detected.[5] This is not surprising, as 1,2,4-trimethoxybenzene, which is oxidized more readily than **1**, is completely consumed during electrolysis. Attention is attracted by the obvious similarity of the structures of the products of oxidative functionalization of **1** by various nucleophiles obtained in pervious studies;[1—5] in our opinion, this attests to common key steps of these two processes. This conclusion, which is generally in line with the rules of anodic azolation,[1—3] cyanation,[4] and methoxylation[5] of **1**, fully contradicts the reported acetoxylation mechanism.[6] Indeed, as opposed to the obtained data,[1—5] it was postulated[6] that 2,5-dimethoxyphenyl acetate **6**, the only product of anodic acetoxylation **1**, is formed exclusively upon the *ortho*-attack of the nucleophile *via* the following sequence: **1** → **2** → **3d*** → **5d** → **6d** (Scheme 2, *cf.* Scheme 1). It should be emphasized that the acetoxylation product was obtained only upon electrolysis of **1** in AcOH[6] containing AcO^- ions, whereas attempts to carry out the same process in MeCN (*cf.*, for example, Ref. 7) proved unsuccessful. This stimulated us to consider once again the anodic acetoxylation of **1**, in particular, the selection of the appropriate solvent.

A series of experiments on electrooxidative acetoxylation of **1** in MeCN, MeOH, mixtures of these solvents with CH_2Cl_2, and in neat CH_2Cl_2 gave results that are summarized in Table 1.

Electrolysis of **1** in MeCN containing a minor amount of AcOH in the presence of Bu_4NClO_4 was found to yield no acetoxylation products (run 1). Most likely, this is due to the absence of the nucleophilic acetate-ion "seed" in the beginning of the process, while during the electrolysis, the current concentration of the nucleophile could be maintained due to cathodic deprotonation of AcOH (see Ref. 8). Indeed, this electrolysis with Et_4NOAc as the supporting electrolyte gives *ortho*-substituted product **6d** in 18% yield (run 2).

If Scheme 1 is taken as a general mechanism of anodic functionalization of **1** (see above), its acetoxylation would be expected to give *bis*-acetyl ketals **7d** in addition to the *ortho*-substituted product **6d**. Nevertheless, it was found that compound **6d**, as in the previous study,[6] is the only identified product of electrolysis. Presumably, the relatively unstable *ipso*-bis-addition products are formed in the process but decompose during the workup of the final reaction mixture, as happens in some cases in the electro-

Scheme 2

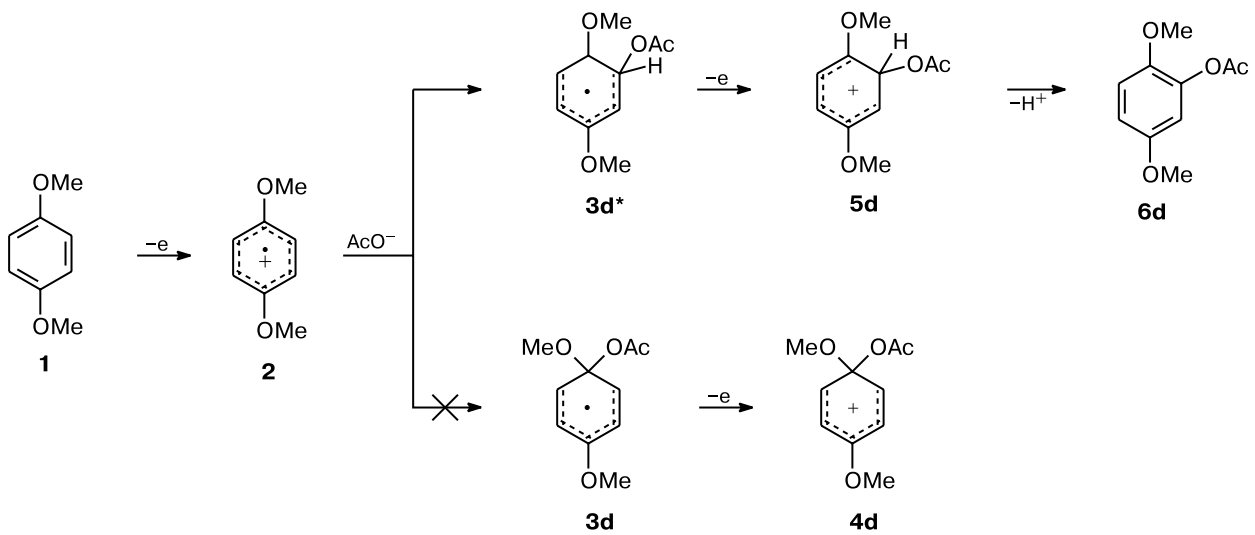


Table 1. Anodic acetoxylation of 1,4-dimethoxybenzene (**1**). Effect of the nature and the composition of the medium on the yield of 2,5-dimethoxyphenyl acetate (**6d**)[a]

Run	Solvent	Salt (3 mmol)	AcOH (3 mmol)	Yield of **6d** (%)
1	MeCN	Bu_4NClO_4	+	—
2	MeCN	Et_4NOAc	+	18
3	MeCN	Et_4NOAc	—	—
4	MeOH	Et_4NOAc	—	—[b]
5	MeOH	Et_4NOAc	+	14.5[b]
6	MeCN/CH_2Cl_2 (1 : 1)	Et_4NOAc	+	19
7	MeCN/CH_2Cl_2 (1 : 2)	Et_4NOAc	—	20
8	MeCN/CH_2Cl_2 (1 : 2)	Et_4NOAc	+	40
9	MeOH/CH_2Cl_2 (1 : 2)	Et_4NOAc	—	5[b]
10	MeOH/CH_2Cl_2 (1 : 2)	Et_4NOAc	+	15[b]
11	CH_2Cl_2	Et_4NOAc	+	56

[a] Pt electrodes, $Q = 2\ F$ per mole of **1**; $I = 0.2$ A; the amount of **1** is 2 mmol.

[b] 1,1,4,4-Tetramethoxycyclohexa-2,5-diene is the major product of electrolysis.

synthesis of *N*-dimethoxyphenylazoles.[1–3] However, as opposed to previous works,[1–3] our numerous attempts to perform this workup under the mildest possible conditions, including removal of the solvent at a temperature of ≤20 °C, did not result in detection of even traces of *ipso*-bis-acetoxylation product **6d**.

Note that the lack of direct experimental evidence supporting the attack of the acetate ion on the *ipso*-position of radical cation **2** prompted the authors[6] to describe the acetoxylation mechanism only in terms of the nucleophile attack on the *ortho*-position (see Scheme 2). This feature of oxidative acetoxylation of compound **1** distinguishes it from a series of related processes such as azolation,[1–3] cyanation,[4] and methoxylation[5] for which the *ipso*-attack of the nucleophile in the functionalization of **1** has been proven experimentally.

It is expedient to discuss the acetoxylation pattern in more detail. First of all, note that **1** is more readily oxidized than AcO^-; therefore, the transfer of the first electron is followed by the chemical reaction of AcO^- as a nucleophile with radical cation **2**. The spin density distribution in this radical cation calculated from ESR data indicates that the *ipso*- rather than the *ortho*-position is most favorable for the nucleophilic attack.[6] This conclusion was also confirmed by quantum-chemical data[9] on the general positive charge distribution and the LUMO electron density for radical cation **2**. Thus, the structure of the only isolated product of electrolysis, 2,5-dimethoxyphenyl acetate **6d** is the only argument in favor of the acetoxylation mechanism involving the *ortho*-attack of the nucleophile (see Scheme 2). However, the pathway to **6d** shown in Scheme 2 is by no means the only possible one.

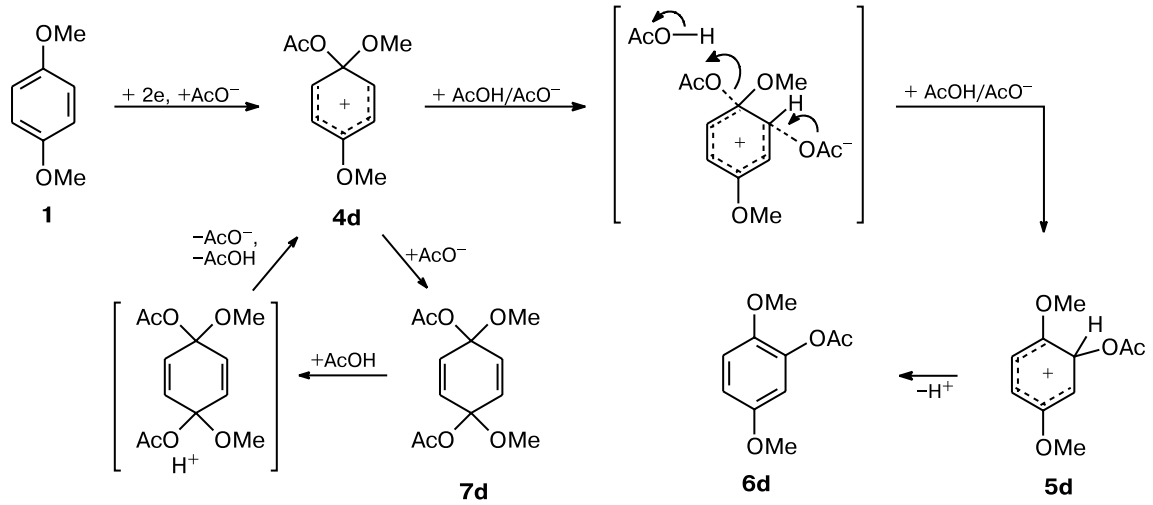
Compound **6d** could, in principle, be formed according to Scheme 1 *via* the sequence **1** → **2** → **3** → **4** → **5** → **6**. However, the fact that **6d** is formed as the only product implies that of the two competing routes of reaction between the nucleophile and the intermediate arenonium cation, **4** → **7** and **4** → **5**, only the **4** → **5** route is implemented in the acetoxylation of **1** for some reason. One more "oddity" distinguishing the anodic acetoxylation of **1** from related functionalizations of this compound attracts attention. During the electrolysis of **1** in MeCN in the presence of Et_4NOAc as a nucleophile, no acetoxylation takes place, unlike, for example, cyanation of **1** under similar conditions.[4,10] On the one hand, this obviously indicates that the acetate ion is a weaker nucleophile. On the other hand, it was found that the formation of **6d** requires that AcOH be present in the reaction mixture in addition to Et_4NOAc (*cf.* runs 2 and 3). The same is true for acetoxylation of **1** in MeOH (*cf.* runs 4 and 5).

In our opinion, all these effects can be related to the stability of the intermediate arenonium cation **4d** presented in Scheme 2. If we assume, relying on the results of calculations (see above) and contrary to the conclusions made previously,[6] that the *ipso*-attack of the acetate ion gives adsorbed radical **3d** (see Scheme 2), as in the cyanation of **1**,[10] this radical is expected to be oxidized under the given conditions to arenonium cation **4d**. Assuming (*cf.* Ref. 6) that among the Az, NC, MeO, and AcO substituents, AcO is the best leaving group, one may infer that the arenonium cation **4d** is least stable in the series studied and the fragmentation rate of this cation would be higher than the rate of reaction of **4d** with a nucleophile. In our opinion, this may account for the fact that its acetoxylation in a medium containing only one nucleophile (AcO^-) does not take place (runs 3 and 4). The situation changes when the electrolyzed system contains AcOH together with AcO^-. Previously[3] (see Scheme 1), we found that components of the medium acting as acids have a pronounced influence on the competing *ipso*- or *ortho*-interaction of the intermediate arenonium cation **4** with the azole nucleophile. In principle, the same can be true for the anodic acetoxylation of **1** (Scheme 3).

In our opinion, during the rearrangement of the arenonium cation **4d** → **5d**, which occurs by the *cine*-substitution mechanism, the AcOH molecule does not only assist the elimination of the acetoxy group but simultaneously facilitates the *ortho*-attack of the acetate ion due to the induced bond polarization. As regards the *ipso*-interaction of cation **4d** with the acetate ion, resulting in **7d**, this should be completely shifted to the left in the presence of AcOH, as is usually the case in the electrochemical *N*-dimethoxyphenylation of azoles.[3]

Subsequently, our effort was aimed at the variation of the experimental conditions in order to increase the yield

Scheme 3



of product **6d**. Previously,[1,2] in the development of electrosynthesis of *N*-dimethoxyphenylazoles, the yield of product **6a** was noted to increase substantially when the MeCN solvent was replaced by CH_2Cl_2, whose use in electrooxidative processes is often due to its ability to efficiently stabilize the cationic intermediates.[11]

However, it turned out that Et_4NOAc is poorly soluble in CH_2Cl_2; therefore, mixtures of CH_2Cl_2 with MeCN were used for the anodic acetoxylation of **1**. Whereas electrolysis in a 1 : 1 mixture of MeCN and CH_2Cl_2 gave **6d** in an almost invariable yield (*cf.* runs 2 and 6), even a twofold excess of CH_2Cl_2 resulted in a twice higher yield, which became 40% (run 8). Generally, it can be concluded that an increase in the CH_2Cl_2 concentration in the initial solution, starting with a 50% content, is accompanied by a parallel increase in the yield of the *ortho*-product **6d**. Indeed, in neat CH_2Cl_2 (run 11), the yield of **6d** was 56%, which is only 10% lower than its yield in the electrolysis in AcOH (*cf.* Ref. 6). Note that in run 11, Et_4NOAc undissolved in CH_2Cl_2 disappeared only at the end of electrolysis; hence, during the process the current concentration of the acetate anion remained virtually unchanged due to the gradual dissolution of the acetate as it was consumed. Thus, we found that not only AcOH, but also CH_2Cl_2 or its mixtures with MeCN or MeOH are applicable as solvents for the anodic acetoxylation of arenes.

Generally, the data of runs 6—11 confirm the stabilizing action of CH_2Cl_2 on intermediates of type **2** or **4**; in addition, they are in line with the mechanism of anodic acetoxylation of **1** presented in Scheme 3. In any case, this mechanism accounts for the sharp increase in the yield of **6d** upon the addition of AcOH to a reaction mixture containing acetate ions (*cf.* runs 7 with 8 and 9 with 10).

In conclusion, we would like to state that our study resulted in the development of new views on the mechanism of anodic acetoxylation of **1** and showed that the efficiency of this process depends on the factors that determine the stability and reactivity of the intermediate arenonium cation **4**.

Experimental

^1H NMR spectra of solutions in DMSO-d_6 were recorded on a Bruker AC-300 instrument.

Commercial 1,4-dimethoxybenzene (**1**), glacial AcOH (analytical pure grade), and Et_4NOAc (purity 98—99%, Aldrich) were used; MeCN was purified and dehydrated by refluxing and distillation from $KMnO_4$, two distillations from P_2O_5, and the subsequent distillation from calcined K_2CO_3; commercial CH_2Cl_2 was distilled prior to use from P_2O_5 and MeOH was distilled from calcined K_2CO_3; Bu_4NClO_4 was prepared by exchange reaction of Bu_4NBr with $NaClO_4$ followed by recrystallization from ethanol.

Amperostatic (I = 200 mA) electrolysis of **1** (2 mmol) in 45 mL of reaction mixtures of different compositions (see Table 1) was carried out in an undivided cell equipped with a magnetic stirrer and coaxial cylindrical Pt electrodes with an area of 12.3 cm^2 (cathode) and 37.2 cm^2 (anode) by passing 2 F of electricity per mole of substrate **1**, the temperature being kept at 20 °C. The chosen process conditions were maintained using a B5-50 dc source. During electrolysis, the solution was deaerated by an argon flow. After completion of the electrolysis, the solvent was evaporated on a rotary evaporator at ~20 °C (25 Torr) and the residue was analyzed by ^1H NMR.

2,5-Dimethoxyphenyl acetate (6d). ^1H NMR, δ: 2.24 (s, 3 H, CH_3COO), 3.70 and 3.71 (both s, 3 H each, 2 MeO), 6.73 (d, 1 H, CH_{arom}, J = 2.94 Hz), 6.79 (dd, 1 H, CH_{arom}, J = 2.94 Hz, J = 9.56 Hz), 7.04 (d, 1 H, CH_{arom}, J = 9.56 Hz). The resulting spectrum fully corresponds to reported data.[12]

The yield of the *ortho*-substituted product was determined in relation to taken **1** by comparing the integral intensities of the

unambiguously identified signal from the Me group of the product (singlet with $\delta = 2.24$) and the signals for the Me groups of the ammonium cations of tetraethylammonium acetate ($\delta = 0.9$—1.1).

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