Electrochemical Trimerization of Catechol to 2,3,6,7,10,11-Hexahydroxytriphenylene Using a Flow Microreactor

Yuto NAKAMURA,a Yasushi SATO,b,§ Naoki SHIDA,a,*,§ and Mahito ATOBEa,*,§

a Graduate School of Science and Engineering, Yokohama National University, 79-5 Tokiwadai, Hodagaya-ku, Yokohama 240-8501, Japan
b Innovation Technology Center, ENEOS Corporation, 8 Chidori-cho, Naka-ku, Yokohama 231-0815, Japan

* Corresponding authors: shida-naoki-gz@ynu.ac.jp (N. S.), atobe@ynu.ac.jp (M. A.)

ABSTRACT

In this study, we report one step electrochemical trimerization of catechol to 2,3,6,7,10,11-hexahydroxytriphenylene (HHTP) for the first time. Electrochemical trimerization was demonstrated in a flow microreactor, which offers advantages for reaction screening owing to short reaction time and small reaction scale, as well as avoiding the further oxidation of HHTP. The use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent was essential for the efficient production of HHTP. Computational simulation, pKa calculation, and electrochemical measurements gave some important insights into the mechanism of the electrochemical oxidation of catechol in HFIP.

© The Author(s) 2021. Published by ECSJ. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (CC BY, http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse of the work in any medium provided the original work is properly cited. [DOI: 10.5796/electrochemistry.21-00053].

Keywords : 2,3,6,7,10,11-Hexahydroxytriphenylene, Flow Microreactor, Electrochemical Trimerization, 1,1,1,3,3,3-Hexafluoro-2-propanol

1. Introduction

2,3,6,7,10,11-Hexahydroxytriphenylene is a common structural motif in discotic liquid crystals (DLCs) which are widely used as optical compensator films for displays, gas sensors, and OLEDs.1 HHTP is a cyclic trimer of 1,2-dihydroxybenzene, i.e., catechol, thus oxidative trimerization of catechol or its derivative to HHTP is the most straightforward synthetic pathway (Scheme 1).2

Trimerization of catechol to HHTP requires three consecutive C–C bond formations. However, the oxidative coupling of phenolic compounds including catechol often been disturbed by C–O coupling.3–6 Several strategies to inhibit C–O bond formation have been devised in previous studies to enable the synthesis of HHTP. A simple solution for this problem is the protection of phenolic hydroxy group. In this vein, oxidative trimerization of veratrole (1,2-dimethoxybenzene) or catechol ketal produces triphenylene derivatives, and the subsequent acidic hydrolysis affords HHTP.7–9 These methods require an additional step for deprotection of hydroxy group, and therefore one-step HHTP synthesis based on the trimerization of catechol would be more idealistic.

Oxidative trimerization of catechol in the strongly acidic media, such as 70% H2SO4 aqueous solution, using suitable oxidants such as hydrogen peroxide, ammonium persulfate, or iron(III) oxide affords HHTP in good yields,10–12 presumably due to the suppression of the dissociation of phenolic proton under acidic conditions. When catechol is oxidized with iron(III) chloride,13–15 which forms hexa-coordinated iron complex with three molecules of catechol,16 HHTP is obtained in a neutral aqueous solution. Kita and co-workers demonstrated the oxidation of catechol with a hyper-
valent iodine reagent by using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent to afford HHTP. Although these strategies excellently achieved consecutive formation of three C–C bonds from catechol, they require the use of a stoichiometric or excess amount of oxidant. Contrastingly, the electrochemical oxidation proceeds with electrical energy without using high potential chemicals, thus realizing highly safe and wasteless process.

In this work, we report preliminary attempts on the electrochemical trimerization of catechol to HHTP. To the best of our knowledge, there is only one report on the electrochemical synthesis of HHTP via anodic trimerization of protected catechol so far, and thus, there is no precedent for the electrochemical trimerization of unprotected catechol. The electrochemical trimerization of catechol was performed in an electrochemical flow microreactor, and it was revealed that the use of HFIP as a solvent is essential for the selective electrochemical trimerization of catechol to HHTP. Based on the computational simulation, \( \text{pK}_a \) calculation, and electrochemical measurements, mechanism of the electrochemical oxidation of catechol was discussed with the special emphasis on the effect of H$_2$O in HFIP.

2. Experimental

2.1 Instruments

Electrolysis was carried out with a galvanostat (Hokuto Denko HABF-501A). HPLC analysis was performed with a LC pump (Shimadzu LC-20AD), a UV detector (Shimadzu SPD-20A), and a column (Kanto Kagaku Mightysil Si 60 250-4.6). Chromatograms were recorded by a LC workstation (Shimadzu LabSolutions DB).

2.2 Materials

All reagents were purchased from commercial supplier and used without further purification. Catechol and THF were purchased from Kanto Chemical Co. Tetrabutylammonium hexafluorophosphate (Bu$_4$NPF$_6$) and HFIP were purchased from Tokyo Chemical Industry.

2.3 Computational simulation

Geometric structures of catechol and its oxidized states were optimized using Becke's three-parameter hybrid functional, B3, with non-local correlation of Lee-Yang-Parr, LYP, abbreviated as B3LYP, method. This method, based on Density Functional Theory (DFT) for a uniform electron gas (local spin density approximation), is used with the 6-31G (d) basis set. An open-shell spin-unrestricted formalism was used for radical cation structure. Calculation was carried out with Gaussian 16 Revision A.03 suite.

2.4 Flow microreactor

Figure 1 shows schematic illustration of the electrochemical flow microreactor. The reactor was constructed from a graphite plate and a Pt plate (3 cm width, 3 cm length). A spacer (80 µm thickness double faced adhesive tape) was used to leave a rectangular channel exposed, and the two electrodes were simply sandwiched together (area of the two electrodes: 1 × 3 cm$^2$). After connecting Teflon tubing to inlet and outlet, the reactor was sealed with epoxy resin.

2.5 A general procedure for electrochemical trimerization of catechol to HHTP using a flow microreactor

A KdScientific model 100 syringe pump was used to pump the reaction solution. The solution containing catechol (50 mmol dm$^{-3}$), supporting electrolyte (100 mmol dm$^{-3}$ of tetrabutylammonium hexafluorophosphate) in HFIP, acetonitrile, acetone or THF was introduced into the reactor. Constant current electrolysis was conducted at a current density of 10.0 mA cm$^{-2}$ using the electrochemical flow microreactor composed of a graphite plate anode and a Pt plate cathode (exposed area of electrode, 1 × 3 cm$^2$). In this operation, 2 × 96485 C of electricity were consumed per 1 mol of catechol substrate introduced into the reactor. After the electrolysis, a product residue in the reactor channel was also collected by washing with THF. Then, THF and HFIP in the collected solutions were removed by evaporation under reduced pressure. Subsequently, the residue was subjected to silica-gel column chromatography to remove the supporting electrolyte. The resulting solution was analyzed using HPLC to determine the yield of HHTP (the eluent was THF/hexane/TFA = 50/50/0.4).

2.6 Cyclic voltammetry measurement

Cyclic voltammograms were recorded on an ALS electrochemical analyzer 630C at room temperature in HFIP/H$_2$O (= 80/20, 50/50, 100/0.1, 100/0) containing 100 mmol dm$^{-3}$ tetrabutylammonium hexafluorophosphate. CVs were recorded by scanning the potential at a rate of 0.1 V s$^{-1}$. The working electrode was a glassy carbon disk (Φ 3.0 mm), the counter electrode was a Pt plate (2 × 2 cm$^2$), and the reference electrode was an Ag/AgCl electrode.
Table 1. Electrochemical trimerization of catechol to HHTP in a flow microreactor by using various organic solvents.

| Solvent | Donor number | HHTP yield (%) |
|---------|--------------|----------------|
| HFIP    | ≈0.20        | 20             |
| Acetonitrile | 14.1 ± 27   | 4              |
| Acetone | 17.0 ± 27    | N.R.           |
| THF     | 20.0 ± 27    | N.R.           |

*aExperimental conditions: anode, graphite plate; cathode, Pt plate; current density, 10.0 mA cm⁻²; flow rate, 11.2 mL h⁻¹; substrate: 50 mmol dm⁻³ of catechol, supporting electrolyte, 100 mmol dm⁻³ of tetrabutylammonium hexafluorophosphate. bDetermined by HPLC.

3. Results and Discussion

First, we conducted the electrochemical oxidation of catechol in a flow microreactor by using various organic solvents (Table 1). Flow microreactor enables time-saving in reaction screening, owing to shorter reaction time and smaller reaction scale compared with conventional beaker-type electrolysis cells. It is also expected that the use of flow micro reactor avoid the oxidation of HHTP, which is oxidized more easily compared to catechol. When HFIP and acetonitrile were used as reaction media, HHTP was obtained in 20% and 4% yields, respectively, whereas the use of acetone or THF gave no HHTP. HFIP and acetonitrile have smaller donor numbers (DN) than acetone and THF, which means that the cation affinity (Lewis basicity) of HFIP and acetonitrile is weaker than the others. From these results, it can be suggested that the acid-base interactions between a cationic intermediate and solvents are involved in reaction mechanism.

The redox behavior of catechol in conjunction with proton transfer is described in Fig. 2.22 Catechol (H₂C, in Fig. 2) is converted to a radical cation (SH₂) via one-electron oxidation. In the acid dissociation equilibrium of the radical cation, a semiquinone radical (SH) is produced via one-proton elimination from SH₂ (pKₐ ≈ -1). A following disproportionation reaction of SH gives a SH₂ and an o-benzoquinone (Q).23

We conducted DFT calculation of catechol in the radical cation state (SH₂) and the semiquinone radical state (SH) to gain some insights into the spin density at each atom. As shown in Fig. 3, in case of the radical cation (SH₂), large spin densities were found on carbon atoms at 4- and 5-positions, whereas in the semiquinone radical (SH), the largest spin density was found on the deprotonated O atom.

In general, the electrochemical coupling of aromatic molecules proceeds via homo coupling of radical cation species and following deprotonation. Thus, the bond formation takes place between atoms with high spin densities on the monomer radical cations. From this point of view, the electrochemical trimerization of catechol is considered to proceed at 4,5-positions from radical cation (SH₂), or the deprotonated O atom of semiquinone radical (SH). A plausible reaction mechanism of HHTP formation is shown in Scheme 2, which is based on the C–C coupling of radical cations (SH₂).

In any case, mechanism of catechol trimerization is strongly dependent on the electronic structures of reaction intermediates. In the results of Table 1, yields of HHTP were relatively large when solvents of weak cation affinities (smaller donor numbers) were used. We assumed that there is an interference with acid dissociation in HFIP and acetonitrile for its weak affinity for protons, and the reaction intermediate is assumed to be one of the structures in the upper side of Fig. 2, i.e., SH₂ and SH.

Although moderate yield of HHTP was obtained by electrochemical trimerization in HFIP, we found that the use of moisture absorbed HFIP results in a significant yield loss (20% → 4%). Then, we further investigated electrochemical trimerization of catechol in HFIP/H₂O systems (Table 2). The use of HFIP/H₂O = 80/20 and 50/50 gave no HHTP.

To gain insights into the effect of H₂O in HFIP, cyclic voltammetry (CV) measurements of catechol were performed in HFIP or HFIP/H₂O mixture (Fig. 4). The voltammogram recorded in HFIP showed two distinct peaks at 0.84 V and 1.13 V (vs. Ag/AgCl), respectively, suggesting that catechol underwent a two-step one-electron oxidation (H₂C → SH₂ → QH₂, or H₂C → SH → QH in Fig. 2) (Fig. 4a). On the other hand, only one anodic peak was observed both in HFIP/H₂O = 80/20 and 50/50 mixtures (Figs. 4b and 4c). The voltammetric feature of catechol in HFIP/H₂O mixture resembled to that recorded in aqueous solutions at pH 1.0–7.0 in a previous report.25 Since the acidity of SH₂ is estimated to be pKₐ = -1.0, a SH₂ was deprotonated to form a SH followed by disproportionation to a catechol (H₂C) and an o-benzoquinone (Q).25

Thus, we attributed the single oxidation peak of catechol observed in H₂O/HFIP to the simultaneous two-electron oxidation induced by the deprotonation of SH₂. It is noteworthy that the addition of 0.01% of H₂O into HFIP, i.e., HFIP/H₂O = 100/0.01, altered the voltammogram relatively indistinct, suggesting that the trace amount of water can significantly affect the oxidation process of catechol. This observation is in consistent with the result of electrolysis using moisture-absorbed HFIP, where the yield of HHTP was significantly lowered in comparison with the yield using dry HFIP.
Electrochemical trimerization of catechol to HHTP in a flow microreactor by using HFIP/H2O solvents.

Table 2. Electrochemical trimerization of catechol to HHTP in a flow microreactor by using HFIP/H2O solvents.

| Solvent                  | HHTP yield (%) |
|--------------------------|----------------|
| HFIP                     | 20             |
| HFIP (moisture absorbed) | 4              |
| HFIP/H2O = 80/20 (vol/vol) | N.R.          |
| HFIP/H2O = 50/50 (vol/vol) | N.R.          |

Experimental conditions: anode, graphite plate; cathode, Pt plate; current density, 10.0 mA cm⁻²; flow rate, 11.2 mL h⁻¹; substrate; 50 mmol dm⁻³ of catechol, supporting electrolyte, 100 mmol dm⁻³ of tetrabutylammonium hexafluorophosphate. More than six months have passed since the package was opened. Determined by HPLC.

Figure 4. Cyclic voltammograms of catechol (1 mM) at a scan rate of 100 mV/s. (a) In HFIP. (b) In HFIP/H2O = 80/20 vol/vol. (c) In HFIP/H2O = /H2O = 50/50 vol/vol. (d) In HFIP/H2O = 100/0.01 vol/vol. Supporting electrolyte, 100 mmol dm⁻³ of tetrabutylammonium hexafluorophosphate; working electrode, glassy carbon disk (Φ = 3 mm); counter electrode, Pt plate (2 cm × 2 cm); reference electrode, Ag/AgCl.

Electron transfer from catechol is followed by an acid dissociation equilibrium, which shifts with solvent dielectric constants. We conceived to model the dielectric constants of HFIP/H2O mixed solvents, where the addition of water enables a wide range of dielectric constants of the medium. We also performed a calculation to predict pKₐ values of catechol radical cation to clarify the relationship between solvent compositions and acid dissociation equilibrium.

A solvent composition of HFIP-H2O is represented as Eq. (1).

\[
\text{HFIP/H2O} = x/100 - x \text{ vol/vol}
\]  

(1)

Then, the dielectric constant is approximated as Eq. (2), because the dielectric constant is linearly proportional to the volume mixing ratio in HFIP-H2O system.

\[
\varepsilon_r(\text{HFIP/H2O}) = \frac{\varepsilon_r(\text{HFIP}) \times x + \varepsilon_r(\text{H2O}) \times (100 - x)}{100} 
\]

(2)

where \(\varepsilon_r\) is the relative permittivity of the solvents.

When the Gibbs energy change of acid dissociation is written as \(\Delta G\), \(pK_a\) is given as shown in Eq. (3).

\[
pK_a = -\log[H^+] = -\log(e^{-\Delta G/kT}) \\
= \frac{-\Delta G/kT}{2.30} = \frac{-\Delta G/(1.38 \times 10^{-23} \times 298)}{2.30} \\
= 9.46 \times 10^{-27}
\]  

(3)

where \(k\) is the Boltzmann’s constant; \(T\) is the temperature. \(\Delta G\) changes with the solvent composition are then represented as Eq. (4).

\[
\Delta(\Delta G) = \frac{e^2}{r} \left(\frac{1}{\varepsilon_r(\text{HFIP/H2O})} - \frac{1}{\varepsilon_r(\text{H2O})}\right) \\
= \frac{1.60 \times 10^{-19}}{2 \times 10^{-10} \times 8.85 \times 10^{-12}} \times \left(\frac{78.5 - 0.618x^-1}{78.5}\right) \\
= 1.45 \times 10^{-17} \times \left(78.5 - 0.618x^-1\right) - \frac{1}{78.5}
\]  

(4)

On these bases, the \(pK_a\) value in HFIP/H2O mixed solvent is represented as Eq. (5).

\[
pK_a(\text{in HFIP/H2O}) - pK_a(\text{in H2O}) = \frac{-\Delta(\Delta G)}{9.46 \times 10^{-27}} \\
= 1533 \times \left(\frac{78.5 - (78.5 - 0.618x^-1)}{78.5}\right)
\]  

(5)

Based on the above equations and given that \(pK_a\) (in H₂O) of catechol radical cation is -1.0, the \(pK_a\) value changes as shown.
in Fig. 5. The results indicate that the pKa value of reaction intermediate (like a radical cation, SH2) decreases greatly with H2O addition to HFIP. It is suggested that in the moisture-absorbed HFIP, acid dissociation from reaction intermediate was promoted (toward the lower side in Fig. 2), and HHTP formation was inhibited as in THF or acetone.

4. Conclusion

We have successfully demonstrated electrochemical trimerization of catechol to HHTP. The reaction was demonstrated in a flow microreactor, which offers advantages for reaction screening owing to the short reaction time and small reaction scale, as well as avoiding overoxidation of HHTP. Electrosynthetic method presented herein is more environmentally-friendly compared to conventional synthetic methods due to the no use of oxidants or protecting groups. The use of HFIP as a solvent was found to be essential for the production of HHTP directly from catechol via electrochemical oxidation. The influence of the H2O contamination in HFIP solvent on the reaction mechanism was explained by the estimation of pKa value of the catechol radical cation. These findings will give a new insight in the oxidative coupling chemistry of catechol.

Acknowledgments

This work was financially supported by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2707: Middle Molecular Strategy, Grant Number: JP15H05847) and Scientific Research (B) (Grant Number: JP20H02513).

References

1. T. Wöhle, I. Wurzbach, J. Kirres, A. Kostidou, N. Kapernaum, J. Litterscheidt, J. C. Haenle, P. Staffeld, A. Baro, F. Giesselmann, and S. Laschat, Chem. Rev., 116, 1139 (2016).
2. K. Morimoto, T. Dohi, and Y. Kita, Eur. J. Org. Chem., 2013, 1659 (2013).
3. J. M. Malkowsky, C. E. Rommel, K. Wedeking, R. Fröhlich, K. Bergander, M. Niegert, C. Quaiser, U. Griesbach, H. Pütter, and S. R. Waldvogel, Eur. J. Org. Chem., 2006, 241 (2006).
4. J. Barjau, P. Königs, O. Kataeva, and S. R. Waldvogel, Synlett, 2008, 2309 (2008).
5. K. Tanaka and H. Gotob, Tetrahedron, 75, 3875 (2019).
6. J. Barjau, G. Schnakenburg, and S. R. Waldvogel, Angew. Chem., Int. Ed., 50, 1415 (2011).
7. J. M. Chapuzet, N. Simonet-Gueguen, I. Taillepied, and J. Simonet, Tetrahedron Lett., 32, 7405 (1991).
8. D. Basuk, S. Christensen, S. K. Surampudi, C. Versek, D. T. Toscano, M. T. Tusminen, R. C. Hayward, and D. Venkataraman, Chem. Commun., 47, 5566 (2011).
9. C. Regenbrecht and S. R. Waldvogel, Beilstein J. Org. Chem., 8, 1721 (2012).
10. D. Takano, T. Kato, T. Fujinaka, and K. Sakamoto, WO patent, 2009-020166 (2009).
11. T. Kameshima, WO patent, 2005-037754 (2005).
12. S. Hirota, JP patent, JP-A-2008-115117 (2008).
13. H. Bengs, O. Karthaus, H. Ringsdorf, C. Budhr, M. Ebert, and J. H. Wendorff, Liq. Cryst., 10, 161 (1991).
14. S. Komatsu and T. Kaminade, JP patent, JP-A-Hei-9-301906 (1997).
15. S. Komatsu and Y. Kohori, JP patent, JP-A-Hei-9-118642 (1997).
16. J. Bijlsma, W. J. C. de Bruijn, J. A. Hageman, P. Goos, K. P. Velikov, and J. P. Vincenek, Sci. Rep., 10, 8288 (2020).
17. A. D. Becke, J. Chem. Phys., 98, 5648 (1993).
18. C. Lee, W. Yang, and R. G. Parr, Phys. Rev. B, 37, 785 (1988).
19. E. Yurtsever, Synth. Met., 135-136, 427 (2003).
20. T. Kashiwagi, B. Eksler, S. R. Waldvogel, T. Fuchigami, and M. Atobe, J. Electrochem. Soc., 160, G3058 (2013).
21. R. A. Miranda-Quintana and J. Smiatek, J. Mol. Liq., 322, 114506 (2021).
22. Q. Li, Q. Li, C. Batchelor-Mauley, and R. G. Compton, J. Phys. Chem. C, 119, 1489 (2015).
23. J. Heinze, Organic Electrochemistry (Eds. O. Hammerich and H. Lund), 4th Ed., Marcel Dekker, Inc., New York, p. 1312 (2000).
24. R. Fujishiro, G. Wada, and R. Tamamushi, Ioueki no seishitsu II, Tokyo Kagaku Dojin, Tokyo, p. 146 (1968). [in Japanese]
25. M. Fioroni, K. Burger, A. E. Mark, and D. Roccatano, J. Phys. Chem. B, 105, 10967 (2001).
26. T. R. Varga, Z. Fazekas, S. Katoh, M. Harada, Y. Ikeda, and H. Tomiyasu, Spectrochim. Acta. Part A, 56, 1781 (2000).
27. P. G. Jessop, D. A. Jessop, D. Fu, and L. Phan, Green Chem., 14, 1245 (2012).