Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 795–800

TETRAHEDRON

Unambiguous detection of 2,4,6-cycloheptatrien-1-ol by NMR spectroscopy and trapping with phenyltriazolinedione

Mitsunori Oda,* Kazuya Okawa, Hitoshi Tsuri and Shigeyasu Kuroda

Department of Applied Chemistry, Faculty of Engineering, Toyama University, Gofuku 3190, Toyama 930-8555, Japan

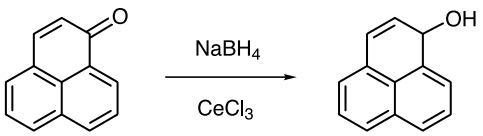
Received 30 October 2002; accepted 9 December 2002

Abstract—For the first time, the title alcohol **3** was unambiguously detected as a transient intermediate leading to ditropylether (**6**) in a cation–anion reaction between the tropylium ion (**5**) and hydroxide ion in an aqueous solution by NMR spectroscopy. It was also found that **6** gives **3** as a transient product in acid-catalyzed disproportionation of **6** into a mixture of tropone (**4**) and 1,3,5-cycloheptatriene (**7**) in chloroform containing water. Furthermore the existence of **3** in the latter reaction was confirmed by trapping with 4-phenyl-1,2,4-triazoline-3,5-dione to afford the [4+2]cycloadduct of the norcaradiene form of **3**. © 2003 Elsevier Science Ltd. All rights reserved.

The thermodynamic stability of carbocations can be evaluated by their pK_{R+} values. One method for determining the value is based on pH dependence of the electronic absorption spectrum, assuming the equilibrium between a carbocation and its corresponding alcohol (Eq. (1)).[1] While the alcohol corresponding to a thermodynamically unstable carbocation is stable enough to be isolated, the alcohol corresponding to a thermodynamically stable cation is basically unstable because of its facile dissociation back to the cation. In some cases, its easy and irreversible disproportionation to the correspnding ketone and hydrocarbon species is observed. For example, 1-phenalenol (**1**) had been elusive until Sugihara and Murata found special protocols for isolating it in 1989;[2] they used sodium borohydride in the presence of ceric chloride for reduction of phenalenone (**2**) and isolated **1** by particular workup and crystallization. However, they reported that application of their method was unsuccessful in isolation of the title alcohol, 2,4,6-cycloheptatrien-1-ol (**3**),[3,4] from tropone (**4**).[5] Although the equilibrium between the tropylium ion (**5**) and the alcohol **3** (in Eq. (1); R=2,4,6-cycloheptatrien-1-yl) was postulated, particularly well in pK_{R+} value measurements of **5**, such as in the pioneering work by Doering et al. in 1954,[6] **3** has, surprisingly, been neither observed nor isolated yet in the half century since the definite finding of the tropylium ion. Doering et al. found that **5** affords only ditropylether (**6**) as a single isolable product under the basic aqueous conditions. Later on, it was also found that disproportionation of **6** under acidic conditions gave tropone (**4**) and 1,3,5-cycloheptatriene (**7**),[7] that makes it harder to detect **3** (Schemes 1–3).

$$R^+X^- + H_2O \rightleftharpoons ROH + HX \quad (1)$$

Meanwhile, in 1976 Franzus et al. reported that a base-catalyzed rearrangement of 7-norbonadienol (**8**) provides the tropyl skeleton.[8] They suggested that the first product observed in the rearrangement under basic conditions could be the alkoxide of **3** by NMR analysis. However, signals in the 60 MHz NMR spectrum can be assigned either to those of the alkoxide or to those of **6**, as pointed out by the authors themselves. It is notorious that the signals did not show time-dependent change after the disappearence of **8**. Thus, it is hard to concede that definite detection of either **3** equilibrated with its alkoxide or the alkoxide itself is achieved in the study of Franzus et al. In this paper we describe the unambiguous detection of **3** as a transient species under acidic and basic conditions by NMR spectroscopy and its trapping with phenyltriazolinedione as a dienophile (Scheme 4).



2 **1**

Scheme 1.

1. Results and discussion

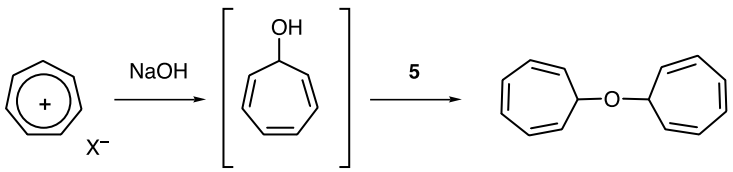
1.1. Detection of 3 in the reaction of the tropylium cation and hydroxide anion

Our approach to detection of the title alcohol **3** was

Keywords: carbocation; alcohol; tropylium ion; cycloaddition; phenyltriazolinedione.

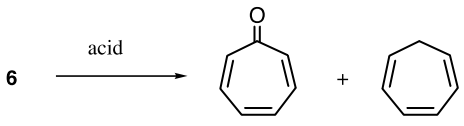
* Corresponding author. Tel.: +81-76-445-6820; fax: +81-76-445-6819; e-mail: oda@eng.toyama-u.ac.jp

PII: S0040-4020(02)01617-4



5 3 6

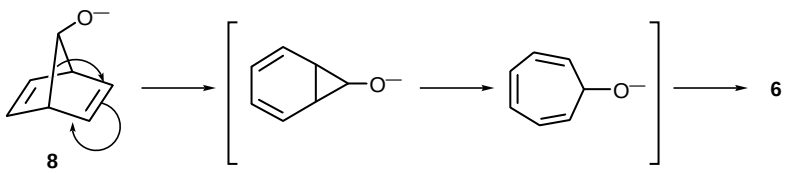
Scheme 2.



4 7

Scheme 3.

straightforward. Initially we monitored the reaction of the tropylium cation and sodium hydroxide in deterium oxide by NMR spectroscopy. Fortunately, we were able to achieve our purpose by this simple experiment which has not appeared in the literature. Tropylium tetrafluoroborate was added to a solution of 2 equiv. of NaOD in D_2O in an NMR tube and the reaction mixture was monitored by ^1H NMR analysis with sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) as an internal standard at 23°C of the probe temperature. At the beginning of the NMR measurements, the signals of **5** had already disappeared. Growing signals for **6** and decreasing signals were observed in a time range of about 40 min (Fig. 1). After then the spectrum showed only the signals of **6** and the resulted mixture looked cloudy because of its low solubility in the aqueous solution. The latter transient signals disappeared with a half life-time of 4 min under the conditions and with the slightly longer half life-time of 7 min at 7°C. The ^1H NMR spectrum after 2 min is shown in Figure 2. The signals consist of four different protons with their integrals of 1:2:2:2 ratio, the same as seen in that of **6**. This splitting pattern is similar to that of **6**, but the chemical shifts are different from those of **6**, clearly indicating the existence of a new 7-substituted 1,3,5-cycloheptatriene. Based on the integral pattern and the chemical shifts observed, this fleeting intermediate is best regarded as the title alcohol **3**. The signals of **3** appear broadened probably due to slow equilibrium between **3** and **5**, because unimolecular dynamic processes for **3**, such as ring inversion and norcaradiene-cycloheptariene tautomerization, and equilibrium with the corresponding alkoxide are expected to be very fast at the NMR temperature. Monitoring the reaction by ^{13}C NMR spectroscopy also supports the existence of an intermediate into **6** and its



8

Scheme 4.

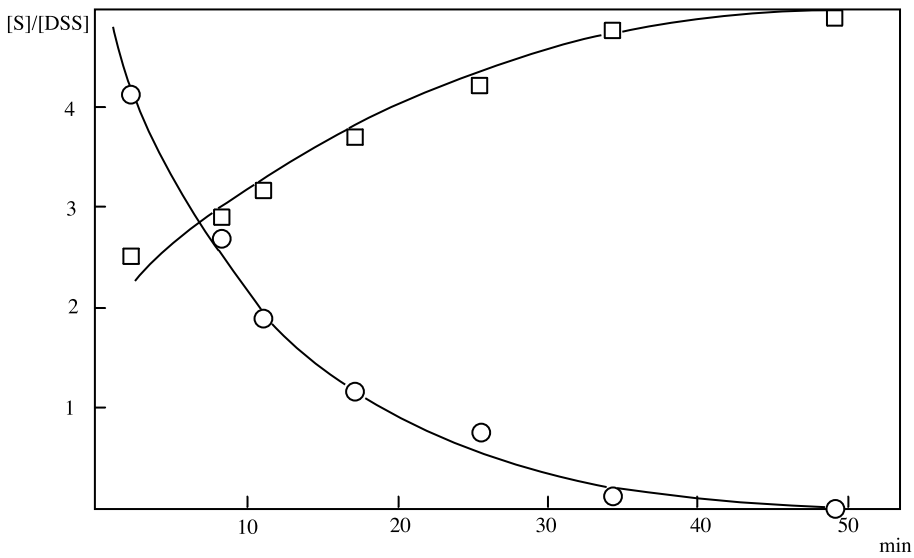


Figure 1. Change in time-dependent product ratio in the reaction of the tropylium ion (**5**) and sodium deuteroxide in D_2O at 23°C. The ordinate shows the molar ratios of 2,4,6-cycloheptatrien-1-ol (**3**, ○) and ditropylether (**6**, □) to the internal standard (DSS) and the abscissa time in min.

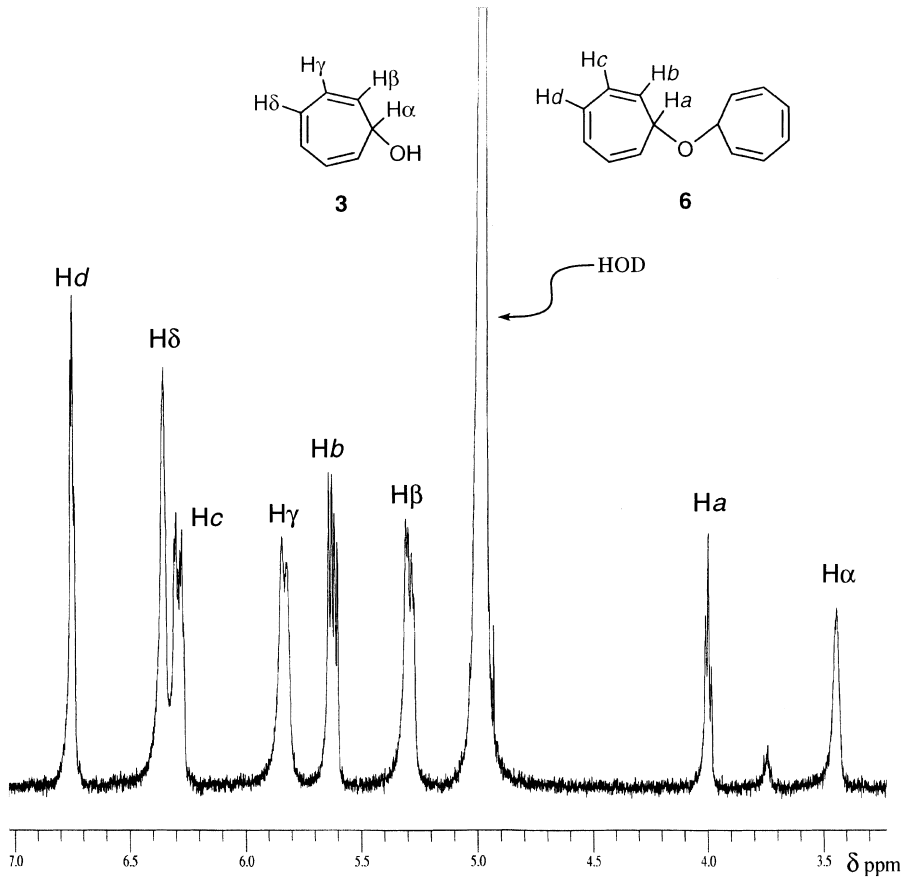


Figure 2. The ^{1}H NMR spectrum of the reaction mixture of the tropylium ion (**5**) and sodium deuteoxide in deuterium hydroxide after 2 min at 23°C.

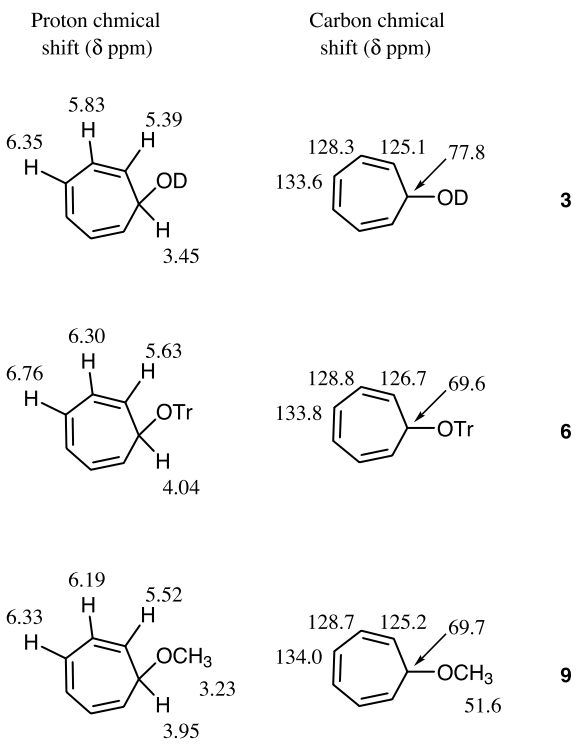


Figure 3. Proton and carbon chemical shifts of 2,4,6-cycloheptatrien-1-ol (**3**) and ditropylether (**6**) in NaOD-D_2O and 7-methoxy-1,3,5-cycloheptatriene (**9**) in D_2O with DSS as an internal standard.

structure as **3**. The assignment of carbon and proton signals for **3**, **6**, and 7-methoxy-1,3,5-cycloheptatriene (**9**) for comparison are listed in Figure 3. Chemical shifts of the hydrogens at the 1–3 positions of **3** were observed at higher magnetic field. Particularly, the hyrogen of the 1 position of **3** resonated relatively at higher field by more than 0.5 ppm compared with those at the corresponding position of **6** and **9**. This may be attributed to the effect of the electronic nature of the alkoxide which naturally exists in equilibrium with **3** under basic conditions. The final product **6** was isolated from this reaction mixture in more than 90% yield as reported.[5]

1.2. Detection of 3 in acid-catalyzed disproportionation reaction of 6 and trapping with 4-phenyl-1,2,4-triazoline-3,5-dione as a dienophile

Encouraged by the experiments for the detection of **3** from **5**, we proceeded to detect **3** in acid-catalyzed disproportionation[7] of ditropylether (**6**) into a mixture of tropone (**4**) and 1,3,5-cycloheptatriene (**7**). A reaction mixture of **6** and trifluoroacetic acid (TFA, 6 equiv. to **6**) in $CDCl_3$ saturated with D_2O was monitored at 23°C. As the signals of **6** decreased, the signals of both **4** and **7** increased in the course of reaction time. Along with these signal changes, it was observed that another set of signals grew up to half of the reaction period and then gradually disappeared (Fig. 4). After 65 min, the reaction provided a quatitative yield of a 1:1 mixture of **4** and **7**. The transient product observed in the reaction can be regarded best also as **3** from its ^{1}H NMR

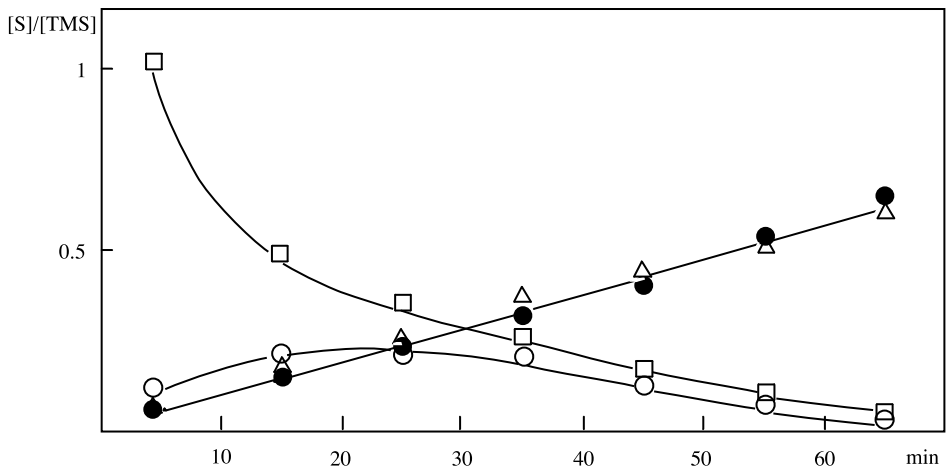


Figure 4. Change in time-dependent product ratios in the disproportionation of ditropylether (**6**) in $CDCl_3$–CF_3CO_2D at 23°C. The ordinate shows the molar ratios of 2,4,6-cycloheptatrien-1-ol (**3**, ○), ditropylether (**6**, □), tropone (**4**, ●), and 1,3,5-cycloheptatriene (**7**, △) to the internal standard (TMS) and the abscissa time in min.

signals in the mixture. While all proton signals of **6** in acidic $CDCl_3$ were observed at slightly higher field than those in basic D_2O, all proton signals of **3** in acidic $CDCl_3$ were observed at lower field than those in basic D_2O (Figs. 3 and 5). In this case also, the hydrogen at the 1 position shifts most to lower field, probably due to more effective protonation of the hydroxy group of **3** than the ether functional group. The proton chemical shifts of **6** and **9** seem to be affected mainly by solvent polarity. Thus, the greater dielectric constant of the solvent used, the lower chemical shifts of hydrogens of **6** and **9** were observed. On the other hand, the proton chemical shifts of **6** and **9** seem to be affected rather by pH of the solution.

Further confirmation of the existence of **3** was made by its trapping with a dienophile. Under the same reaction conditions with undeuterated solvents, we succeeded in trapping **3** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). The PTAD adduct **10**, to the norcaradiene form of **3**, was obtained in 72% yield based on twice amounts of **6** used, accompanied with a mixture of previously known adducts **11**[9] and **12**[10] in 22 and 21% yields based on the amount of **6** used, respectively. The stereochemistry of the hydroxy group on the cyclopropane ring in **10** was assigned to be exo based on the vicinal coupling constant ($^3J_{H-H}$=1.2 Hz) between the hydrogen on the carbon atom attached by the hydroxy group and the neighboring methine hydrogens on the cyclopropane ring.[11] The yield of **10** decreased in higher concentration of TFA and increased in its lower concentration as shown in Table 1. Nozoe has previously proposed two possible pathways from **6** into a mixture of **4** and **7**;[7]acid-catalyzed cleavage of the ether linkage of **6** provides **3** and **5** and subsequent intermolecular hydride shift from **3** into either **5** or **6** ends up with a mixture of **4** and **7**. The dependence of the yields on the amount of the acid in the trapping experiments clearly indicates that the acid favors consumption of **3** rather than its accumulation, assuming that the adduct formation step is not affected by the acid. Although the definite mechanism of the formation of **4** and **7** must await further meticulous kinetic study, the existence of **3** under these reaction conditions is evident (Scheme 5).

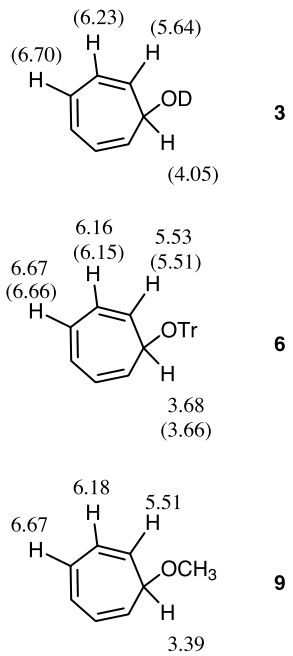


Figure 5. Proton chemical shifts (δ ppm) of tropyl derivatives in $CDCl_3$. The values in parentheses were observed in the disproportionation mixture in $CDCl_3$–CF_3CO_2D. TMS was used as an internal standard.

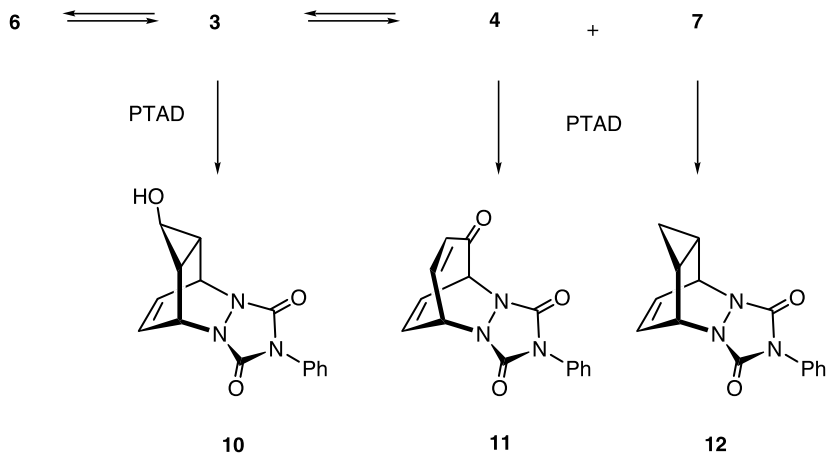
Table 1. Result of trapping experiments of **3** with PTAD under the conditions with various concentrations of TFA

TFA (molar equiv. to **3**)	Yield of the adducts (%)		
	10[a]	**11**[b]	**12**[b]
20	16	81	77
5	65	27	25
1	72	22	21

[a] Molar ratio based on twice amounts of **3** used.
[b] Molar ratio based on the amount of **3** used.

2. Summary

For the first time, we have observed the title alcohol, 2,4,6-cycloheptatrien-1-ol (**3**), as a transient species by NMR spectroscopy in the cation–anion reaction. The half-life



Scheme 5.

time of **3** in this reaction was found to be in order of several minutes. Also, **3** was detected in disproportionation of ditropylether (**6**). In the latter reaction in the presence of PTAD, **3** was trapped as a [4+2]cycloadduct of its norcaradiene form to give the adduct **10** along with previously known **11** and **12**. The stereochemistry of the hydroxy group at the cyclopropane ring in **10** was found to be *exo*. The yield of **10** in the trapping experiments was found to be dependent on the concentration of TFA. These results will help in elucidating the definite mechanism of the disproportionation of **6** which is a basic reaction in troponoid chemistry.

3. Experimental

3.1. General

Melting points were measured on a Yanaco MP-3 and are uncorrected. IR spectra were recorded on a JASCO IR-810 and Perkin–Elmer Spectrum RX I spectrometers. UV spectra were measured on a Shimadzu UV-1600 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 Hz) were recorded on a JEOL α400. Mass spectra were measured on a JEOL GC-Mate mass spectrometer. Column chromatography was done with Merck Kieselgel 60 Art 7734. Deuterium oxide (isotope purity; >99.9%) from Sigma-Aldrich Co., chloroform-*d* (isotope purity; >99.5%) from Wako Co. and 40% (w/w) sodium deuteroxide in deuterium oxide (isotope purity; 99%) from Merck Inc. were used without purification. DSS was purchased from Merck Inc. Tropylium tetrafluoroborate was prepared by the method of Dauben et al.[12] and was purified by recrystallization from a mixture of dichloromethane and hexane. PTAD was prepared according to the method in the literature.[13]

3.2. Detection of 2,4,6-cycloheptatrien-1-ol (3) in the reaction of the tropylium cation and hydroxide anion

In an NMR tube was charged 0.60 ml of a 0.1 M deuterium hydroxide solution and 2 mg of DSS in deuterium oxide. To this solution was added 5.0 mg (28 μmol) of tropylium tetrafluoroborate in one portion. The NMR tube was quickly shaken and was loaded into the NMR probe. The reaction was monitored at the probe temperature of 23°C or the controlled temperature of 7°C by ^{1}H NMR spectroscopy. The same procedure was repeated for monitoring at 23°C by ^{13}C NMR spectroscopy. After the monitoring, the resulted mixture of one experiment was poured into water and extracted with hexane (5×10 ml). The combined organic layer was dried with $MgSO_4$ and the solvent was removed to give 2.6 mg (94%) of **6**[6,7] as a brown oil.

3.3. Detection of 2,4,6-cycloheptatrien-1-ol (3) in the disproportionation of the ditropylether (6)

In an NMR tube was charged a solution of 10.0 mg (50.1 μmol) of **6** and 5mg of DSS in 0.60 ml of chloroform-*d*. To this solution was added 50 μl (300 μmol) of TFA. The reaction mixture was monitored by ^{1}H NMR spectroscopy at 23°C.

After 3 h, the resulted mixture was poured into a phosphate buffer (pH 6.86) and extracted with dichloromethane (5×10 ml). The combined organic layer was dried with $MgSO_4$ and the solvent was removed to give 9.6 mg (96%) of a 1:1 mixture of **4** and **7** as a yellow oil.

3.4. Trapping experiments of 2,4,6-cycloheptatrien-1-ol (3) with PTAD in the disproportionation of the ditropylether (6)

A solution of **6** (45.5 mg, 0.230 mmol) in in 2 ml of chloroform was added 5 μl of water and 18 μl (0.23 mmol) of TFA, followed by addition of 95.2 mg (0.460 mmol) of PTAD. After being stirred for 5 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel chromatography with a 1:1 mixture of chloroform and ethyl acetate as eluent to give **12**, **11**, and **10** in this order. The yields in the reactions with other TFA concentrarions are shown in Table 1.

3.4.1. Compound 12. 12.7 mg, 21%; colorless microcrystals, mp=199–200°C (lit.[10] 186–188°C). ^{1}H NMR ($CDCl_3$) δ=0.32 (dt, *J*=6.6, 3.8 Hz, 1H), 0.67 (q, *J*=7.1 Hz, 1H), 1.61 (m, 2H), 5.21 (m, 2H), 6.10 (m, 2H), 7.32–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=6.22, 8.40, 53.66, 125.18, 125.56, 128.24, 129.11, 131.42, 156.71.

3.4.2. Compound 11. 14.2 mg, 22%; yellow prisms,

mp=169–170°C (lit.[9] 178–180°C). ^{1}H NMR ($CDCl_3$) δ=5.38 (dd, J=7.3, 2.0 Hz, 1H), 5.44 (t-like, J=7.3 Hz, 1H), 6.02 (dd, J=10.9, 2.0 Hz, 1H), 6.93 (t-like, J=8.1 Hz, 1H), 7.11 (dd, J=7.8, 7.6 Hz, 1H), 7.35–7.51 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=51.38, 63.55, 124.28, 125.46, 128.52, 129.22, 130.88, 131.17, 136.23, 143.35, 151.77, 152.39, 188.47.

3.4.3. Compound 10. 87.6 mg, 72%; colorless microcrystals, mp=202–203°C. ^{1}H NMR ($CDCl_3$) δ=1.54 (s, 1H), 1.88 (m, 2H), 2.88 (t, J=1.2 Hz, 1H), 5.24 (m, 2 H), 6.21 (t-like, J=3.7 Hz, 2H), 7.33–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=13.37, 51.41, 60.17, 125.51, 126.49, 128.40, 129.17, 131.19, 156.59. IR (KBr) ν=3449brm, 1770m, 1713s, 1500m, 1457w, 1403s, 1233m, 1160m, 1138m, 1045m, 1022m, 899w, 867w, 843w, 773m, 736m, 720m, 640w cm^{-1}; MS (70 eV) m/z (rel intensity) 283 (M^+, 0.5), 177 (23), 119 (41), 106 (30), 105 (30), 91 (100), 77 (50); UV λ_{max} (CH_2Cl_2) 230 nm (log ε=3.99), 256 (3.60). Found: C, 63.78; H, 4.70; N, 14.93%. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83%.

Acknowledgements

The present work is supported by the Grant-in-Aid for Scientific Research (No. 13640528 to M. O.) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Mr T. Fujimura at Toyama University for the technical assistance at the beginning of this study and also Dr R. Miyatake at Toyama University for help in preparing manuscript of this paper. We also thank Professor Y. Sugihara at Yamaguchi University and Professor T. Machiguchi at Saitama University for helpful discussions.

References

1. Franklin, J. L. *Carbonium Ions*; Olah, G. H., Schleyer, P. v. R., Eds.; Interscience: New York, 1968; Vol. 1, pp 77–110, Chapter 2.
2. Sugihara, Y.; Kawanaka, H.; Murata, I. *Angew. Chem.* **1989**, *101*, 1258–1259, *Angew. Chem. Int. Ed.* **1989**, *28*, 1258–1269.
3. For isomeric enol-type compounds, 1,3,5-cycloheptatrien-1-, -2-, and -3-ols, see: Lew, C. S. Q.; Capon, B. *J. Org. Chem.* **1997**, *62*, 5344–5353.
4. Although an iron tricaronyl complex of **3** has been known, cleavage of iron from this complex for either detection or trapping was so far unsuccessfull despite our efforts. For the synthesis of this complex, see: Mayr, H.; Müller, K. H.; Ofinal, A. R.; Bühl, M. *J. Am. Chem. Soc.* **1999**, *121*, 2418–2424.
5. Sugihara, Y.; Murata, I. Private communications.
6. Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 3203–3206. Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1957**, *79*, 352–356.
7. Ikemi, T.; Nozoe, T.; Sugiyama, H. *Chem. Ind. (London)* **1960**, 923. Borg, A. P. T.; Helden, R. V.; Bickel, A. F.; Renold, W.; Dreiding, A. S. *Helv. Chim. Acta* **1960**, 457–458. Machiguchi, T. *Synth. Commun. 12,* **1982**, 1021–1025.
8. Franzus, B.; Shceinbaum, M. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 1241–1247.
9. Sasaki, T.; Kanematsu, K.; Hayakawa, K. *J. Chem. Soc. (C)* **1971**, 2142–2147.
10. Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *J. Chem. Soc. (C)* **1967**, 1905–1909.
11. Adam, et al. prepared the *exo*-adduct of 7-methoxycycloheptatriene having a similar small coupling constant of 1.4 Hz Adam, W.; Balci, M.; Pietrzak, B. *J. Am. Chem. Soc* **1979**, *101*, 6285–6291.
12. Dauben, Jr. H. J.; Gadecki, P. A.; Harman, M. K.; Peason, D. L. *J. Am. Chem. Soc.* **1957**, 1957–1958.
13. Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Organic Synthesis*; Wiley: New York, 1988; Coll. Vol. 6, pp 936–940.