Kinetic stabilization of the o-quinoidal 3,4-benzotropone system

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<th>富田正, 佐野啓子, 小野和彦, 素野克広, 鈴木賢, 中村隆信</th>
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Kinetic stabilization of the o-quinoidal 3,4-benzotropane system

Masakazu Ohkita, Kieko Sano, Katsuhiko Ono, Katsuhiro Saito, Takanori Suzuki and Takashi Tsuji

Graduate School of Engineering, Nagoya Institute of Technology, Nagoya 466-8555, Japan.
E-mail: ohkita.masakazu@nitech.ac.jp; Fax: +81-(0)52-735-5604; Tel: +81-(0)52-735-5604
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

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Kinetic stabilization of the o-quinoidal 3,4-benzotropane system was investigated. The parent 3,4-benzotropane 1 undergoes rapid \([\pi^8 + \pi10]\) dimerization in fluid solution even at \(-78^\circ C\) while triptycene-fused derivative 5 having a tert-butyl group at the C(6) position of the tropone moiety was found to be stable indefinitely under similar conditions. The relative importance of the triptycene moiety and the tert-butyl group in 5 for the kinetic stabilization was evaluated.

Introduction

3,4-Benzotropenes, in which the benzo component is fused to the tropone ring in a manner to form an o-quinoidal structure, have long been a subject of theoretical and experimental interest. We have previously reported\(^a\) the generation of the parent 3,4-benzotropane 1 using the electrocyclic ring-opening reaction of the corresponding benzocyclobutene isomer 2. UV-vis and IR spectroscopic studies have revealed that 1 is electronically significantly polarized in the ground state, consistent with a substantial contribution of polarized resonance structure 1b. Despite the unique electronic structure, however, the thermal instability of 1 has thwarted the exploration of its physical and chemical properties; 1 is persistent only under matrix isolation conditions at low temperature and is rapidly consumed in fluid solution even at \(-78^\circ C\). We were interested in investigating the kinetic stabilization\(^b\) of 1 to gain a more detailed understanding of this system. The lability of o-quinoidal 1 arises from its high propensity to undergo dimerization to form dimers 3 and 4. This tendency suggests that the system may be kinetically stabilized, to some extent at least, by introducing sterically demanding substituents that specifically shield the reaction sites, and we designed derivatives 5-8. Herein we report the results of synthetic investigation of 5-8 aimed at generating the kinetically stabilized derivatives of 1.

Results and discussion

A major path of the thermal decomposition of 1 is a kinetically controlled \([\pi^8 + \pi10]\) dimerization at the 2,5- and 2,7-positions to form 3 and 4.\(^4\) To prevent such dimerization, triptycene-fused derivative 5 having a tert-butyl group at the C(6) position was designed as an initial target molecule. Related compounds 6 and 7 were also investigated to evaluate the relative importance of the tert-butyl group and the fused triptycene moiety for the kinetic stabilization of this system.

On the basis of our previous successful generation of 1 from the benzocyclobutene valence isomer 2, we envisaged 13 as a promising precursor for 5, and 13 was prepared as outlined in Scheme 1. Thus, addition of benzene to 9\(^a\) afforded triptycene derivative 10 in 73% yield. Bromination of 10 followed by dehydrobromination and deprotection afforded enone 12 in 47% yield. 1,2-Addition of tert-butyl lithium to 12 followed by PCC oxidation produced 13 in 61% yield. On the other hand, 1,2-addition of tert-butyl lithium to 2\(^a\) followed by PCC oxidation produced 14 in 58% yield (Scheme 2).

The photochemical generation of 5 from 13 was examined under matrix isolation conditions at low temperature and the reaction was monitored by UV-vis spectroscopy. When a degassed EPA (a 5:5:2 mixture of ether, isopentane, and ethanol) solution of 13 in a Pyrex tube was frozen at liquid nitrogen temperature (\(-196^\circ C\)) and irradiated with a high-pressure mercury lamp, a new absorption extending to long-wavelength region with \(\lambda_{\text{max}}\) around 450 nm was observed (Fig. 1). This newly developed absorption is almost superimposed on that reported\(^d\) for 1 with \(\lambda_{\text{max}}\) at 353, 372, 392, 458, 482 (sh), 506 (sh) and 518 (sh) nm. Similarly, irradiation of 12 or 14 in an EPA glass at \(-196^\circ C\) led to the development of a new absorption characteristic of the 3,4-benzotropane system (see experimental section). Thus, we concluded that 3,4-benzotropane derivatives 5, 6 and 7 were generated photochemically from 13, 12 and 14, respectively. The generated orange species 5-7 were stable in the frozen EPA glass, but were consumed smoothly in the fluid EPA solution at 0 °C. The decay of the absorption followed second-order kinetics (Fig. 2), so that dimer formation should be still a dominant pathway for their thermal decomposition. The rate constants (Table 1) for the dimerization of 5, 6 and 7 in EPA at 0 °C were determined to be 30 ± 6 M\(^{-1}\) s\(^{-1}\), 166 ± 33 M\(^{-1}\) s\(^{-1}\) and 60 ± 12 M\(^{-1}\) s\(^{-1}\), respectively. These observations demonstrate that
of 18 with 1-(ethynylsulfonyl)-4-methylbenzene followed by dehydrogenation gave 19 in 83% yield. Bromination of 19 followed by dehydrobromination and deprotection afforded 21 in 52% yield.

1,2-Addition of tert-butyllithium to 21 followed by PCC oxidation produced 22 in 32% yield.

The photochemical generation of 8 from 22 was examined as described for 5–7. However, unexpectedly, when a degassed EPA solution of 22 in a Pyrex tube was irradiated with a high-pressure mercury lamp at −196 °C, development of no absorption extending to long-wavelength region characteristic of the 3,4-benzotropone system was observed, even after prolonged irradiation. Molecular modeling suggests that 8 would be distorted from its ideal planar structure due to the steric repulsion between the tert-butyl group at the C(2) position and the hydrogen atom at the peri-position (Scheme 4). To relieve the steric repulsion, 8 may undergo, if it is generated, rapid pericyclic ring-closing photochemical reaction to form norcaradiene derivative 23. A similar photochemical transformation has been reported for related compounds.

Fig. 1 Absorption spectral changes observed upon irradiation of 13 with a high-pressure mercury lamp through Pyrex in an EPA glass at −196 °C: before irradiation (dashed line) and after irradiation (solid line; λmax 353 (sh), 373, 394, 452, 473 (sh), 498 (sh) and 510 (sh) nm).

We next turned our attention to the generation of 8 having two tert-butyl groups at the C(2) and C(6) positions of the tropone moiety in anticipation of generating more stabilized derivative than 5–7. Since the dimerization of 1 proceeds at the 2,5- and 2,7-positions, introduction of the sterically demanding tert-butyl group at the C(2) position was expected to be quite effective for the kinetic stabilization. The desired benzocyclobutene precursor 22 was prepared as outlined in Scheme 3. Irradiation of 3-tert-butyl-2-cyclopenten-1-one (15) with (E)-1,4-dichloro-2-butene afforded \([\pi^2 + \pi^2]\) photocycloadduct 16 as a mixture of stereoisomers in 82% yield. Acetalization of 16 followed by two-fold dehydrochlorination produced diene 18 in 86% yield. Diels–Alder reaction of 18 with 1-(ethynylsulfonyl)-4-methylbenzene followed by dehydrogenation gave 19 in 83% yield. Bromination of 19 followed by dehydrobromination and deprotection afforded 21 in 52% yield.

1,2-Addition of tert-butyllithium to 21 followed by PCC oxidation produced 22 in 32% yield.

Table 1 Kinetic stabilities of the 3,4-benzotropones in EPA

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<th>Compound</th>
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<tr>
<td>1</td>
<td>−78</td>
<td>12 ± 3</td>
<td>reference 4</td>
</tr>
<tr>
<td>5</td>
<td>−78</td>
<td>stable</td>
<td>this study</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>30 ± 6</td>
<td>this study</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>166 ± 33</td>
<td>this study</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>60 ± 12</td>
<td>this study</td>
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The photochemical generation of 8 from 22 was examined as described for 5–7. However, unexpectedly, when a degassed EPA solution of 22 in a Pyrex tube was irradiated with a high-pressure mercury lamp at −196 °C, development of no absorption extending to long-wavelength region characteristic of the 3,4-benzotropone system was observed, even after prolonged irradiation. Molecular modeling suggests that 8 would be distorted from its ideal planar structure due to the steric repulsion between the tert-butyl group at the C(2) position and the hydrogen atom at the peri-position (Scheme 4). To relieve the steric repulsion, 8 may undergo, if it is generated, rapid pericyclic ring-closing photochemical reaction to form norcaradiene derivative 23. A similar photochemical transformation has been reported for related compounds.
Conclusions
The lability of o-quinooidal 3,4-benzotropone 1 arises from its high propensity for undergoing dimerization and this tendency suggests that the system may be kinetically stabilized by introducing sterically demanding substituents that specifically shield the reaction sites. In fact, the skeleton of 1 is kinetically stabilized in derivatives 5–7. The related stabilities of 5–7 in EPA at 0 °C indicate that the tert-butyl group at the C(6) position is more effective than the fused-tripticyclic moiety for kinetic stabilization of the 3,4-benzotropone system. Preparation of 8 having two tert-butyl groups at the C(2) and C(6) positions of the tropone moiety was also examined using the corresponding benzocyclobutene derivative 22 as a precursor. However, photochemical generation of 8 from 22 could not be confirmed even under matrix isolation conditions at low temperature, possibly because of the photochemical lability of 8 for intramolecular rearrangement.

Experimental
General
1H and 13C NMR spectra were recorded at 300 and 75 MHz, respectively, on a JEOL EX-300 spectrometer using tetramethylsilane as an internal reference. IR spectra were taken on a Hitachi 8100 spectrophotometer. Mass spectra were recorded on a JEOL JMS-SX102 spectrometer. GLC work was done on Hitachi 163 gas chromatographs. Preparative chromatography was performed on Merck Kieselgel 60 (70–230 mesh). The light source for photochemistry was a Halos (Eiko-sha, Japan) 450 W high-pressure Hg lamp.

6.7-(2′,3′-(9′,10′-Dihydro-9′,10′-benzenoanthro)bicyclo-[3.2.0]hept-6-en-2-one ethylene acetal (10). To a refluxed solution of 9 (1.46 g, 4.83 mmol) in DME (70 mL) was added a solution of anthranilic acid (16.5 g, 121 mmol) in DME (70 mL) and isopentyl nitrite (14.1 g, 121 mmol) from respective dropping funnels over 7 h. The mixture was cooled to room temperature, poured into water (500 mL) and extracted with benzene (3 × 500 mL). The extracts were combined, washed successively with water (2 × 500 mL), 5% aqueous HCl (2 × 500 mL), 10% aqueous NaHCO3 (2 × 500 mL) and brine (3 × 500 mL), dried with Na2SO4, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (1 : 9) to give 10 (1.33 g, 73%); mp 237–243 °C; (Found 376.1463); m/z (FD) 378 (M+).
brine (50 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (1:9) to give 12 (0.50 g, 90%; mp 256–257 °C (ether); (Found 332.1196, C₇H₅NO₂ requires 332.1191); ν<sub>max</sub> (KBr/cm<sup>-1</sup>) 1696; δ<sub>H</sub> (300 MHz, CDCl₃) 3.97 (d, J = 3.0 Hz, 1 H), 4.44 (d, J = 3.0 and 2.6 Hz, 1 H), 5.38 (s, 1 H), 5.39 (s, 1 H), 5.95 (d, J = 5.5 Hz, 1 H), 6.95–7.00 (m, 4 H), 7.21 (s, 1 H), 7.27–7.4 (m, 4 H) and 7.70 (d, J = 5.5 and 2.6 Hz, 1 H); δ<sub>C</sub> (75 MHz, CDCl₃) 49.87, 51.83, 54.17, 54.25, 118.39, 119.54, 123.22, 123.25, 123.37, 123.41, 124.96, 123.98, 125.02, 125.07, 133.44, 137.95, 137.97, 143.22, 144.65, 144.71, 144.73, 144.79, 145.20, 161.53 and 205.06; m/z (FD) 332 (M<sup>+</sup> 100%).

5-tert-Butyl-6,7-bis(chloromethyl)bicyclo[3.2.0]heptan-2-one (17). To a solution of 17 (64 mg, 0.19 mmol) in dry THF (5 mL) was added 1.6 M tert-butylthiurium in pentane (0.24 mL, 0.38 mmol) over 1 min at −78 °C. The mixture was stirred at the same temperature for 1 h, allowed to warm to room temperature, diluted with ethyl acetate (50 mL), washed with brine (30 mL), dried with Na₂SO₄, and concentrated. The residue was subjected to chromatography on silica gel eluted with ether/hexane (1:9) to give 17 (0.93 g, 91% as a mixture of stereoisomers; (Found 306.1142, C₇H₇Cl₂O₂, requires 306.1153); ν<sub>max</sub> (neat/cm<sup>-1</sup>) 1100; δ<sub>H</sub> (300 MHz, CDCl₃) 0.91 (s, 9 H), 1.49–1.96 (m, 1 H), 1.82–1.93 (m, 2 H), 2.03–2.11 (m, 3 H), 2.46–2.49 (m, 1 H), 3.46–3.72 (m, 4 H) and 3.88–3.95 (m, 4 H); m/z (FD) 310 (M<sup>+</sup> + 4, 14.4%), 308 (M<sup>+</sup> + 2, 66.2%) and 306 (M<sup>+</sup> 100%).

5-tert-Butyl-6,7-bis(methylthiocarbonylbicyclo[3.2.0]heptan-2-one (18). To a solution of 18 (358 mg, 1.17 mmol) in dry THF (50 mL) was added potassium tert-butoxide (392 mg, 3.5 mmol) and the mixture was stirred at room temperature under argon for 3 h and then evaporated. Water (100 mL) was added to the residue and the mixture was extracted with ether (3 × 70 mL). The extracts were combined, washed with brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 18 (260 mg, 95%) as a colorless oil; (Found 234.1608, C₇H₈O₂ requires 234.1620); ν<sub>max</sub> (neat/cm<sup>-1</sup>) 1098; δ<sub>H</sub> (300 MHz, CDCl₃) 0.94 (s, 9 H), 1.80–2.20 (m, 4 H), 2.77 (s, 1 H), 3.92–3.96 (m, 4 H), 4.81 (br s, 1 H), 4.84 (br s, 1 H), 5.23 (br s, 1 H) and 5.25 (br s, 1 H); m/z (FD) 234 (M<sup>+</sup> 100%).

5-tert-Butyl-6,7-benzobicyclo[3.2.0]heptan-2-one (19). To a solution of 18 (0.48 g, 2.1 mmol) and 1-ethylthiobenzyltrimethylsilane (0.37 g, 2.0 mmol) in benzene (5 mL) was refluxed for 5 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with water (50 mL), dried with Na₂SO₄, and concentrated. The residue was added DMSO (75 mL), water (75 mL), Na₂SO₄ (0.95 g, 5.4 mmol) and NaHCO₃ (1.0 g, 11.9 mmol) and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with water (100 mL) and extracted with ether (4 × 100 mL). The extracts were combined, washed successively with aqueous water (2 × 100 mL) and brine (100 mL), dried with Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:9) to give 19 (0.43 g, 83%); mp 167.5–168 °C (hexane); (Found 258.1612, C₇H₈O₂ requires 258.1620); ν<sub>max</sub> (KBr/cm<sup>-1</sup>) 1090; δ<sub>H</sub> (300 MHz, CDCl₃) 0.91 (s, 9 H), 1.58–1.70 (m, 2 H), 1.94–2.05 (m, 2 H), 3.33 (s, 1 H), 3.90–4.04 (m, 4 H), 7.03–7.06 (m, 1 H), 7.10–7.13 (m, 1 H) and 7.17–7.22 (m, 2 H); m/z (FD) 258 (M<sup>+</sup> 100%).

5-tert-Butyl-6,7-benzobicyclo[3.2.0]heptan-2-one (20). To a solution of 19 (400 mg, 1.55 mmol) in dichloromethane (12 mL) was added pyridinium tribromide (545 mg, 1.71 mmol) in one portion, and the mixture was stirred at room temperature for 40 h and then poured into a mixture of benzene (100 mL) and 10% aqueous Na₂SO₄ (50 mL). The organic layer was separated, washed with brine (50 mL), dried with Na₂SO₄, and concentrated. The residue was dissolved in dry THF (50 mL) was added potassium tert-butoxide (358 mg, 3.0 mmol) in dichloromethane (2 mL) was added to the mixture and the mixture was refluxed for 5 days, cooled to room temperature, and evaporated. Water (100 mL) was added to the residue and the mixture was extracted with chloroform (3 × 50 mL). The extracts were combined, washed with brine (100 mL), dried with Na₂SO₄, and concentrated.

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The residue was subjected to chromatography on silica gel eluted with ether/hexane (1:9) followed by preparative GPC (chloroform) to give 20 (236 mg, 61%) mp 162–164 °C (hexane); (Found 256.1474, C13H8O requires 256.1463; fmax (KBr)/cm−1 1152, 1072 and 1020; δH (300 MHz; CDCl3) 1.03 (s, 9 H), 3.70 (s, 1 H), 3.98–4.12 (m, 4 H), 5.49 (d, J = 4.2 Hz, 1 H), 6.38 (d, J = 4.2 Hz, 1 H) and 7.06–7.19 (m, 4 H); m/z (FD) 256 (M+1, 100%).

5-tert-Butyl-6,7-benzo[bicyclo[3.2.0]heptan-3-6-dien-2-one (21). To a solution of 20 (200 mg, 0.78 mmol) in THF (30 mL) was added 10% aqueous HCl (3 mL) and the mixture was heated at 50 °C for 15 h. The mixture was cooled to room temperature, diluted with chloroform (50 mL), washed successively with 10% aqueous NaHCO3 (30 mL) and brine (30 mL), dried with Na2SO4, and concentrated. The residue was chromatographed on silica gel eluted with ether/hexane (1:4) to give 21 (143 mg, 86%); mp 182–183 °C (hexane); (Found 212.1209, C13H10O requires 212.1201; fmax (KBr)/cm−1 1706; δH (300 MHz; CDCl3) 1.08 (s, 9 H), 3.97 (s, 1 H), 5.92 (d, J = 5.8 Hz, 1 H), 7.16–7.19 (m, 4 H), 7.83 (d, J = 5.8 Hz, 1 H); m/z (FD) 212 (M+, 100%).

1,4-Di-tert-butyl-6,7-benzo[bicyclo[3.2.0]heptan-3-6-dien-2-one (22). To a solution of 21 (100 mg, 0.47 mmol) in dry THF (5 mL) was added 1.6 M tert-butylithium in pentane (1.18 mL, 1.89 mmol) over 1 min at −78 °C. The mixture was stirred at the same temperature for 1 h, allowed to warm to room temperature, diluted with ether (70 mL), washed with brine (30 mL), dried with Na2SO4, and concentrated to give the crude alcohol as a brown oil (90 mg), which was diluted in 5 mL of dry dichloromethane and added to a suspension of PCC (100 mg, 0.46 mmol) and molecular sieves 4A (100 mg) in dichloromethane (2 mL). After 46 h at room temperature, ether (40 mL) was added and the mixture was filtered through a short pad of Florisil. The filtrate was washed with water (30 mL), dried with Na2SO4, and concentrated. The residue was subjected to chromatography on silica gel eluted with ether/hexane (1:4) followed by preparative GPC (chloroform) to give 22 (32 mg, 52%) as a viscous oil; (Found 268.1819, C13H8O requires 268.1827; fmax (neat)/cm−1 1702; δH (300 MHz; CDCl3) 1.03 (s, 9 H), 1.30 (s, 9 H), 4.65 (s, 1 H), 5.80 (s, 1 H), 7.16–7.19 (m, 3 H), 7.26–7.30 (m, 1 H); m/z (FD) 268 (M+1, 100%).

Measurement of the electronic absorption spectra of 5–7. A solution of precursor 12, 13 or 14 in EPA was placed in a Pyrex tube and degassed by freeze-thaw cycles. The sealed tube was immersed in liquid nitrogen in a Dewar having two parallel windows facing each other and the sample was irradiated through the window with a high pressure Hg lamp. When a solution of the precursor (3.2 × 10−4 M) in EPA was irradiated at −196 °C for 10 min, development of a new absorption assigned to 5–7 was observed. For 5: fmax 331 (sh), 353, 373, 394, 452, 473 (sh), 498 (sh) and 510 (sh) nm. For 6: fmax 331 (sh), 352 (sh), 371, 392, 445, 472 (sh), 496 (sh) and 507 (sh) nm. For 7: fmax 351, 369, 389, 453, 482 (sh), 503 (sh) and 517 (sh) nm. The absorption assigned to 5 remained unchanged for more than 10 h at −78 °C, but disappeared rapidly at 0 °C. The decay of the absorption followed second-order kinetics and the rate constant determined by monitoring the decay at 458 nm was 30 ± 6 M−1 s−1 in EPA at 0 °C. The molar absorptivity of 5–7 at 458 nm in EPA was estimated to be 2500 ± 500. Similarly, the rate constants for the dimerization of 6 and 7 in EPA at 0 °C were determined to be 166 ± 33 M−1 s−1 and 60 ± 12 M−1 s−1, respectively.

Attempted photochemical generation of 8 from 22. A degassed EPA solution of 22 (3.0 × 10−4 M) in a Pyrex tube was irradiated with a high pressure Hg lamp at −196 °C and the reaction was monitored by UV-vis spectroscopy. In contrast to the photolysis of 12–14 described above, development of no absorption extending to long-wavelength region characteristic of the 3,4-benzotrope system was observed, even after irradiation for 150 min. TLC analysis of the photolysole showed complete consumption of 22 together with the formation of two products. However, preparative scale photolysis of 22 (16 mg, 0.06 mmol) in EPA (50 mL) at 12 °C resulted in the formation of a complex mixture. Similar medium dependent photochemical behavior has been reported65 for parent 2.

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References