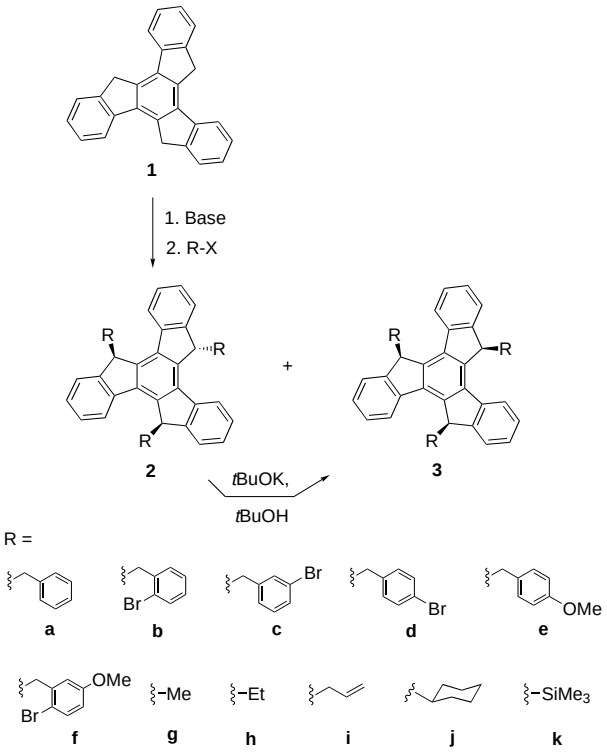
syn-Trialkylated Truxenes: Building Blocks That Self-Associate by Arene Stacking**

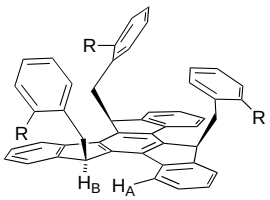
Óscar de Frutos, Berta Gómez-Lor, Thierry Granier, M. Ángeles Monge, Enrique Gutiérrez-Puebla, and Antonio M. Echavarren*

The development of a practical synthesis of bowl-shaped fragments of fullerenes[1] would allow the construction of molecular cages with polycyclic aromatic walls which could encapsulate metal cations or small molecules.[2] Truxene (**1**)[3] could be used as a starting material for the synthesis of C_3 tripods by *syn* trialkylation.[4] However alkylation of the red sodium trianion of **1** gave exclusively *anti* derivatives **2**.[3a] We have now found that, contrary to intuition, *anti*-**2** could be isomerized to the more stable *syn*-trialkylated truxenes **3**, some of which self-associate tightly in solution.



Deprotonation of **1** with NaH (3.1 equiv, DMF, sonication, 4 °C, 45 min) followed by reaction with *o*-bromobenzyl bromide (3.5 equiv, 10 min) led exclusively to *anti* derivative **2b** (60–66 %). However, reaction of **1** with KH (3.1 equiv, THF, sonication, 4 °C, 15–30 min) or *n*BuLi (3.1 equiv, THF, −78 to −10 °C, 4 h) led to red solutions of the corresponding trianions, which reacted with a variety of alkyl halides to give 1:1 to 3:1 mixtures of *anti*- and *syn*-trialkylated derivatives from which the more insoluble *syn* derivatives **3** could be isolated by trituration with EtOAc (14–32 % yields). Notably, derivatives **2** could be almost quantitatively converted into **3** by heating with *t*BuOK (1 equiv, *t*BuOH, reflux, 12 h).[5] Therefore, routine alkylation of **1** (*n*BuLi deprotonation) followed by base-catalyzed isomerization of the crude mixture of trialkylated products gave **3** in 59–79 % yields.[6]

Functionalized truxenes **3** were easily obtained from the alkylated derivatives without significant isomerization to the *anti* isomers. Thus, Stille coupling of **3b** with vinyltributylstannane afforded **3l** (72 %),[7] which was converted into the trialdehyde **3m** (98 %) by ozonolysis followed by treatment with PPh_3. On the other hand, palladium-catalyzed coupling of **3b** with (trimethylsilylethynyl)tributylstannane[8] gave trialkyne **3n** (55 %), which afforded **3o** (80 %) after treatment with K_2CO_3 in MeOH/THF.



3l : R = -CH=CH$_2$
3m : R = -CHO
3n : R = -C≡C-SiMe$_3$
3o : R = -C≡C-H

The structure of **3b** was confirmed by single-crystal X-ray diffraction.[9] After refinement in the triclinic cell (223 K), two enantiomers with different conformations are found in the unit cell (Figure 1). Both molecules show the benzyl groups approximately perpendicular to a slightly curved truxene skeleton. Molecules of **3b** pack in the crystal with a staggered face-to-face arrangement of their truxene moieties (distance between the faces 3.69–3.71 Å).[10]

Truxenes **3** showed NMR data consistent with C_3 symmetry. Interestingly, the ^{1}H NMR chemical shifts in $CDCl_3$ were dependent on the concentration. The highest variations were observed for H_A and H_B, which moved upfield as the concentration increased (Figure 2). This suggested that truxenes **3** self-associate in this solvent.[11] Assuming that the predominant association is due to a momomer–dimer equilibrium, the K_{assoc} values in Table 1 were determined. The highest K_{assoc} values were obtained for tribenzyltruxenes, while **3g–k** associate weakly. In fact, to the best of our knowledge, **3c** shows the highest K_{assoc} value determined for a self-association in solution which does not involve hydrogen bonds.[11, 12] A van't Hoff analysis of K_{assoc} ($CDCl_3$) as a function of the temperature carried out on **3a** afforded $\Delta H = -5.9 \pm 0.2$ kcal mol^{-1} and $\Delta S = -8.4 \pm 0.9$ cal mol^{-1} K^{-1}, which indicates that the association is an enthalpically driven process.[8] In contrast, no association was observed for the *anti* isomers **2** in $CDCl_3$.

[*] Prof. Dr. A. M. Echavarren, Ó. de Frutos, Dr. B. Gómez-Lor, Dr. T. Granier
Departamento de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco, E-28049 Madrid (Spain)
Fax: (+34) 9-1-3973966
E-mail: anton.echavarren@uam.es
Dr. B. Gómez-Lor, Dr. M. A. Monge, Dr. E. Gutiérrez-Puebla
Instituto de Ciencia de Materiales de Madrid, CSIC
Cantoblanco, E-28049 Madrid (Spain).

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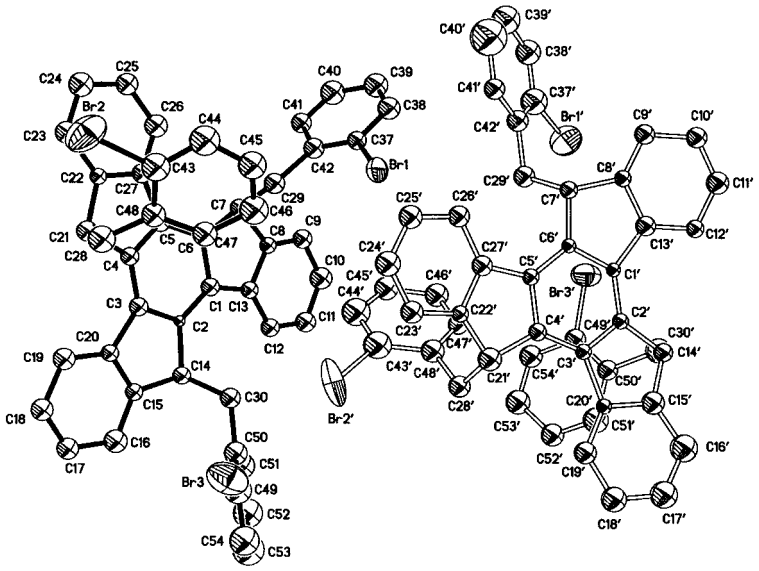


Figure 1. ORTEP diagram of the two independent conformers of **3b**.

Table 1. Association constants of truxenes **3a–i**, **3k**, **3m**, and **3n**.

Truxene	K_{assoc} [M^{-1}][a]	Truxene	K_{assoc} [M^{-1}][a]
3a	270	**3g**	9
3b	100	**3h**	8
3c	580	**3i**	10
3d	390	**3k**	2
3e	200	**3m**	180
3f	62	**3n**	200

[a] The constants were measured in $CDCl_3$ at 25 °C.

Alkylation of **1** with tribenzyl bromide **4**[13] gave truxenephane **5** (66 %) yield.[14, 15] X-ray diffraction shows that the distance between the centroids of the almost planar truxene (C1 to C6) and the parallel benzene ring (C31 to C36) is 3.36 Å (Figure 3a). Cyclophane **5** shows similar packing to that of **3b**; the truxene portions exhibit a distance between

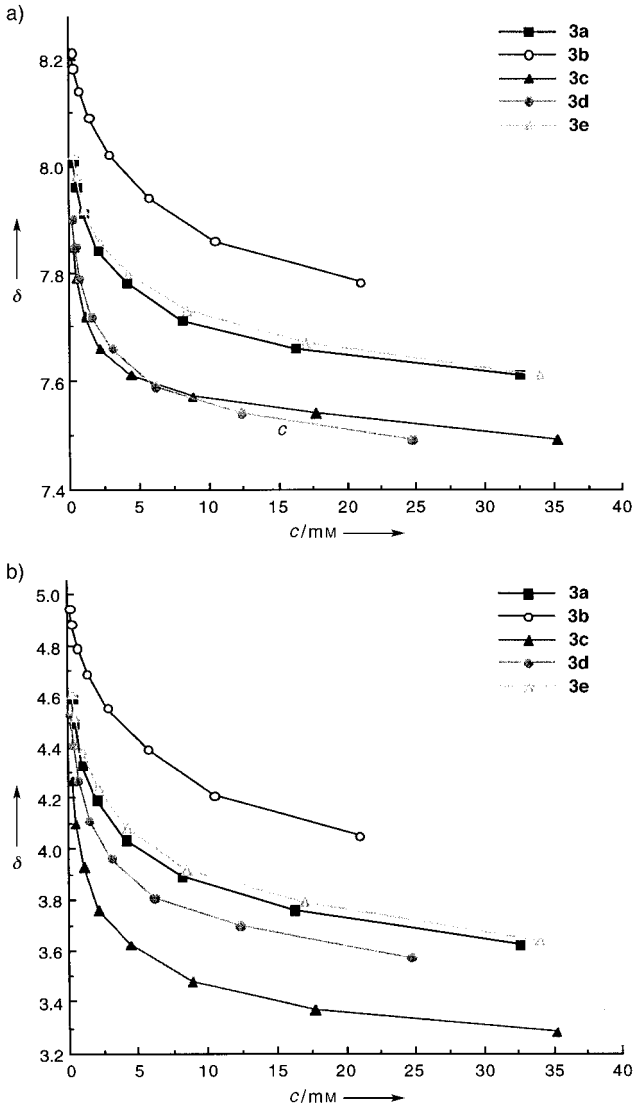
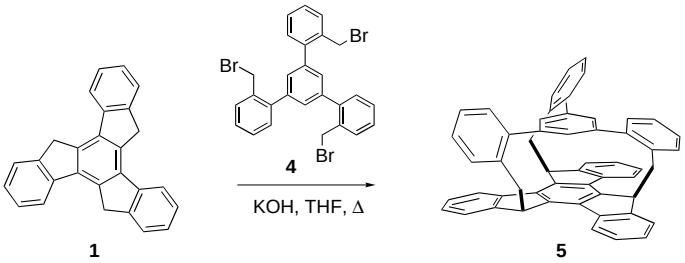


Figure 2. Chemical shifts H_A (a) and H_B (b) as a function of concentration for selected truxenes **3** ($CDCl_3$, 24 °C; see structures **3l–3o** for hydrogen labeling).



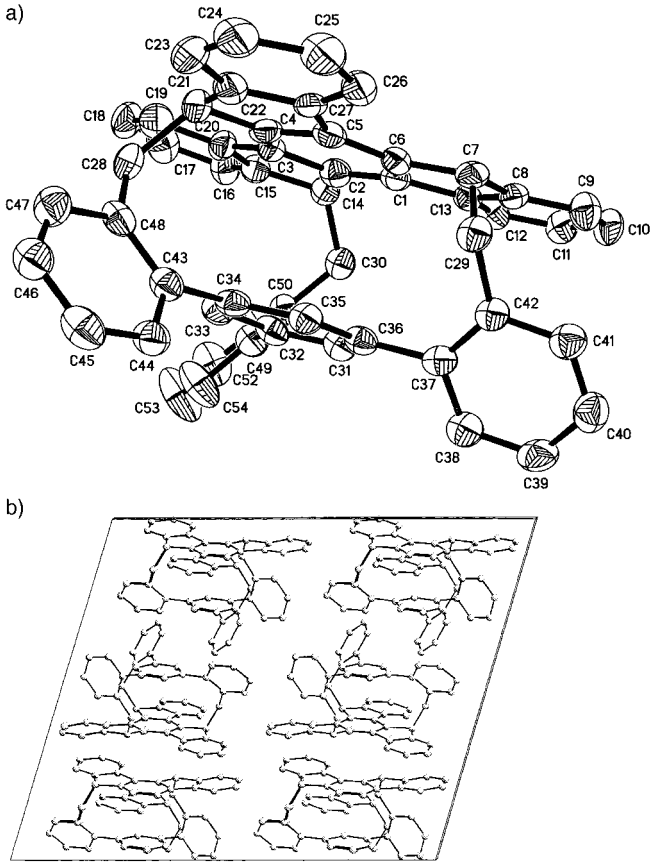


Figure 3. a) ORTEP diagram of **5**; b) crystallographic packing of **5**.

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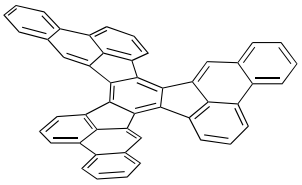
their centroids (atoms C1 to C6) of 3.70 Å (Figure 3b). Interestingly, the ^{1}H NMR spectrum of **5** in $CDCl_3$ does not change with concentration ($0.6-35\times10^{-3}$ M), which indicates that the association observed for **3** in solution is not a result of a truxene/truxene interaction. On the other hand, the significant shift observed for H_A and H_B (Figure 2) and the higher associations obtained for the benzyl derivatives suggest that the association in solution maximizes the aromatic interactions[10, 11, 16] between the truxene portion of one molecule and the concave cavity of a second molecule.

The tris(*ortho*-bromobenzyl) derivatives **2b** and **3b** could be used for the synthesis of C_{48} hydrocarbon **6** by using the palladium-catalyzed intramolecular arylation reaction that we have used before for the preparation of benz[*e*]acephenanthrylenes and related polycyclic aromatic hydrocarbons.[17] Interestingly, by using $Pd(OAc)_2$ as the catalyst *syn*-**3b** cyclized more readily (DMF, 130 °C, 24 h) than its isomer **2b** (DMF or DMA, 36 h, 150–165 °C) to give **6** in good yields (71–79 %).



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In summary, a variety of *syn*-trialkylated truxenes **3** can be readily synthesized in gram amounts from **1**. Some of these aromatic derivatives self-associate strongly in solution. A more extensive study of the arene stacking in these systems is in progress.[18] Syntheses of higher analogues of **6** as well as efforts directed towards the preparation of large cyclophanes by dimerization of functionalyzed derivatives of **3b** (i.e., **3o**) and **3c** are underway.

Experimental Section

General procedure for the synthesis of *syn*-trialkylated truxenes **3**: To a mixture of **1** (1.5 mmol) in THF (50 mL) at −78 °C was added *n*BuLi (3.1 equiv) and the mixture was slowly allowed to warm up to −10 °C (4 h). The resulting red solution was treated with the electrophile (3.5 equiv) in THF (10 mL). After 30 min the mixture was diluted with EtOAc and washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated. The residue was triturated with hexanes to yield a mixture of *anti*- and *syn*-trialkylated truxenes (3:1) as a pale yellow solid. The solid was heated under refluxing conditions with *t*BuOK (1 equiv) in *t*BuOH (30 mL) for 12 h. After being cooled, the mixture was partially evaporated, filtered, and the filtrate was evaporated. The residue was triturated with hexanes to give **3**. Further recrystallization from EtOH or toluene yielded pure compounds.

Truxenephane **5**: To a solution of **1** (137 mg, 0.4 mmol) in THF (80 mL) under refluxing conditions was added KOH (224 mg, 4 mmol). After being heated for 30 min, **4** (240 mg, 0.408 mmol) was added, and the mixture was heated for 2 h under refluxing conditions. After standard extractive workup, the residue was chromatographed (1:1 hexane/EtOAc) to give **5** (180 mg, 66 %) as a white solid, which was recrystallized from EtOH or MeCN: M.p. > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 7.8$ Hz, 3H), 7.42 (d, $J = 7.1$ Hz, 3H), 7.34 (d, $J = 7.8$ Hz, 3H), 7.27–7.24 (m, 3H), 7.12–7.08 (m, 6H), 6.95 (dt, $J = 7.5$, 1.3 Hz, 3H), 6.88 (s, 1H), 6.70 (dt, $J = 7.6$, 1.2 Hz, 3H), 5.05 (d, $J = 14.1$ Hz, 3H), 4.70 (d, $J = 10.5$ Hz, 3H), 3.74 (dd, $J = 14.2$, 10.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 146.60$, 142.92, 142.16, 141.50, 140.90, 137.34, 136.73, 134.41, 131.31, 128.73, 127.14, 126.88, 126.86, 126.69, 125.80, 122.34, 46.30, 33.87 (one C signal was not observed); EI-MS: *m*/*z* (%): 684 (53) [M^+], 341 (100), 253 (10); elemental analysis calcd for $C_{54}H_{38}\cdot0.5$ EtOH (%): C 93.31, H 5.55; found C 93.41, H 5.47.

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[1] a) L. T. Scott, *Pure Appl. Chem.* **1996**, *68*, 291; b) P. W. Rabideau, A. Sygula, *Acc. Chem. Res.* **1996**, *29*, 235; c) Y. Rubin, *Chem. Eur. J.* **1997**, *3*, 1009.

[2] Lead references on molecular capsules: a) J. M. Rivera, T. Martín, J. Rebek, *Science* **1998**, *279*, 1021; b) F.-Q. Liu, G. Harder, T. D. Tilley, *J. Am. Chem. Soc.* **1998**, *120*, 3271; c) E. V. Piatnitski, K. D. Deshayes, *Angew. Chem.* **1998**, *110*, 1022; *Angew. Chem. Int. Ed.* **1998**, *37*, 970; c) P. J. Stang, *Chem. Eur.* J. **1998**, *4*, 19; d) J. Yoo, D. J. Cram, *J. Am. Chem. Soc.* **1997**, 119, 11796.

[3] a) E. V. Dehmlow, T. Kelle, *Synth. Commun.* **1997**, *27*, 2021; b) R. Seka, W. Kellermann, *Chem. Ber.* **1942**, *75*, 1730; c) F. S. Kipping, *J. Chem. Soc.* **1894**, *65*, 272; d) J. Hausmann, *Chem. Ber.* **1889**, *22*, 2022.

[4] Review on C_3-symmetrical receptors: C. Moberg, *Angew. Chem.* **1998**, *110*, 260; *Angew. Chem. Int. Ed.* **1998**, *37*, 249.

[5] a) Semiempirical calculations (PM3 Hamiltonian,[5b] CS MOPAC Pro version) show that *syn*-trialkylated truxenes are more stable than the *anti* isomers ($\Delta\Delta H = 0.3$ (R = Me), 0.5 (R = cyclohexyl), 4.1 (R = *t*Bu) kcal mol^{-1}); b) J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209. c) Attractive van der Waals interaction between the side chains may be responsible, at least in part, for the higher stability of the *syn*-trialkylated truxenes. For a discussion of this effect on the conformational equilibrium of 1,3,5-trialkylbenzenes: J. E. Anderson, V. Bru-Capdeville, P. A. Kirsch, J. S. Lomas, *J. Chem. Soc. Chem. Commun.* **1994**, 1077, and references therein.

[6] *syn*-Truxenes **3f**, **3j**, and **3k** were obtained directly from **1** (*n*BuLi deprotonation) (30, 33, and 43 % yields, respectively). Alkylation of **1** with *p*-bromobenzyl bromide gave predominantly **2d** (68 %) which was isomerized with base to **3d** (61 % overall yield). For **2e**, best results were obtained by using KH as the base.

[7] D. R. McKean, G. Parrinello, A. F. Renaldo, J. K. Stille, *J. Org. Chem.* **1987**, *52*, 422.

[8] B. Gómez-Lor, A. M. Echavarren, A. Santos, *Tetrahedron Lett.* **1997**, *38*, 5347.

[9] Crystal data for **3b**·0.5 MeCN: crystal dimensions $0.04\times0.12\times0.16$ mm^3, triclinic, space group $P\bar{1}$, $a = 14.984(2)$, $b = 15.435(2)$, $c = 18.020(2)$ Å, $\alpha = 80.914(3)$, $\beta = 74.251(3)$, $\gamma = 66.706(2)°$, $V = 3678.2(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.545$ g cm^{-3}. Crystal data for **5**·0.5H_2O: crystal dimensions $0.10\times0.10\times0.20$ mm^3, triclinic, space group $P\bar{1}$, $a = 11.037(1)$, $b = 13.154(1)$, $c = 15.440(1)$ Å, $\alpha = 67.227(2)$, $\beta = 69.677(2)$, $\gamma = 65.345(2)°$, $V = 1831.7(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.279$ g cm^{-3}. Equipment: CCD Siemens diffractometer (sealed tube, 2.4 kW), $\lambda(Mo_{K\alpha}) = 0.71073$ Å. Data collections were performed at 223 K. Hemispheres of 8896 and 7535 data were collected at 223 K by 0.3ω scans over 2θ ranges of 2.45–34.5° and 2.25–42.0° for **3b** and **5**, respectively; an empirical absorption correction from ϕ scans was applied to the data of **3b** ($\mu = 3.32$ mm^{-1}). Structural solutions by direct methods and least-squares refinements (based on F^2) were performed with SHELXTL (version 5.1994). Due to the instability and the poor diffraction spectrum of **3b**, the structure has been refined only isotropically (442 parameters/0 restraints); 3406 merged reflections converged at $R_1(F) = 0.13$, $\omega R_2(F^2) = 0.24$ for all data; $R_1(F) = 0.092$, $\omega R_2(F^2) = 0.21$ for observed data ($I > 2\sigma(I)$) GOF(F^2) = 1.013. Compound **5** was refined anisotropically (510 parameters/0 restraints); 3219 merged reflections converged at $R_1(F) = 0.094$, $\omega R_2(F^2) = 0.18$ for all data; $R_1(F) = 0.082$, $\omega R_2(F^2) = 0.18$ for observed data ($I > 2\sigma(I)$), GOF(F^2) = 1.120. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-101806 and CCDC-101807. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[10] Stacking of aromatic rings: G. V. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.* **1998**, *120*, 3641, and references therein.
[11] a) A. S. Shetty, J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019; b) Y. Tobe, N. Utsumi, A. Nagano, K. Naemura, *Angew. Chem.* **1998**, *110*, 1347; *Angew. Chem. Int. Ed.* **1998**, *37*, 1285.
[12] For the self-association of porphyrins: R. J. Abraham, S. C. M. Fell, H. Pearson, K. M. Smith, *Tetrahedron* **1979**, *35*, 1759.
[13] a) Prepared by coupling of 1,3,5-tribromobenzene with *o*-tolylboronic acid followed by benzyl bromination[13b] of 1,3,5-tris(2-methylphenyl)benzene; b) M. J. Plater, M. Praveen, *Tetrahedron Lett.* **1997**, *38*, 1081.
[14] G. J. Bodwell, *Angew. Chem.* **1996**, *108*, 2221; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2085.
[15] The FAB mass spectra show complexation of cyclophane **5** with Ag^+ (*m*/*z* 791) and $Ag_2(OSO_2CF_3)^+$ (*m*/*z* 1049). For the silver ion extraction with cyclophanes: J. Gross, G. Harder, F. Vögtle, H. Stephan, K. Gloe, K. *Angew. Chem.* **1995**, *107*, 533; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 481.
[16] C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525.
[17] J. J. González, N. García, B. Gómez-Lor, A. M. Echavarren, *J. Org. Chem.* **1997**, *62*, 1286.
[18] Liquid crystals based on truxenes: D. Sandström, M. Nygren, H. Zimmermann and A. Maliniak, *J. Phys. Chem*. **1995**, *99*, 6661, and references therein.

Reactivity of Peroxo- and Bis(μ-oxo)dicopper Complexes with Catechols**

Lisa M. Berreau, Samiran Mahapatra, Jason A. Halfen, Robert P. Houser, Victor G. Young, Jr., and William B. Tolman*

The aerobic oxidation of catechols to *o*-quinones mediated by copper ions is an important catalytic process in both synthetic and metalloprotein systems. Catechol oxidase[1] and tyrosinase,[2] both of which cycle through a (μ-η^2:η^2-peroxo)-dicopper active site intermediate, are capable of such catecholase activity, notwithstanding some controversy surrounding the involvement of discrete catechol intermediates in phenol oxidation by tyrosinase and model systems.[3] Many mechanistic studies of catalytic catechol oxidation by dissolved copper complexes have appeared, with copper–dioxygen species often postulated as being responsible for formation of quinone and H_2O_2 in the key reaction step [Eq. (1)].[4]

$$Cu^{II}(O_2^{2-})Cu^{II} + \text{catechol} \longrightarrow o\text{-quinone} + 2\,Cu^{I} + H_2O_2 \qquad (1)$$

[*] Prof. W. B. Tolman, Dr. L. M. Berreau, Dr. S. Mahapatra, J. A. Halfen, R. P. Houser, Dr. V. G. Young, Jr.
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota
207 Pleasant Street S.E., Minneapolis, MN 55455 (USA)
Fax: (+1) 612-624-7029
E-mail: tolman@chem.umn.edu

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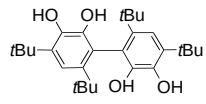
We have directly evaluated the feasibility of this transformation by examining the reaction of catechols with isolated (μ-η^2:η^2-peroxo)- and bis(μ-oxo)dicopper complexes[5] relevant to the tyrosinase and catechol oxidase active site species. In the only other reported study of this type,[6] a tris(pyrazolyl)hydroborate-capped (μ-η^2:η^2-peroxo)dicopper compound converted 3,5-di-*tert*-butylcatechol (dbcat) to the coupled product **1** under argon and to a mixture of **1** and the quinone **2** catalytically under O_2. Herein we report that instead of promoting these conversions or the reaction shown in Equation (1), complexes with isomeric $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O)_2]^{2+}$ and $[Cu_2(\mu\text{-}O)_2]^{2+}$ cores coordinated to amine macrocycles cleanly oxidize two equivalents of catechol to yield monocopper-semiquinone complexes by a heretofore unreported synthetic route to such species (Scheme 1).



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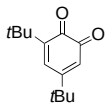

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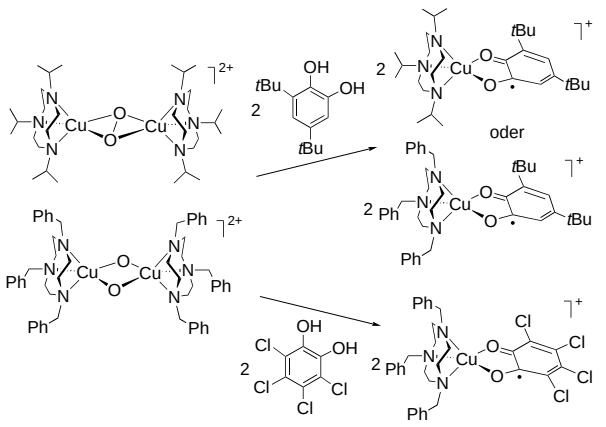
Addition of two equivalents of dbcat to solutions[7] of orange $[\{Cu(L^{Bn_3})\}_2(\mu\text{-}O)_2](SbF_6)_2$ or red-brown $[\{Cu(L^{iPr_3})\}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)](O_3SCF_3)_2$ in CH_2Cl_2 or THF at $-80\,^\circ C$ caused bleaching of their respective optical absorption features (L^{R_3} = *N*,*N*,*N*-trisubstituted 1,4,7-triazacyclononane). Upon subsequent warming and work-up, the deep green-brown complexes [Cu(L)(dbsq)]X (dbsq = 3,5-di-*tert*-butylsemiquinonato; $L = L^{Bn_3}$, $X = SbF_6$; $L = L^{iPr_3}$, $X = O_3SCF_3$) were isolated as crystalline solids in 93% and 81% yields, respectively. The complex $[Cu(L^{Bn_3})(Cl_4sq)]ClO_4$ (Cl_4sq = 3,4,5,6-tetrachlorosemiquinonato) was prepared analogously (90% yield of isolated product) from the ClO_4^- salt of the bis(μ-oxo)dicopper precursor and 3,4,5,6-tetrachlorocatechol monohydrate ($Cl_4cat \cdot H_2O$). When <2.0 equivalents of dbcat were added to the bis(μ-oxo) compound, $[Cu(L^{Bn_3})(dbsq)]^+$ was generated in the corresponding substoichiometric amount and **1** or **2** were not produced (monitored by ^1H NMR spectroscopy).[8]

The reaction products were identified as Cu^{II}–semiquinonato species on the basis of spectroscopic comparisons to previously reported examples,[9] electrochemical properties, and X-ray crystallography. Notable diagnostic spectral features for the dbsq and Cl_4sq complexes include rich UV/Vis



Scheme 1. Oxidation of catechol to monocopper semiquinone complexes.

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