Synthesis, Structure, and Reactivity of Enediyne Macrocycles

Burkhard König* and Wolfgang Pitsch

Institut für Organische Chemie der Technischen Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

Iris Thondorf

Institut für Biochemie der Martin-Luther-Universität Halle, D-06099 Halle, Germany

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The reaction of bis-propargyl bromide enediyne **4** with weakly basic nucleophiles allows the facile synthesis of acyclic and macrocyclic enediynes. Depending on the bis-nucleophile employed, 12- to 16-membered enediyne macrocycles were obtained. The thermal stability of the new cyclic enediynes was investigated by differential scanning calorimetry. Upon coordination of the macrocycle **5c** with $Hg(O_2CCF_3)_2$, a drop of the enediyne cyclization temperature of nearly 100 K was observed.

Aromatic diradicals have been identified as the active species in several natural products with antitumor activity. Here, the cytotoxic action is explained as being caused by hydrogen abstraction from DNA by the radical, leading to strand cleavage and cell death.[1] The reactive intermediates are formed by the cyclization of enediynes or ene-yne-allenes to arene diradicals. Pharmaceutical applications of these highly cytotoxic compounds depend on a selective trigger for radical formation. Several approaches have been taken to generate such a trigger mechanism in the enediyne prodrug, including bioreduction and activation by light, bases, metal ions, or nucleophiles.[2] Throughout, the activation on the molecular level is caused by the increased strain of the unsaturated cycle or the lowered energy of the cyclization transition state.[3] We describe here a new synthetic route to functionalized macrocyclic enediynes and the modulation of their chemical reactivity by metal ion coordination.[4]

Results and Discussion

We have developed compound **4**[5] as a versatile building block in the synthesis of functionalized acyclic and cyclic enediynes *via* nucleophilic displacement of the bromine substituents. The basicity of the nucleophile is important in this process. Strong bases induce the formation of unstable ene-yne-allenes by propargyl−allene tautomerization,[6] whereas carboxylates, phenolates, electron-rich pyridines, and malonates[5] yield the desired bis-substitution products **5**. The *cis*-preorganization of **4** favors the formation of cyclic compounds with suitable bis-nucleophiles. High dilution conditions are therefore not necessary to obtain the cyclic enediynes **5a**−**e** with ring sizes from 12 to 16 atoms. Palladium-catalyzed coupling[7] of *cis*-1,2-dichloroethene (**1**) with **2**, followed by OTHP/bromine[8] exchange with PPh_3/Br_2, provides **4** in multigram quantities.

The thermal stability of the new cyclic enediynes was investigated by differential scanning calorimetry (DSC),[9] clearly indicating an exothermic, irreversible reaction at elevated temperatures (see Table 1). The 2,2′-bipyridine moiety of **5c** is an excellent ligand for transition metal ions[10] and allows the conformation of the macrocycle to be altered by complexation.[11] Without metal ion coordination, a less strained *transoid* orientation of the 2,2′-bipyridine (biaryl torsion angle $\theta = 63.1°$) should be favored according to force field calculations.[12] On addition of $Hg(O_2CCF_3)_2$ to a suspension of **5c** in methanol, a clear solution is formed instantaneously and a significant change in the ^{1}H-NMR spectra indicates metal ion coordination. The preserved symmetry of the compound suggests that both nitrogens coordinate symmetrically.

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Scheme 1

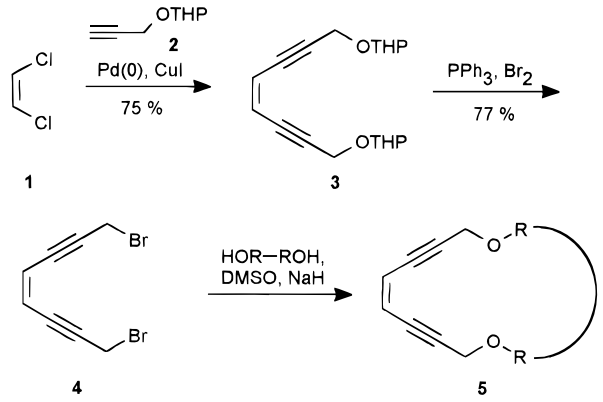
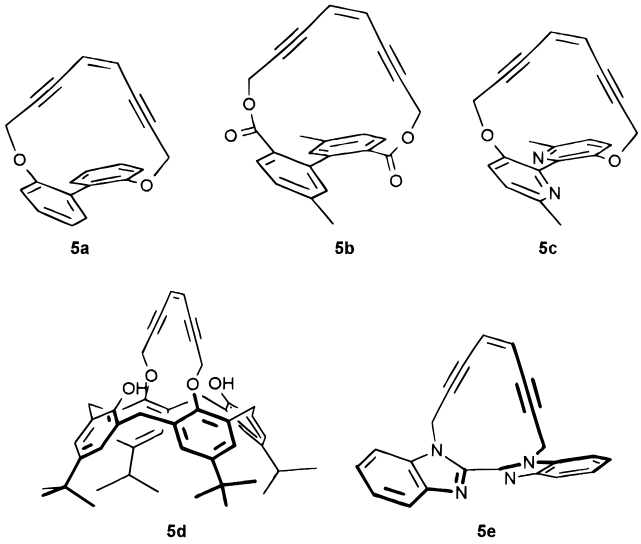


Table 1. Synthesis of Acyclic and Macrocyclic Enediynes by the Reaction of 4 with Nucleophiles



entry	H-OR—RO-H	yield of **5** (%)	cyclization temp[a]
a	2,2′-dihydroxybiphenyl	35	162
b	2,2′-biphenyl-dicarboxylic acid	45	172
c	3,3′-dihydroxy-6,6′-dimethyl-2,2′-bipyridine	54	237
d	1,3-*p*-*tert*-butylcalix[4]arene[b]	55	>260
e	bis(benzimidazole)[c]	13	207

[a] Measured by differential scanning calorimetry. [b] K_2CO_3 as base. [c] bis(benzimidazole) with 30% 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline as byproduct was used. The cyclic alkylation product of 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline and **4** was isolated in 15% yield. See supporting information for details.

However, the metal ion must induce a change in the conformation of the 2,2′-bipyridine unit to a predominantly *cisoid* orientation for complex formation. The comparison of the difference in calculated strain energies ΔSE[12] (see Table 2) for both conformations predicts an increase in reactivity on complexation. For the calculations the hydrogen-trapped cyclization product was used as a surrogate of the transition state. The 2,2′-bipyridine macrocycle **5c** shows an exothermic reaction at approximately 237 °C[13] as measured by DSC, whereas the stabilization of the energetically higher ground state in

(13) The thermally induced cyclization and radical polymerization of the material are superimposed. However, if **5c·Hg(O$_2$CCF$_3$)** was heated in decalin or ethylene glycol the hydrogen trapped product of the Bergman cyclization **6** could be identified by NMR, high resolution mass spectra, and TLC. The compound was synthesized independently for comparison from 3,3′-dihydroxy-6,6′-dimethyl-2,2′-bipyridine and α,α′-dibromo-*o*-xylylene. See supporting information for details.

Scheme 2

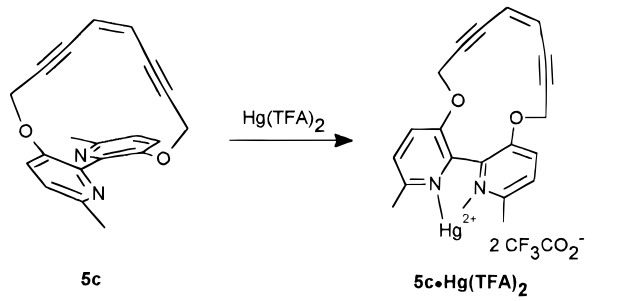


Table 2. Calculated Steric Energies[a] of 5c and 5d

	conformation	FSE[a] enediyne	FSE[a] cyclization product	ΔSE[b]
5c	$\theta = 63.1°$ [c,d]	39.1	50.5	11.4
	θ[d] constrained to 0°	53.9	50.5	−3.4
	θ[d] constrained to 20°	47.5	50.5	3.0
5d	cone[e]	27.5	50.1	22.6
	partial cone	40.6	52.8	12.2
	1,3-alternate	37.3	63.0	25.7

[a] All energies in kcal mol^{-1}; $E_{bond} = E_{compression} + E_{bend} + E_{bend-bend} + E_{stretch-bend} + E_{torsion} + E_{torsion-stretch}$; E_{vdW} denotes the sum of all van der Waals interactions; E_{elec} denotes the energy resulting from the electrostatic term, FSE denotes the final steric energy. [b] Difference in strain energy ΔSE = FSE (transition state) − FSE (ground state); FSE (hydrogen trapped cyclization product) is used for FSE (transition state) in this model. [c] No constraint was applied to the 2,2′-bipyridine torsion angle θ for calculation. [d] The torsion angle θ refers to the 2,2′-bipyridine nitrogen atoms: *trans* rotamer $\theta = 180°$; *cis* rotamer $\theta = 0°$. No energy minimum was observed while varying θ between 0° to 20° in small increments. [e] For the notation of calixarene conformations see ref 12d.

the coordination compound is reflected in a decrease of the cyclization temperature to 145 °C.[14] Without the suitable 2,2′-bipyridine binding site for a strong metal coordination, as in the case of **5a**, the cyclization temperature is not affected by $Hg(O_2CCF_3)_2$. Likewise, mixtures of **5b** and $Hg(O_2CCF_3)_2$ show the exothermic reaction in the DSC at the same temperature as pure **5b**.[15]

In contrast to the above results, a rigid molecular conformation can stabilize an enediyne moiety against thermally induced cyclization. No exothermic reaction is observed if compound **5d** is heated to 260 °C. Force field calculations suggest that among the three possible conformations,[12d] cone, partial cone, and 1,3-alternate, the cone conformation is energetically the most stable.[16] Unfavorable van der Waals contacts between enediyne and *tert*-butyl groups may account for the substantially higher energy of both the partial cone and the 1,3-alternate conformation. Furthermore, the calculations indicate that the cyclization product resulting from the cone conformation is characterized by an enormous steric strain.

The reaction of **4** with weakly basic bisnucleophiles provides a facile synthesis of acyclic and macrocyclic enediynes. The cyclization of the macrocycles **5a**−**e** is

(14) With the assumption of the same rate of reaction at the given cyclization temperatures, a 20% decrease in activation energy by the induced conformation change can be estimated.

(15) To investigate the possible influence of the morphology of the solids on their reactivity, DSCs were recorded from single crystals and powders of **5b**. The observed temperatures of the exothermic cyclization are identical.

(16) The simple NMR spectra of **5d** suggest either a single conformer of high symmetry or rapid interconversion between conformers at room temperature.

observed at elevated temperatures, whereby the reactivity of **5c** is significantly altered by metal ion coordination that changes its conformation. The use of even more strained bicyclic enediynes[17] might allow the development of compounds that can be triggered selectively by a chemical signal at room temperature.

Experimental Section

Melting points were taken on a hot-plate microscope apparatus and are not corrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in chloroform-d_3 solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quart}) for quarternary carbons. Compound **4** was prepared as previously described.[5]

General Procedure (GP) for the Reaction of 4 with Nucleophiles. A 262 mg (1 mmol) amount of **4** was dissolved in 2 mL of DMSO and added to a solution of 2 mmol of the nucleophile (see supporting information for details) or 1.0 mmol of the bis-nucleophile (entry **a**−**e**) and 4 mmol of KOH in 30 mL of DMSO at room temp. The reaction mixture was stirred for 6 h, poured into 100 mL saturated aqueous NH_4Cl and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*, and the products were purified by column chromatography (CC) on silica gel.

8,17-Dioxatricyclo[16.4.0.0^{2,7}]docosa-1(18),2(7),3,5,12,-19,21-heptaene-10,14-diyne (5a). **4** (262 mg, 1 mmol) was allowed to react with 2,2′-dihydroxybiphenyl (186 mg, 1 mmol) according to the *GP* and gave after CC (PE:CH_2Cl_2 1:1; R_f = 0.5) 100 mg (35%) of **5a** as a white solid: mp 160 °C dec.; ^{1}H-NMR δ 4.77 (d, ^2J = 16.0 Hz, 2 H), 4.88 (d, ^2J = 16.0 Hz, 2 H), 5.84 (s, 2 H), 6.92 (d, ^3J = 7.6 Hz, 2 H), 7.03 (dt, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 2 H), 7.22 (dd, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 2 H), 7.33 (m, 2 H); ^{13}C-NMR δ 56.4 (−), 85.0 (C_{quart}), 93.4 (C_{quart}), 111.3 (+), 121.0 (+), 121.1 (+), 128.5 (C_{quart}), 128.7 (+), 131.5 (+), 155.2 (C_{quart}); IR (KBr): ν 3064 cm^{-1}, 1592, 1442; UV/vis ($CHCl_3$) λ_{max} (log ϵ) = 202 nm (4.644), 280 (4.023); MS (70 eV) *m*/*z* (%) 286 (100) [M^+]; HRMS calcd for $C_{20}H_{14}O_2$ 286.099, found 286.099.

9,18-Dioxatricyclo[18.4.0.0^{2,7}]tetracosa-1(20),2(7),3,5,-13,21,23-heptaene-11,15-diyne-8,19-dione (5b). **4** (262 mg, 1 mmol) and 242 mg (1 mmol) of biphenyl-2,2′-dicarboxylic acid were allowed to react according to the *GP*. CC (CH_2Cl_2, R_f = 0.5) yielded 157 mg (46%) of **5b** as clear crystals: mp 170 dec; ^{1}H-NMR δ 4.70 (d, ^2J = 15.1 Hz, 2 H), 4.94 (d, ^2J = 15.1 Hz, 2 H), 5.77 (s, 2 H), 7.18 (dd, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 2 H), 7.44 (dt, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 2 H), 7.57 (dt, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 2 H), 8.16 (dd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 2 H); ^{13}C-NMR δ 52.2 (−), 83.0 (C_{quart}), 91.4 (C_{quart}), 119.2 (+), 127.2 (+), 128.0 (C_{quart}), 130.0 (+), 130.4 (+), 132.2 (+), 144.3 (C_{quart}); IR (KBr): ν 2957 cm^{-1}, 1721, 1133; UV/vis ($CHCl_3$) λ_{max} (log ϵ) = 202 nm (4.689), 278 (4.078); MS (70 eV) *m*/*z* (%) 342 (16) [M^+], 225 (100). Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 76.82; H, 4.04.

4,21-Dimethyl-8,17-dioxa-3,23-diazatricyclo[16.4.0.0^{2,7}]-docosa-1(18),2(7),3,5,12,19,21-heptaene-10,14-diyne (5c). Compound **4** (262 mg, 1 mmol) was allowed to react with 216 mg (1 mmol) of 6,6′-dimethyl-3,3′-dihydroxy-2,2′-bipyridine following the *GP* to give after CC (CH_2Cl_2:MeOH 20:1; R_f = 0.4) 171 mg (54%) of **5c**, as a white solid: mp 237 °C dec; ^{1}H-NMR (C_6D_6) δ 2.42 (s, 6 H), 4.18 and 4.19 (s, 4 H), 5.39 (s, 2 H), 6.50 (d, ^3J = 8.5 Hz, 2 H), 6.61 (d, ^3J = 8.5 Hz, 2 H); ^{13}C-NMR δ 23.6 (+), 56.5 (−), 85.4 (C_{quart}), 92.6 (C_{quart}), 119.5 (+), 121.2 (+), 123.4 (+), 147.3 (C_{quart}), 150.0 (C_{quart}), 150.6 (C_{quart}); ^{1}H-NMR (methanol-d_4) δ 2.50 (s, 6H), 4.82 and 5.00 (d, ^2J = 16.2 Hz, 4H), 5.94 (s, 2H), 7.31 (d, ^3J = 8.5 Hz), 7.46 (d, ^3J = 8.5 Hz); IR (KBr): ν 2956 cm^{-1}, 2218, 786; UV/vis ($CHCl_3$) λ_{max} (log ϵ) = 196 nm (4.771), 246 (4.239), 282 (4.429); MS (CI, NH_3, neg) *m*/*z* (%): 316 (100) [M^+]. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N 8.85. Found: C, 75.73; H, 5.27; N, 8.82.

4,21-Dimethyl-8,17-dioxa-3,23-diazatricyclo[16.4.0.0^{2,7}]-docosa-1(18),2(7),3,5,12,19,21-heptaene-10,14-diyne Mercury(II) Bis(trifluoroacetate) [5c·Hg(O_2CCF_3)$_2$]. Equimolar amounts (0.5 mmol) of **5c** and $Hg(O_2CCF_3)_2$ were mixed in 5 mL of acetonitrile under nitrogen, and the mixture was stirred for 5 h. The reaction mixture was poured into 50 mL of ether and the precipitate was collected by filtration, washed with ether, and dried *in vacuo*. The crude product was recrystallized from acetonitrile/ether and gave 220 mg (59%) **5c·Hg(O_2CCF_3)$_2$** as a yellow solid: mp 150 °C dec; ^{1}H-NMR (methanol-d_4) δ 2.74 (s, 6H), 5.05 (bs, 4H), 6.04 (s, 2H), 7.68 (d, ^3J = 8.7 Hz), 7.84 (d, ^3J = 8.7 Hz); ^{13}C-NMR δ 26.6 (+), 57.5 (−), 85.3 (C_{quart}), 91.5 (C_{quart}), 119.0 (+), 120.6 (+), 122.4 (+), 147.7 (C_{quart}), 150.4 (C_{quart}), 150.6 (C_{quart}); MS (ESI) *m*/*z* (%) 631.07 (15) [**5c·Hg(O_2CCF_3)**$^+$]. Anal. Calcd for $C_{24}H_{16}N_2O_6F_6Hg$: C, 38.80; H, 2.17; N, 3.77. Found: C, 38.50; H, 2.10; N, 3.43.

Thermal Cyclization of [5c·Hg(O_2CCF_3)$_2$]. A 250 mg amount (0.34 mmol) of **[5c·Hg(O_2CCF_3)$_2$]** was heated under N_2 in 80 mL of decalin to reflux for 1 h. The solvent was removed *in vacuo* and the residue chromatographed to yield 15 mg (14%) of **10,11-benzo-4,17-dimethyl-8,13-dioxa-3,18-diazatricyclo[12.4.0.0^{2,7}]octadeca-1(18),2,4,6,10,14,16-heptaene (6)**, as a white solid: mp 110 °C; ^{1}H-NMR δ 2.49 (s, 6 H), 5.19 (bs, 4 H), 7.02 (d, ^3J = 8.3 Hz), 7.29 (d, ^3J = 8.3 Hz), 7.31 (m, 4 H); ^{13}C-NMR δ 23.9 (+), 71.5 (−), 123.2 (+), 123.3 (+), 129.2 (+), 131.3 (+), 135.5 (C_{quart}), 147.4 (C_{quart}), 151.3 (C_{quart}), 152.4 (C_{quart}); HRMS calcd for $C_{20}H_{18}N_2O_2$ 318.136, found 318.136.

26,28-Dihydroxy-25,27-dioxaocta-4-ene-2,6-diynyl-*p*-*tert*-butylcalix[4]arene (5d). **4** (262 mg, 1 mol) was allowed to react with 648 mg (1 mmol) of *p*-*tert*-butylcalix[4]arene according to a modified *GP*, in which K_2CO_3 was used as base. CC (PE:CH_2Cl_2 1:3; R_f = 0.4) yielded 411 mg (55%) **5d** as a white solid: mp > 300 °C; ^{1}H-NMR δ 1.19 (bs, 36 H), 3.35 (d, ^2J = 12.7 Hz, 4 H), 4.39 (d, ^2J = 12.7 Hz, 4 H), 4.85 (s, 4 H), 5.99 (s, 2 H), 6.97 (s, 4 H), 7.09 (s, 4 H), 8.60 (s, 2 H); ^{13}C-NMR δ 31.2 (+), 31.5 (+), 32.5 (−), 33.8 (C_{quart}), 34.2 (C_{quart}), 63.3 (−), 84.9 (C_{quart}), 91.3 (C_{quart}), 118.9 (+), 125.3 (+), 126.0 (+), 127.6 (C_{quart}), 128.4 (C_{quart}), 134.3 (C_{quart}), 141.8 (C_{quart}), 148.1 (C_{quart}), 150.1 (C_{quart}); IR (KBr) ν 3390 cm^{-1}, 2960, 1484; UV/vis ($CHCl_3$) λ_{max} (log ϵ) = 200 nm (4.992), 270 (3.992); MS (70 eV) *m*/*z* (%) 748 (0.5) [M^+], 648 (100). Anal. Calcd for $C_{52}H_{60}O_4$: C, 83.37; H, 8.08. Found: C, 83.24; H, 8.10.

1,2:7,8-Dibenzo-3,6,15,18-tetraazatricyclo[13.3.0.0^{2,6}]-octadeca-1(18),2,4,10,16-pentaene-8,12-diyne (5e) and 11,12-Benzo-13,14-naphtho-1,10-diazabicyclo[8.2.2]-tetradeca-5,11,13-triene-3,7-diyne (5f).[18] Following the *GP*, 262 mg (1 mmol) of **4**, 234 mg (1 mmol) of bis(benzimidazole), containing 30% 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline, and 48 mg (2 mmol) of NaH were allowed to react. CC (CH_2Cl_2:MeOH 99:1) yielded two fractions: I 15 mg (15%) of **5f** (R_f = 0.9), as bright yellow crystals: ^{1}H-NMR δ 4.56 (d, ^2J = 18.4 Hz, 2 H), 5.53 (d, ^2J = 18.4 Hz, 2 H), 5.65 (s, 2 H), 6.92 (m, 2 H), 7.00 (m, 2 H), 7.37 (m, 2 H), 7.58 (m, 2 H); ^{13}C-NMR δ 42.4 (−), 82.4 (C_{quart}), 93.3 (C_{quart}), 119.3 (+), 120.5 (+), 124.3 (+), 126.3 (+), 127.0 (+), 135.2 (C_{quart}), 138.8 (C_{quart}), 147.7 (C_{quart}); IR (film, cm^{-1}) 1567; UV (CH_3CN, λ_{max} [log ϵ]) 192 (4.653), 228 (4.378), 418 (3.958); MS (70 eV) *m*/*z* (%) 334 (100) [M^+]; HRMS calcd for $C_{22}H_{14}N_4$ 334.121, found 334.121.

II 30 mg (13%) **(5e)** (R_f = 0.2), as yellow crystals from $CHCl_3$: mp 207 °C dec; ^{1}H-NMR δ 4.99 (d, ^2J = 18.2 Hz, 2 H), 5.53 (s, 2 H), 6.22 (d, ^2J = 18.2 Hz, 2 H), 7.41 (m, 4 H), 7.50 (m, 2 H), 7.90 (m, 2 H); ^{13}C-NMR δ 35.3 (−), 83.2 (C_{quart}), 92.2 (C_{quart}), 110.1 (+), 120.8 (+), 121.0 (+), 123.4 (+), 124.6 (+), 135.2 (C_{quart}), 143.3 (C_{quart}), 143.8 (C_{quart}); IR (film, cm^{-1}) 1429; UV (CH_3CN, λ_{max} [log ϵ]) 192 (4.752), 284 (4.276), 314 (4.341); MS (70 eV): *m*/*z* (%): 334 (94) [M^+], 333 (100); HRMS calcd for $C_{22}H_{14}N_4$ 334.121, found 334.121.

(17) The reactivity of highly strained [7.3.1]enediynes is very sensitive to small conformational changes; ref 1b.

(18) Compounds **5e** and **5f** have been characterized by X-ray structure analysis: Jones, P. G.; Dix, I. Unpublished results.

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Supporting Information Available: ^{13}C-NMR spectra of compounds **5a**, **5e**, **5f**, **5h**, and **5k**, ^{1}H- and ^{13}C-NMR spectra of **5c** and **6**, preparation of **6** and **5g**−**l**, electrospray MS of **[5c·Hg(O$_2$CCF$_3$)$_2$]**, DSC analysis of **5c** and **[5c·Hg(O$_2$CCF$_3$)$_2$]**, force field (MM3) minimized structures of **5c**, **6**, and **5d** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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