

molecule. Compounds **4a** and **4b** illustrate the differences in conformation of the complexed and free forms of a single ligand.

With respect to the section of polyether from O3 to O5, the conformation of **3** corresponds to that of **4b**, as would be expected for optimum electrostatic interactions. Alleviation of disadvantageous electrostatic interactions by the presence of a hydrogen bond allows the polyether chains of **1** and **2** to assume the conformation found in **4a**. In each example, the distance from O4 to the adjacent oxygen atoms (O3 and O5) is quite similar, on the order of 2.8 Å. The O3 to O5 separations, however, vary significantly (**1**, 5.010 Å; **2**, 5.022 Å; **4a**, 4.84 Å vs. **3**, 4.258 Å; **4b**, 4.534 Å), as do the torsion angles  $\theta_4$  and especially  $\theta_6$  (vide Table I).

The ability of these ethereal compounds to encircle a water molecule depends on both the conformation of the polyether chain and on the inherent structural spacing produced by the heteroaromatic moiety in the macrocycle. This combination of conformation and spacing in **1** and **2** creates a distinct cavity in the central portion of the host and apparently provides sufficient space in the extreme ether portion so that the water molecule can hydrogen bond well.

Monte Carlo calculations<sup>20</sup> based on the available structural parameters are in progress to determine an energy profile for the complexation of water by these crown compounds.

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(20) See: Mattice, W. L.; Newkome, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 4477-4480 and references cited therein.

## Experimental Evidence for the Absence of Bonding Electron Density between Inverted Carbon Atoms

Pinakpani Chakrabarti, Paul Seiler, and Jack D. Dunitz\*

*Organic Chemistry Laboratory  
of the Swiss Federal Institute of Technology  
CH-8092 Zürich, Switzerland*

Arnulf-Dieter Schlüter and Günter Szeimies\*

*Institute of Organic Chemistry of the University of Munich  
D-8000 Munich, Germany  
Received July 17, 1981*

The nature of the bonding at inverted<sup>1,2</sup> carbon atoms is problematical.<sup>3</sup> Reported distances between such atoms lie in the range 1.55-1.64 Å;<sup>4-9</sup> most are only slightly (0.01-0.03 Å) longer than the normal C-C single-bond distance of about 1.541 Å and are thus similar to bond distances between quaternary carbon

(1) The bridgehead atoms of small-ring propellanes have been dubbed "inverted"<sup>2</sup> because the interatomic vectors emanating from each of them to its four nearest neighbors are directed to one side of a plane.

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(3) For general discussions of the problems involved, see: Ginsburg, D. "Propellanes"; Verlag Chemie: Weinheim, 1975; Chapter 4. Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978; Chapter 6B.

(4) For example, 1.64 Å in a [3.3.1]propellane (1,3-dehydroadamantane derivative);<sup>5</sup> 1.57 Å in a [3.2.1]propellane;<sup>2</sup> 1.55 Å in [4.2.1]-<sup>6</sup>; [4.1.1]-<sup>7</sup> and [3.1.1]propellanes;<sup>8</sup> 1.54 Å in another [4.1.1]propellane.<sup>9</sup>

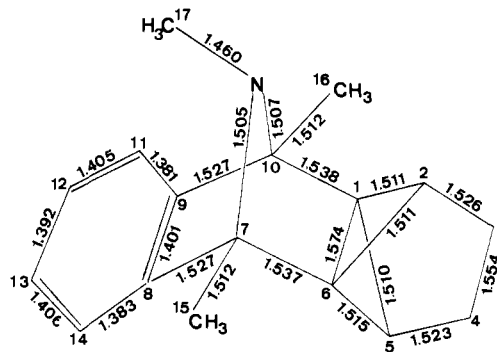
(5) Gibbons, C. S.; Trotter, J. *Can. J. Chem.* **1973**, *51*, 87-91.

(6) Harnisch, J.; Baumgärtel, O.; Szeimies, G.; van Meersche, M.; Germain, G.; Declercq, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 3370-3371.

(7) Declercq, J.-P.; Germain, G.; van Meersche, M. *Acta Crystallogr., Sect. B* **1978**, *34*, 3472-3474.

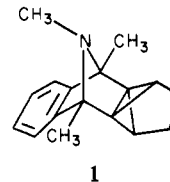
(8) Szeimies-Seebach, U.; Szeimies, G.; van Meersche, M.; Germain, G.; Declercq, J.-P. *Nouv. J. Chim.* **1979**, *3*, 357-358.

(9) Szeimies-Seebach, U.; Harnisch, J.; Szeimies, G.; van Meersche, M.; Germain, G.; Declercq, J.-P. *Angew. Chem.* **1978**, *90*, 904-905. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 848-849.



**Figure 1.** Atom numbering and bond distances. Standard deviations estimated by inversion of the least-squares normal equation matrix are in the range 0.001-0.002 Å.

atoms in less highly strained systems. On the other hand, it is obviously difficult to describe the bond between a pair of inverted carbon atoms in traditional terms. This is a problem where experimental information on the electron-density distribution<sup>10</sup> in the crystalline compound would be helpful. Here we provide such evidence from electron-density difference maps obtained by a low-temperature (95 K) X-ray analysis<sup>11-14</sup> of a crystalline [3.1.1]propellane derivative, 11-aza-9,10-benzo-1,8,11-trimethylpentacyclo[6.2.1.0<sup>2,6</sup>.0<sup>2,7</sup>.0<sup>3,7</sup>]undec-9-ene (**1**).<sup>15</sup>



Bond distances (Figure 1) from our analysis are quite normal for this type of molecule; in particular, the distance of 1.574 (1) Å between the inverted carbon atoms C(1) and C(6) corresponds to a slightly stretched single bond and is by no means extraor-

(10) Dunitz, J. D. "X-ray Analysis and the Structure of Organic Molecules"; Cornell University Press: Ithaca, NY, 1979; Chapter 8 and references therein.

(11) Colorless crystals of C<sub>17</sub>H<sub>19</sub>N are triclinic space group P $\bar{1}$ , cell dimensions  $a = 8.405$  Å,  $b = 8.550$ ,  $c = 10.332$  Å,  $\alpha = 80.19^\circ$ ,  $\beta = 84.67^\circ$ , and  $\gamma = 62.87^\circ$  at 95 K,  $Z = 2$ . Intensity measurements were made with an Enraf-Nonius CAD-4 diffractometer equipped with graphite monochromator (Mo K $\alpha$  radiation) and cooling device for 8474 reflections [6394 with  $F > 10\sigma(F)$  out to  $(\sin \theta)/\lambda = 0.994$  Å<sup>-1</sup>]. Structure determined by direct methods (MULTAN<sup>12</sup>) and refined by full-matrix least-squares analysis using XRAY system.<sup>13</sup> Final  $R = 0.032$  with exponentially modified weighting system ( $w = 1.5 \text{ Å}^{-2}$ )<sup>14</sup> and including extinction correction. The difference maps shown in Figure 2 are based on 4875 ( $F_o - F_c$ ) coefficients with  $(\sin \theta)/\lambda < 0.857$  Å<sup>-1</sup> and  $F_o \geq 10\sigma(F_c)$ . A table of atomic coordinates and vibrational parameters is provided as supplementary material. Full details will be reported later.

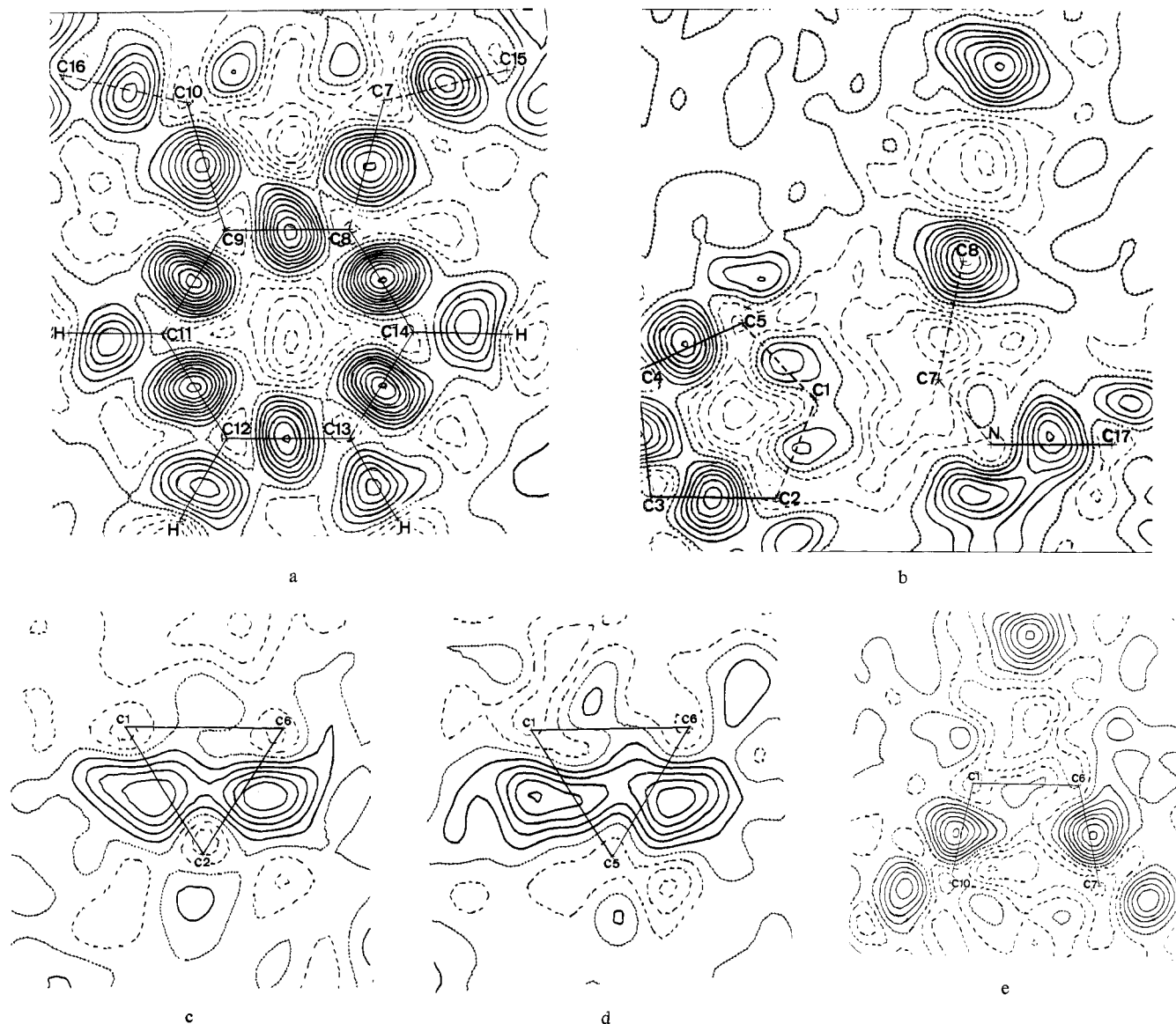
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(15) To a stirred solution of 52.4 mmol of lithium 2,2,6,6-tetramethylpiperidide and 10.0 g (62.8 mmol) of 1,2,3-trimethylisoindole<sup>16</sup> in 30 mL of THF at -30 °C a solution of 4.00 g (34.9 mmol) of 1-chlorotricyclo[3.1.0.0<sup>2,6</sup>]hexane<sup>9</sup> in 20 mL of THF was added dropwise. After stirring the mixture for 1 h at -30 °C and after workup with ether and water, the oily residue of the organic layer was purified by a short-path distillation affording 4.30 g (52%) of **1**, bp 100-120 °C (bath) (0.001 torr), mp 89 °C, after recrystallization from CH<sub>3</sub>CN and ether. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.00-1.60 (m, 4 H, 3-H<sub>2</sub>, 4-H<sub>2</sub>), 1.55 (s, 6 H, CH<sub>3</sub>-C), 1.58 (s, 3 H, CH<sub>3</sub>-N), 1.72 (dt,  $J = 5$  Hz and  $J = 1$  Hz, 1 H, 5-H), 3.99 (dt,  $J = 5$  Hz and  $J = 1$  Hz, 1 H, 2-H), and 7.10 (s, 4 H, aromatic H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  16.5 (q, CH<sub>3</sub>-C), 2.6 (t, C-4), 26.9 (t, C-3), 30.7 (q, CH<sub>3</sub>-N), 34.7 (s, C-1, C-6), 58.2 (d, C-5), 64.1 (d, C-2), 71.6 (s, C-7, C-10), 121.4 (d), 126.3 (d), and 147.2 (s); MS (70 eV),  $m/e$  (relative intensity) 237 (M<sup>+</sup>, 36%), 222 (40%), 56 (100%).

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**Figure 2.** Several sections through the electron-density difference map: (a) plane of benzene ring, (b) mean mirror plane of molecule, (c) planes passing through the inverted carbon atoms and C2, (d) C5, and (e) C7. Contour lines are drawn at intervals of  $0.05 \text{ e} \cdot \text{Å}^{-3}$ , full for positive, dashed for negative, and dotted for zero density.

dinary. In striking contrast, difference Fourier maps calculated at the end of our analysis with coefficients  $F_o - F_c$  show no indication of residual electron density between these atoms, although they do show prominent density peaks between every other pair of bonded atoms in the molecule and also for the nitrogen lone pair. The quality of our maps may be appraised from the sections (Figure 2a) in the plane of the benzene ring and in the mean mirror plane of the molecule (Figure 2b), which contains not only the bonds C(2)–C(3), C(3)–C(4), C(4)–C(5), and N–C(17) but also the midpoints of the bonds C(8)–C(9) and C(12)–C(13).

The absence of significant residual density along the line C(1)–C(6), between the atoms or outside them, is apparent from Figure 2c–e. There are, however, peaks for the other three bonds emanating from each of the inverted atoms; note particularly the bent bonds of the two three-membered rings with some accumulation of residual density at the ring centers. The absence of residual density along the line C(1)–C(6) says that the total charge density along this line is closely similar to the sum of the densities from the isolated spherical atoms.

Newton and Schulman<sup>17</sup> have made LCAO calculations (4–31G

basis set) for [1.1.1]propellane and concluded that “no evidence for a central bond is found in terms of the charge distribution, although the bond length of 1.60 Å is significantly shorter than the corresponding nonbonded distance of 1.87 Å in bicyclo-[1.1.1]pentane”. According to these calculations, the central bond in [1.1.1]propellane is formed from  $sp^4$  hybrid orbitals directed away from each other and with essentially zero overlap population.

Our new results seem to provide a nice, experimental verification of this general kind of description. This is especially gratifying because, although the theoretical and experimental approaches to the problem are both beset with difficulties, the errors and approximations inherent in the one are virtually independent of those in the other.

This and another recent example involving the residual electron density in highly polar C–Li bonds<sup>18</sup> show that there may be a future in experimental electron-density studies of complex organic molecules with interesting bonding features, even though the accuracy must inevitably be lower than that attainable with small molecules.

**Acknowledgment.** This work was supported by the Swiss

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National Science Foundation and the Deutsche Forschungsgemeinschaft.

**Supplementary Material Available:** Table S1 listing atomic coordinates and vibrational parameters (1 page). Ordering information is given on any current masthead page.

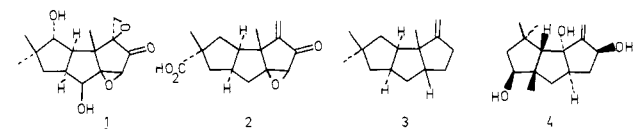
## Synthesis of *dl*-Coriolin

Barry M. Trost\* and Dennis P. Curran

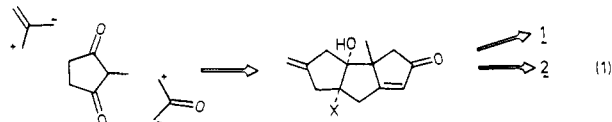
McElvain Laboratories of Organic Chemistry  
Department of Chemistry, University of Wisconsin  
Madison, Wisconsin 53706

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Interest in polycondensed cyclopentanoid natural products such as coriolin (1),<sup>1a</sup> hirsutic acid (2),<sup>1b</sup> hirsutene (3),<sup>1c</sup> and capnellane (4),<sup>1d</sup> among others, stems from their structural novelty and the antibacterial and/or antitumor activity that many possess.



Although several elegant syntheses of hirsutane natural products have appeared, they are all targeted to a single member of this class from an early stage of synthesis.<sup>2,3</sup> We sought an approach which invoked a highly functionalized tricyclic intermediate that would provide flexibility of creating several members of this fascinating series of natural products and which would be available by two cyclopentane annulations (reaction 1)<sup>4,5</sup> via enedione 5.<sup>4,6</sup>



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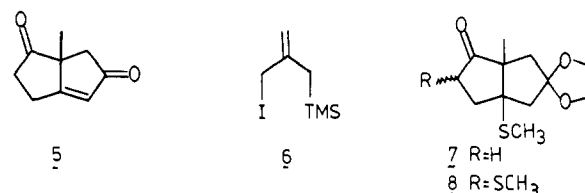
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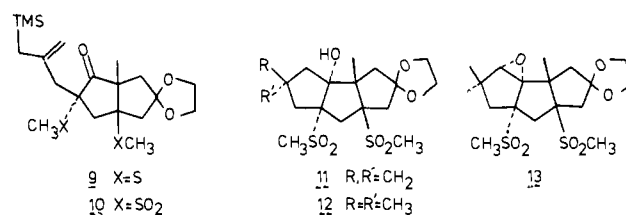
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(6) The absolute configuration of 5 produced with chiral phosphines has been determined. This, along with further asymmetric induction results, will be published shortly: Trost, B. M.; Curran, D. P. *Tetrahedron Lett.*, in press.

In this communication, we wish to illustrate the first application of enedione 5 as a starting material in a synthesis of coriolin (1), the most complex member of the hirsutane class of natural products.



For the annulation of the third five-membered ring bearing appropriate functionality, we envisioned use of 2-(trimethylsilyl)methylallene iodide (6)<sup>7</sup> as an electrophilic synthon for the 1,3-dipole, trimethylenemethane. While the kinetic enolate of enedione 5 reacted in reasonable yield with methylallene iodide, it surprisingly gave unacceptable yields of alkylation product with 6.<sup>8</sup> Assessing the poor results as due to the special reactivity of the strained enone, we converted the enone portion of 5 into a latent form by conjugate addition of methanethiol (catalytic (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N, 0 °C, CH<sub>3</sub>OH, CH<sub>2</sub>Cl<sub>2</sub>, quantitative) and chemoselective ketalization to give 7<sup>9a,c</sup> (0.95 equiv of HOCH<sub>2</sub>CH<sub>2</sub>OH, catalytic camphorsulfonic acid, PhH, Dean-Stark, 70% or 92% based upon recovered starting material).<sup>10</sup> A stereochemical anchor was introduced by clean monosulfenylation to 8<sup>9a,c</sup> (2 equiv of KH, CH<sub>3</sub>SSCH<sub>3</sub>, DME, 40 °C, 79%). At this juncture, alkylation with 6 proceeded smoothly (KH, DME, room temperature) to give 9<sup>9</sup> in 72% yield with the stereoselectivity estimated at >15:1.<sup>11</sup> The creation of the tricyclic nucleus was best per-



formed by oxidation (4.0 equiv of MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, aqueous NaHCO<sub>3</sub>, room temperature, 63%) to the crystalline disulfone 10<sup>9,11b</sup> (mp 116-117.5 °C) and fluoride-induced cyclization<sup>5,12</sup> [(*n*-C<sub>4</sub>H<sub>9</sub>)<sub>3</sub>NF, THF, 50 °C, 87%] to give the key tricyclic intermediate 11.<sup>9,15</sup> It is at this point that divergence into several families of compounds would appear feasible. For example, conversion of the methylene group into an  $\alpha$ -methyl carboxylic acid should provide the structural change leading ultimately to hirsutic acid. Such a transformation has been previously used in hirsutic acid synthesis.<sup>2</sup>

For coriolin, the geminal dimethyl group was efficiently introduced by cyclopropanation<sup>13</sup> [(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>, PhCH<sub>3</sub>, catalytic O<sub>2</sub>, 82%] followed by hydrogenolysis<sup>14</sup> (catalytic PtO<sub>2</sub>, HOAc, NaOAc, 1 atm of H<sub>2</sub>, 94%) to give 12<sup>9a,b,15</sup> which results

(7) Prepared by the action of sodium iodide (acetone) on the corresponding mesylate.<sup>5</sup>

(8) The source of this surprising difference in relative reactivity of 6 and methylallene iodide will be considered in detail in a forthcoming publication.

(9) (a) This compound has been characterized by IR and 270-MHz <sup>1</sup>H NMR spectroscopy. (b) This compound has been characterized by <sup>13</sup>C NMR spectroscopy. (c) Elemental composition has been established by high-resolution mass spectroscopy and/or combustion analysis.

(10) The byproducts were starting 6 and the diketal which was hydrolyzed (H<sub>2</sub>O, HClO<sub>4</sub>) to return 6 which could be easily recycled.

(11) (a) The use of the bis(phenylthio) compound gave greatly reduced stereoselectivities (2 or 3/1). (b) Selective oxidation of the bis(phenylthio) compound to the disulfone was not possible.

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