Molecular Bilateral Symmetry of Natural Products: Prediction of Selectivity of Dimeric Molecules by Density Functional Theory and Semiempirical Calculations

Tatyana Voloshchuk, Nicola S. Farina, Orrette R. Wauchope, Magdalena Kiprowska, Paul Haberfield, and Alexander Greer*

Department of Chemistry, Graduate School and University Center and The City

University of New York (CUNY), Brooklyn College, Brooklyn, New York 11210

*Author to whom correspondence should be addressed. Tel: 718-951-5475.

Fax: 718-951-4607. Email: agreer@brooklyn.cuny.edu

Supporting Information

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The carbon numbering scheme in which the bond distances and bond energies are described is shown in Table S1. AM1, B3LYP/D95**//AM1, HF/3-21G//AM1, and ONIOM calculations predict that C-C bond strengths span a range from 45.0 to 110.3 kcal/mol in the dimeric structures.

Compound **1** possesses a C-1—C-2 bond of 110.3 kcal/mol in energy predicted from the AM1 computed homolysis in a unimolecular cleavage reaction. The C-1—C-2 biaryl bond strength is greater in the dimer is compared to the C-1—C-2 bond of the trimer **1B** (101.8 kcal/mol) and tetramer **1C** (97.0 kcal/mol). From calculations at the HF/3-21G//AM1 level, the C-1—C-2 bond energy of **1** is enhanced compared to **1B** by 16.2 kcal/mol. The C-1—C-2 bond distances in **1** (1.463 Å), **1B** (1.470 Å), and **1C** (1.473 Å) increase incrementally further suggesting a progression for the facile homolysis of C-1—C-2 in the order **1C** > **1B** > **1**. It should be noted that a different type of C—C bond is formed in the progression from **1** to **1B**.
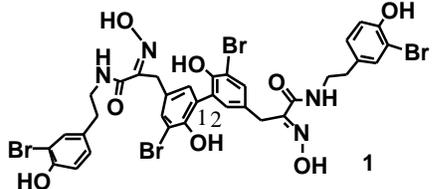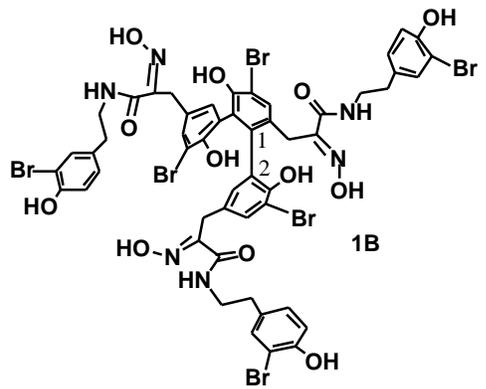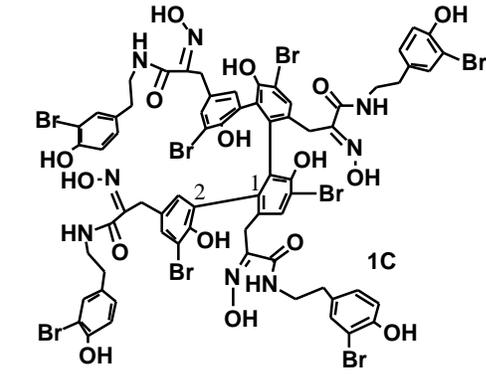
The natural product **2** was optimized with the AM1 and the ONIOM(B3LYP/D95**:AM1) methods as were the structures **2B** and **2C**, which possessed added monomer units to yield hypothetical trimer and tetramer molecules. Subjective decisions were made to extend the cyclobutane substance so that it may be regarded as a trimer (**2B**) and a tetramer (**2C**). Envisioning other combinations to give a trimer and a tetramer would be just as valid. The AM1 method predicts an increase in the C-1—C-2 bond distance of **2** (1.551 Å) compared to **2B** (1.557 Å) and **2C** (1.591 Å), which suggests that the bonding arrangement in this series will lead to a more facile ionization with relief of steric crowding and ring strain. The C-1—C-2 distance is longer in **2B** (0.007 Å) and **2C** (0.040 Å) compared to the cyclobutane precursor, **2**, which accompanies a weakening of the C1-C2 bonds that connect the subunits. The magnitude of the C-1—C-2 energy is reduced by 13.3 kcal/mol when comparing **2** to **2B** and 54.6 kcal/mol when comparing **2B** to **2C**. For this series, AM1 calculations of the C-1—C-2 bond energy are the result of an optimization with C-1 and C-2 separated at a fixed distance of
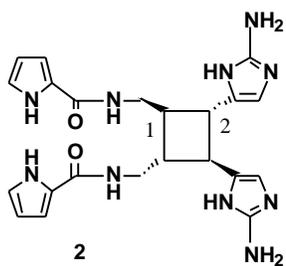
3.0 Å. The 2-layered ONIOM approach allowed an estimate of steric contributions. A similar situation is found where an 45.1 kcal/mol preference for C-1—C-2 in **2** relative to **2C** that can be attributed to an enhanced steric demand and ring strain in **2C**.

We have also investigated the C-1—C-2 bond distance for bromophenol **11** (1.496 Å), **11B** (1.512 Å), and **11C** (1.516 Å) with the AM1 method. Compound **11B** possesses an additional aryl attachment at C-1. Compound **11C** possesses aryl attachments at C-1 and C-3. Similarly, the evolution of energy upon rupture of the C-1—C-2 bond in the natural product dimer is more energetically costly compared to the hypothetical trimer or tetramer molecules. We calculated a 26.2 and 23.7 kcal/mol decrease in the C-1—C-2 bond strength in **11B** and **11C**, respectively, when compared with **11**. This is anticipated for branched ligands in **11B** and **11C**, which can interact within the molecule via unfavorable steric interactions. Calculation at the B3LYP/6-31G*//AM1 level appears to corroborate the structural and energetic features predicted at the semiempirical AM1 level for the C-1—C-2 interaction energy between monomeric units in dimer **11**, trimer **11B**, and tetramer **11C**.

The optimized structure of curcumin **12** possesses a stronger C-1—C-2 bond (89.0 kcal/mol) compared to **12B** (83.9 kcal/mol) and **12C** (66.6 kcal/mol) according to unrestricted B3LYP/D95**//AM1 calculations. The C-1—C-2 distance is also longer in **12B** (1.521 Å) and **12C** (1.536 Å) compared to the curcumin precursor, **12** (1.507 Å). Steric congestion also leads to preferential coordination of monomers as dimers rather than trimers and tetramers in sesquiterpene **13**. The C-1—C-2 bond distance increases from 1.478 (**13**) to 1.523 Å (**13C**) as revealed by AM1 calculations. The C-1—C-2 bond energy of the dimer is approximately 10-15 kcal/mol greater than that of the trimer and tetramer from AM1 calculations. The bond energy is similar for the calculated C-1—C-2 interaction at the HF/3-21G//AM1 level and is thought to reflect the relief of steric strain.

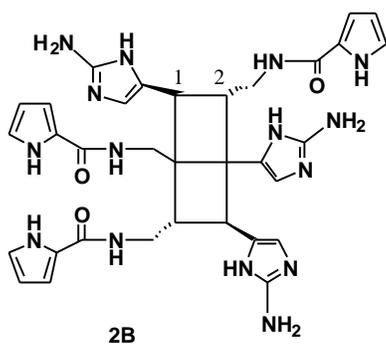Table S1. Calculated values of natural product structural parameters

compound	C-1—C-2 [a]	C-1—C-2 bond energy [a,b]
1	1.463	110.3 [c] 145.2 [d]
1B	1.470	101.8 [c] 129.0 [d]
1C	1.473	97.0 [c]
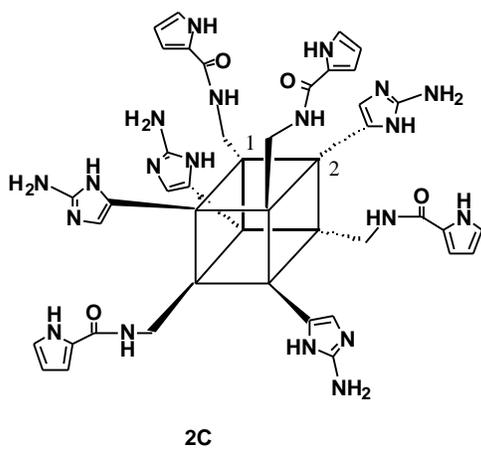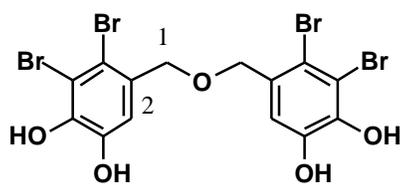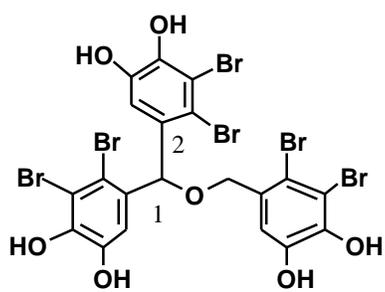
2

1.551

90.0 [e]

87.6 [f]

2B

1.557

76.7 [e]

2C

1.591

22.1 [e]

42.5 [f]

S5

11

1.496

74.0 ^{c}

103.6 ^{g}

11B

1.512

49.9 ^{c}

77.4 ^{g}

11C

1.516

50.5 ^{c}

79.9 ^{g}

12

1.507

89.0 [b]

12B

1.521

83.9 [b]

12C
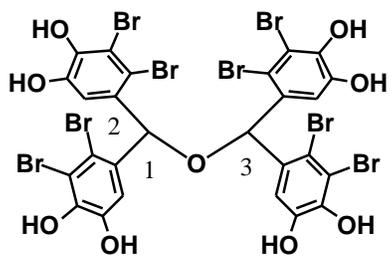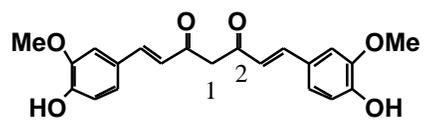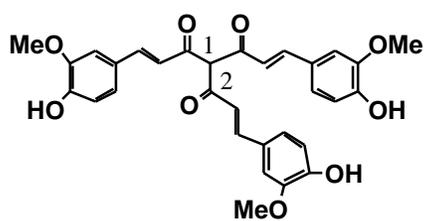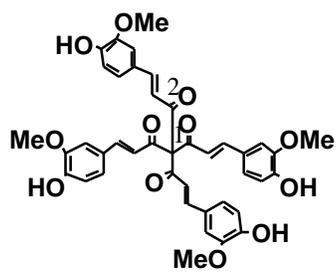
1.536

66.4 [b]

13   1.478   45.0 *c*

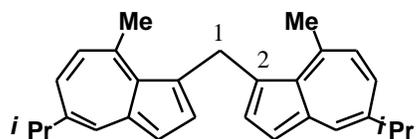**13B**   1.493   25.8 *c*
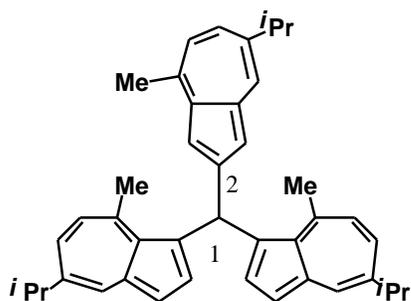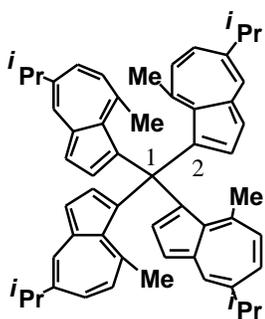

13C   1.523   33.7 *c*

a Distances in Å; bond energies in kcal/mol. *b* Trimers (**1B**, **3B**, **11B**-**13B**), tetramers (**1C**, **3C**, **11C**-**13C**), and oligomers with similar structures to **1**, **2**, and **11**-**13** appear to represent "missing" compounds in Nature. *c* AM1 optimized geometries unless otherwise noted. Unrestricted AM1 calculations provided the C—C bond homolysis energy. *d* HF/3-21G//AM1 calculation. *e* Restricted AM1 calculation with C-1—C-2 isolated at a fixed distance of 3.0 Å. *f* Restricted ONIOM(B3LYP/D95**:AM1) calculation optimized with the resulting species isolated at a fixed distance of 3.0 Å. *g* B3LYP/6-31G*//AM1 calculation. *h* B3LYP/D95**//AM1 calculation.