

## Heterocyclic Routes to Polysubstituted Cyclopentanes: Molecular Modelling of Electrophilic Additions To Di- and Trisubstituted Cyclopentenes

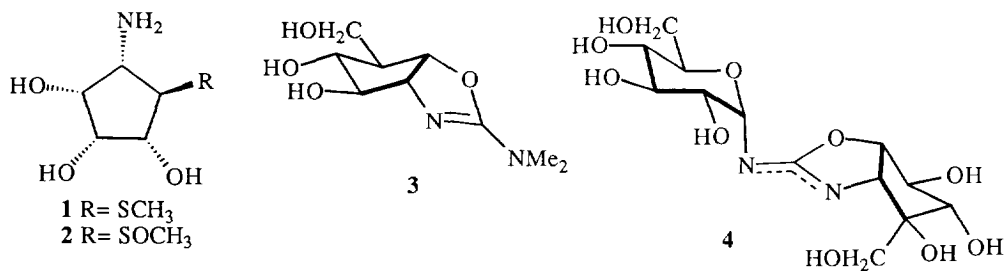
Jason Nichols, Tara Tralka, Bradley K. Goering, Charles F. Wilcox, and Bruce Ganem\*

Department of Chemistry, Baker Laboratory, Cornell University  
 Ithaca, New York 14853-1301 USA

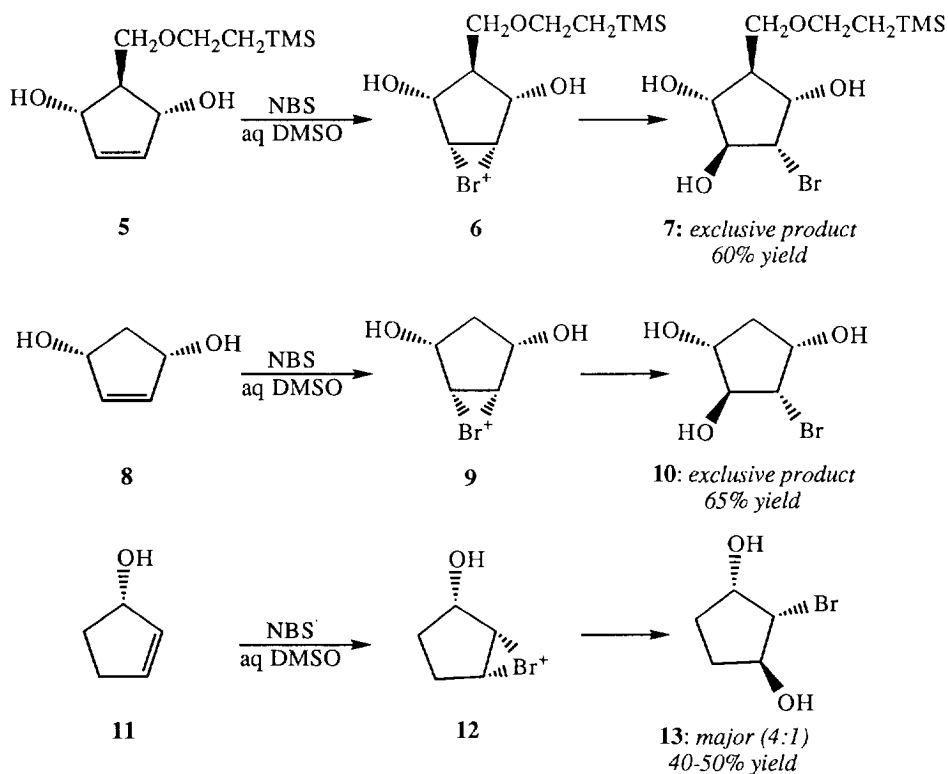
**Abstract:** Using cyclic bromonium ion formation as a model, transition state structures were computed using PM3 semi-empirical calculations for *syn* and *anti*-electrophilic additions of HOBr to allylically and homoallylically functionalized cyclopentenes.

### INTRODUCTION

Glycoside-processing enzymes such as glycosidases play critical roles in mediating cell adhesion<sup>1</sup> and transport, cell-cell recognition, and signal transduction,<sup>2</sup> and effective inhibitors may find use in immunology, tumor oncology, and virology.<sup>3</sup> Over the past few years, a new family of aminocyclopentitol-containing natural products has been discovered whose representatives display potent and selective effects on a variety of biologically important glycosidases. Examples include mannostatins A and B **1-2**, which are selective mannosidase inhibitors,<sup>4</sup> allosamizoline **3**, derived from the allosamidin family of pseudotrisaccharide chitinase inhibitors,<sup>5</sup> and the related chitinase inhibitor trehazolin **4**.<sup>6</sup> Inhibitors **1-4** have aroused considerable interest among synthetic chemists.<sup>7-17</sup>



Several laboratories have reported total synthesis endeavors, either involving (a) use of an enantiomerically pure starting material (typically carbohydrate-based) drawn from the chiral pool,<sup>7-14</sup> or (b) elaboration of di- and trisubstituted cyclopentenes, via osmylation and other vicinal addition reactions, to functionalize the cycloalkene bond stereoselectively.<sup>15-20</sup> While the osmylation of di- and trisubstituted cyclopentenes seems to follow no consistent stereochemical trend,<sup>21</sup> a pattern has emerged in which electrophiles such as  $\text{Br}^+$ ,  $\text{Cl}^+$ , and  $\text{CH}_3\text{S}^+$  add *syn* to allylic substituents in such polyfunctionalized cyclopentenes.<sup>22</sup> For example, in our recent total synthesis of allosamizoline,<sup>19</sup> we reported three cases of highly selective additions of  $\text{HOBr}$  to oxygenated cyclopentenes **5**, **8**, and **11**, which furnished **7**, **10**, and **13**, presumably via *syn*-bromonium ions **6**, **9**, and **12**, respectively.



Such cyclic, three-membered bromonium ions were first proposed in 1937 as intermediates in the electrophilic addition of Br<sub>2</sub> to alkenes,<sup>23</sup> and have long been implicated in electrophilic olefinic additions of other Br<sup>+</sup>-generating reagents.<sup>24</sup> Some relatively stable mono- and bicyclic bromonium ions have also been observed and characterized by NMR spectroscopy<sup>25</sup> and x-ray crystallography.<sup>26, 27</sup> Here we report semi-empirical studies on the putative bridging bromonium ion intermediates **6**, **9**, and **12** and their *anti*-isomers, in order to elucidate what structural and/or stereochemical factors might be invoked to explain the observed preference in HOBr additions to **5**, **8**, and **11**. Calculations suggest that dipole-dipole interactions in the transition state for electrophilic addition favor the intermediate *syn*-bromonium ions.

### METHODS

PM3 semiempirical molecular orbital calculations<sup>28</sup> were carried out on bromonium ion intermediates using the code in MOPAC6.<sup>29</sup> The key words employed were PM3 Charge = 1 Precise GNorm = 0.02. The starting geometry for optimization was obtained by running PCMODEL<sup>30</sup> on the epoxide corresponding to each bromonium ion.

### RESULTS AND DISCUSSION

Despite the seminal role of cyclic bromonium ions<sup>23</sup> in the development of the concept of nonclassical ions,<sup>31</sup> high-level *ab initio* calculations have only been reported on the parent ethylene bromonium ion. Poirer *et al.* employed both a diminished STO-3G basis set and a larger STO-3G basis set to determine the geometry-optimized ethylene bromonium ion structure.<sup>32</sup> Using the diminished basis set, the cyclic bromonium ion was favored over the open structure by 30.10 kcal/mol, and displayed a C-Br bond length of 2.061 Å. Using the larger basis set, the cyclic bromonium ion was somewhat less favored ( $\Delta E = 14.95$  kcal/mol) and the C-Br bond length was found to be longer (2.165 Å). Hamilton and Schaefer carried out both SCF and CISD calculations using several basis sets up to triple- $\zeta$  contracted set with two sets of polarization functions.<sup>33</sup> Their "most reliable" C-Br bond length for the cyclic bromonium ion was 2.025 Å. For all levels of calculation, the cyclic structure represented a global minimum with an energy of 14.7-29.4 kcal/mol below the 2-bromoethyl cation. As would be expected, the C-Br bond length of the 2-bromoethyl cation was significantly shorter (1.909 Å).

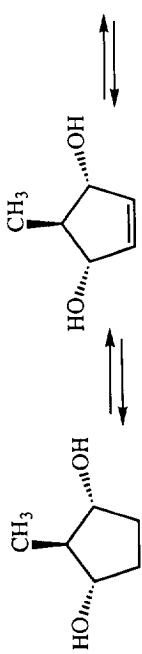
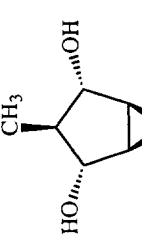
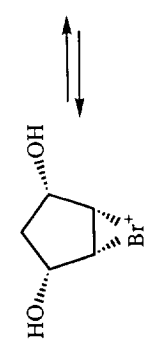
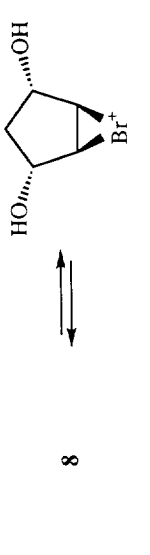
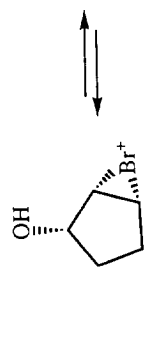
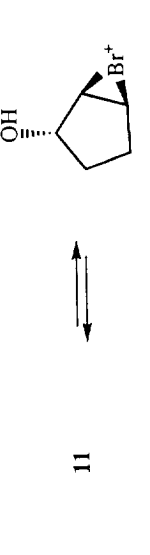
Recently Brown *et al.* have carried out limited MCSCF calculations on the energy surface for the transfer of X between an ethylene halonium ion (C<sub>2</sub>H<sub>4</sub>X<sup>+</sup> where X= Br or I) and a second ethylene.<sup>27</sup>

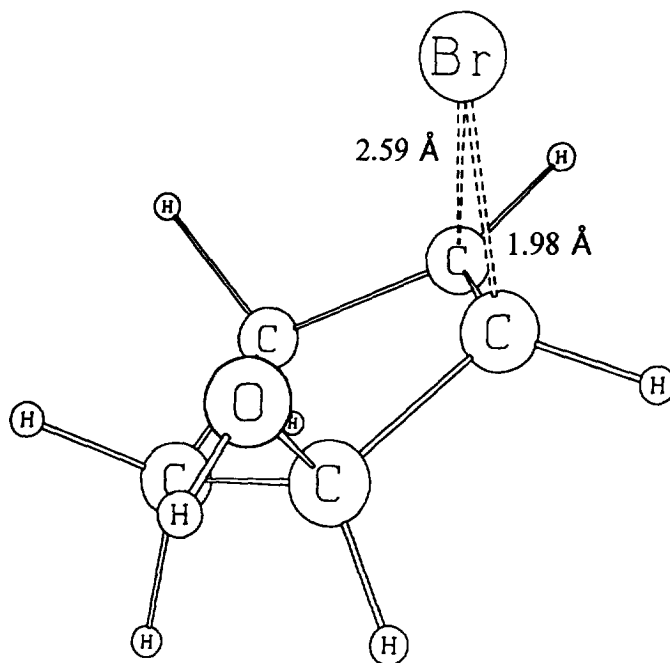
Optimized MCSCF values of geometrical parameters were obtained for the ethylene cyclic bromonium ion and indicated a C-Br bond length of 2.069 Å. The C-C-Br and H-C-Br bond angles were computed to be 69.4° and 108.0°, respectively. These calculated values may be compared with experimental data from crystallographic studies on the bromonium ion of adamantylideneadamantane, which revealed an average C-Br bond length of 2.11 Å and an average C-C-Br bond angle of 69.4°. <sup>27</sup> More recently, the structure of the highly crowded bromonium ion of 7-norbornylidene-7'-norbornane was computed by molecular mechanics using PC MODEL, <sup>34</sup> with a C-Br<sup>+</sup> force constant adjusted to duplicate the known geometry; no relevant bond lengths or bond angles involving the bromine atom were reported.

Because of the size of the molecules we wished to consider, high level *ab initio* calculations were not practical. Instead, we elected to use the semiempirical PM3 model. For comparison, an optimized structure for the ethylene bromonium ion was obtained in which the C-Br bond length was determined to be 2.129 Å. A structure for the 2-bromoethyl cation gave a C-Br bond length of 1.925 Å. Both values were consistent with *ab initio* results. Based on the PM3 models, however, the ethylene cyclic bromonium ion was more stable than the open 2-bromoethyl cation by only 3.7 kcal/mol, far below the *ab initio* results. Because of the poor energy result for this model system, *syn/anti* energy differences for a particular cyclic bromonium ion might well be suspect; nevertheless, it was hoped that the general pattern of energy differences might offer insights into the origins of the experimentally observed stereoselectivities. PM3 calculations were therefore performed on the six cyclic bromonium ions depicted in Table 1. To simplify the calculations, the β-trimethylsilylethoxymethyl side chain of cyclopentene **5** was replaced by a methyl group, as in **14**. No geometric constraints were applied during the optimization.

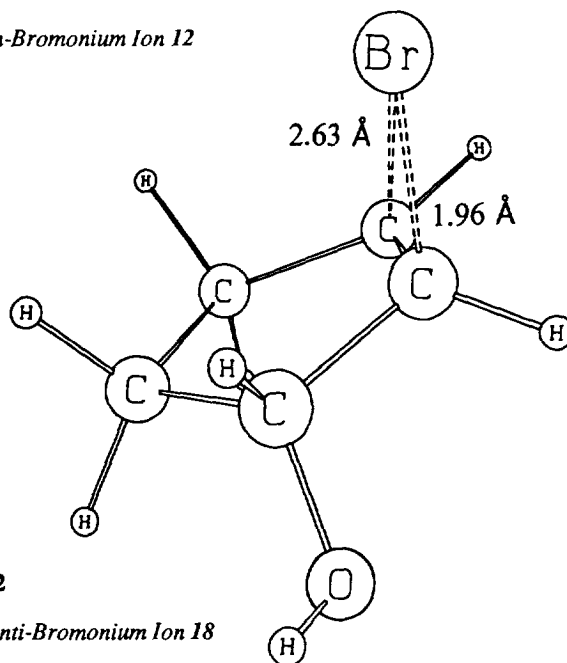
All of the cations adopted C<sub>1</sub> structures with slightly asymmetric three-membered bromonium ions. The calculated structures for the *syn*- and *anti*-bromonium ions derived from 2-cyclopentenol are shown in Figures 1 and 2 as NAMOD ball-and-stick plots. <sup>35</sup> For these hydroxylated structures, the average C-Br bond length of the *syn*-bromonium ions was 2.27 Å, while that of the *anti*-ions was 2.34 Å. Both values were slightly longer than in the unsubstituted ethylene bromonium ion. <sup>32,33</sup> The calculated dipole moments and bromine charges for the six hydroxylated bromonium ions are recorded in Table 1, along with differences in energy between each *syn/anti* pair. The calculated structures for bromonium ions **12** and **18** are shown in Figures 1 and 2, respectively.

TABLE 1. PM3 Calculations on Cyclopentene Bromonium Ions

		$E_{\text{anti}} - E_{\text{syn}}$ (kcal/mol)	
		calculated	observed
	<b>15</b> $\mu = 5.3 \text{ D}$ $q_{\text{Br}} = 0.34$		
	<b>16</b> $\mu = 3.2 \text{ D}$ $q_{\text{Br}} = 0.17$	2.21	>1.8
	<b>9</b> $\mu = 5.9 \text{ D}$ $q_{\text{Br}} = 0.27$		
	<b>17</b> $\mu = 3.1 \text{ D}$ $q_{\text{Br}} = 0.18$	2.30	>1.8
	<b>12</b> $\mu = 7.0 \text{ D}$ $q_{\text{Br}} = 0.22$		
	<b>18</b> $\mu = 5.3 \text{ D}$ $q_{\text{Br}} = 0.16$	0.27	0.84

**FIGURE 1**

*PM3 Calculated Structure for Syn-Bromonium Ion 12*

**FIGURE 2**

*PM3 Calculated Structure for Anti-Bromonium Ion 18*

In all three cyclopentenes, the *syn*-bromonium ion is favored over the *anti*-isomer. More importantly, the pattern of weak-strong-strong *syn*-preference that is experimentally observed in HOBr additions to **15**, **9**, and **12** can be reproduced. Also noteworthy about the calculated structures is the fact that in each *syn/anti* pair, the *syn*-structure displays the higher atomic charge on the bromine as well as the higher dipole moment.

An attractive rationale for the differences in dipole moments, bromine charges, and overall energy differences may be developed by representing the charge distribution as a sum of three components. The first component arises from the dipoles associated with the allylic hydroxyl groups; the second is a unit positive charge centered on the bromine atom; the third is a dipole originating from the double bond and pointing towards the bromine atom. This third component describes the electron donation from the double bond to the bromine cation.

To a first approximation, the first two components are the same for both the *syn*- and *anti*-bromonium ions formed from a given hydroxylated cyclopentene. The third component of charge distribution, the net C-Br dipole, varies markedly in the *syn*- and *anti*-bromonium ions. In the *anti*-structures, the C-Br dipole is relatively large, reflecting the greater transfer of positive charge from bromine to the attached carbons. This larger, anti-dipole moment is oriented in opposition to the dipoles of the substituent hydroxyl groups, thus reducing the molecular dipole moment.

By contrast, in the *syn*-bromonium ions, the C-Br dipole component is smaller, with relatively less charge transfer to the ethylene carbons and a greater net positive charge on the bromine atoms. In the *syn*-bromonium ions, the substituent dipoles are oriented with their negative poles towards the bromine atom, which reinforces the C-Br dipole and leads to a larger molecular dipole moment. The reinforcing dipoles of the *syn*-ions, combined with the greater positive charge on the bromine atom, represent a favorable interaction that lowers the molecular energy relative to the *anti*-ions.

The foregoing calculations apply to gas-phase structures. In solution, however, additional solvent interactions arise that may preferentially stabilize the species with the larger dipole moments. In the present systems, the *syn*-bromonium ions will be additionally stabilized relative to their *anti*-counterparts. The existence of a unit molecular charge on each of the species vitiates any simple Onsager reaction field model<sup>36</sup> because it would tend to saturate the solvent dipole orientation. Nevertheless, it is instructive to estimate the magnitude of the solvent interactions. For a simple spherical cavity embedded in a uniform dielectric constant containing a dipole at the center of the sphere, the dipole charging energy<sup>37</sup> is  $\mu^2(\epsilon - 1)/r^3(2\epsilon + 1)$ , where  $\mu$  is

the dipole moment,  $\epsilon$  is the dielectric constant, and  $r$  is the radius of the cavity. With a cavity radius of 4.1 Å and  $\epsilon$  (DMSO) = 47, the dipole solvation energy of the *syn*-monohydroxy bromonium ion **12** is 5.0 kcal/mol and that of the *anti*-isomer **18** is 2.8 kcal/mol for a differential stabilization energy of 2.2 kcal/mol. For the *syn/anti* pairs **9/17** and **15/16**, the extra *syn*-stabilizing energy differences are 2.6 and 1.8 kcal/mol, respectively.

In conclusion, based on semi-empirical PM3 calculations, the preferential *syn*-addition of Br<sup>+</sup> to hydroxylated cyclopentenes **5**, **8**, and **11** can be accounted for as an electrostatic phenomenon arising from the larger positive charge on the *syn*-bromine interacting more favorably with the hydroxyl dipole(s). The *syn*-isomer has the larger molecular dipole moment and is likely to be additionally stabilized by solvent interaction.

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