

Notes

An *Ab initio* Study on the Structure and Conformational Stability of Bromocyclobutane

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Received September 8, 1997

Introduction

For a decade, we have been engaged in investigating the relative stability of the equatorial and axial conformers of monosubstituted cyclobutanes,¹⁻⁵ $c\text{-C}_4\text{H}_7\text{X}$ (X=F, Cl, Br, and $\text{C}\equiv\text{CH}$). For all of the molecules we have determined that the equatorial conformation is more stable than the axial one. The potential functions for the halocyclobutanes by microwave,^{6,7} far-infrared,⁸ and Raman^{3,9} spectroscopies are all consistent with the equatorial conformation being the thermodynamically preferred form. From analysis of the ring puckering transitions of bromocyclobutanes observed in the Raman spectrum of the gas,⁵ the energy difference and the difference between the puckering angles are found to be $361 \pm 20 \text{ cm}^{-1}$ ($4.31 \pm 0.24 \text{ kJ/mol}$) and 6° , respectively, between the two forms.

From investigations of the Raman spectra of the gaseous fluoro,² chloro,⁴ bromocyclobutanes,⁵ and cyclobutylacetylene,¹ at variable temperatures, the enthalpy differences between the two conformers have been determined as $413 \pm 43 \text{ cm}^{-1}$ ($4.94 \pm 0.15 \text{ kJ/mol}$), $325 \pm 40 \text{ cm}^{-1}$ ($3.89 \pm 0.48 \text{ kJ/mol}$), $\sim 350 \text{ cm}^{-1}$ ($\sim 4.19 \text{ kJ/mol}$), and $282 \pm 49 \text{ cm}^{-1}$ ($3.37 \pm 0.59 \text{ kJ/mol}$), respectively. The differences between puckering angles are found to be 4° , 5° , and 6° with the equatorial conformers having the larger values of 28° , 22° , and 20° , for the fluoro,² chloro,⁴ and bromocyclobutanes.⁵ In addition to the experimental determination of enthalpy differences and puckering angles, these values have been calculated by restricted Hartree-Fock (RHF) method with 3-21G* and 6-31G* basis sets for the fluoro-² and chlorocyclobutane.⁴ At the 6-31G* level the enthalpy differences and puckering angle differences are obtained as 583 cm^{-1} (6.97 kJ/mol) and 615 cm^{-1} (7.36 kJ/mol) and 5° and 7° for the fluoro- and chlorocyclobutane, respectively.

Ab Initio calculation gives a lot of valuable informations in molecular structures, conformational analysis, and vibrational assignments. But until early 1990s this calculation was available only down to the second row elements (from hydrogen to neon). At present, with the relatively fast and larger memory and storage capacity size of workstations and minicomputers and upgraded *ab initio* programs such as Gaussian-94,¹⁰ it is now possible to carry out *ab initio* calculations on molecules which has much larger atoms. With these improvements the combined studies^{1,2,4,11} of the structures and conformational stabilities by *ab initio* calculations and molecular spectroscopy have provided ex-

tremely useful data. It is in this context that we investigate the structure and conformational stability of bromocyclobutane by *ab initio* calculations and compare them with the previous⁵ spectroscopic data.

Calculations

All the calculations were performed with the program Gaussian-94 using the RHF/STO-3G*, LANL1MB, LANL1DZ, MP2/6-311+G(d,p), BLYP/6-311+G(d,p), and B3LYP/6-311+G(d,p) levels of theory. The geometrical model for the equatorial conformer used in this work is depicted in Figure 1 and the optimized geometrical parameters determined with these basis sets are given in Table 1 for the equatorial and axial conformers. Also given in Table 1 are the available structure determined from the microwave and vibrational spectroscopic data. There are no structural differences obtained between the two conformations with STO-3G* and LANL2MB basis sets.

Discussion

On the basis of the previously reported study in the Raman and far-infrared spectra of gaseous bromocyclobutane,⁵ the puckering angles are determined from the potential function as 20° for the equatorial conformer and 14° for the axial form. The uncertainties of these puckering angles are directly related to the uncertainty of the assumed reduced mass (in the previous work⁸ the reduced mass was calculated to be 214 amu assuming planar form of bromocyclobutane). The value of 29° for the equatorial conformation determined from microwave spectrum⁶ is too

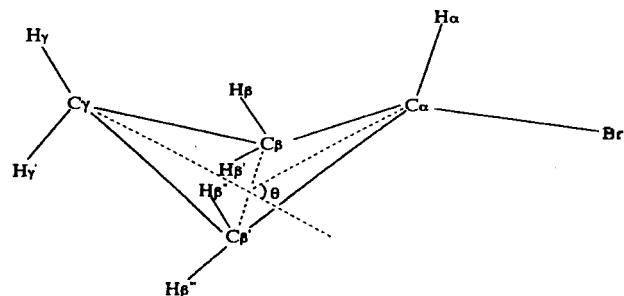


Figure 1. Geometrical model for the equatorial conformer of bromocyclobutane.

Table 1. Structural parameters (bond lengths in Å, angles in degrees), rotational constants (in MHz), and total energies (in Hartrees) obtained for the equatorial and axial conformers of bromocyclobutane^a

Parameter	Theoretical										Experimental				
	STO-3G*		LANL1MB		LANL1DZ		MP2/6-311+G(d,p)		BLYP/6-311+G(d,p)		B3LYP/6-311+G(d,p)		Microwave ^b		Vibrational ^c
	Eq. & Ax.	Eq. & Ax.	Eq.	Ax.	Eq.	Ax.	Eq.	Ax.	Eq.	Ax.	Eq.	Ax.	Eq.	Eq.	Ax.
r(C _α -C _β)	1.558	1.547	1.544	1.549	1.537	1.545	1.549	1.557	1.538	1.546	1.540(3)				
r(C _β -C _γ)	1.552	1.555	1.561	1.559	1.553	1.551	1.571	1.568	1.557	1.554	1.548(3)				
r(C _α -Br)	1.881	2.064	2.024	2.035	1.943	1.951	2.012	2.018	1.980	1.989	1.939*				
r(C _α -H _α)	1.091	1.089	1.076	1.074	1.092	1.090	1.094	1.093	1.088	1.087	1.090*				
r(C _β -H _β)	1.086	1.086	1.080	1.083	1.092	1.092	1.097	1.096	1.091	1.089	1.090*				
r(C _β -H _β ')	1.087	1.087	1.080	1.078	1.094	1.096	1.097	1.101	1.091	1.094	1.090*				
r(C _γ -H _γ)	1.086	1.086	1.080	1.080	1.093	1.092	1.097	1.097	1.092	1.091	1.090*				
r(C _γ -H _γ ')	1.086	1.086	1.081	1.080	1.092	1.092	1.097	1.097	1.090	1.091	1.090*				
∠H _α C _α Br	107.6	103.6	103.9	103.5	106.3	105.9	103.6	103.3	104.2	104.0	111.00				
∠C _β C _α C _β '-Br	131.2	129.3	130.6	123.7	132.8	121.2	132.6	124.6	132.5	123.5	131.00(13)				
∠C _β C _α C _β	89.3	90.6	90.3	90.0	89.1	88.2	90.3	90.0	90.0	89.4	88.68(13)				
∠C _α C _β C _γ	88.9	88.0	87.7	89.4	86.3	90.6	87.0	89.2	87.1	89.1					
∠C _β C _γ C _β '	89.8	90.0	89.0	89.3	87.9	87.8	88.7	89.4	88.6	88.8	88.10(13)				
∠H _β C _β C _β '	137.5	137.5	141.6	136.4	148.1	146.4	144.6	137.4	144.6	140.5	108.73*				
∠H _γ C _γ C _γ '	109.1	109.4	108.8	108.6	109.6	109.6	109.1	108.7	110.0	108.9	110.73*				
θ	9.3	9.9	12.5	-7.3	17.2	-14.7	17.1	-7.3	14.5	-10.0	29.37(13)	20	-14		
A	9650.61	9482.25	9763.09	8124.24	10188.27	7775.15	9789.82	8043.29	9976.44	8012.64	10003.4(130)				
B	1689.01	1550.72	1566.58	1715.84	1616.65	1897.40	1553.69	1715.82	1590.34	1785.29	1629.41(3)				
C	1539.36	1425.63	1435.77	1610.05	1478.55	1805.35	1421.43	1607.44	1454.49	1681.56	1488.48(3)				
-E	2699.05615	166.62949	168.39406	168.39230	2728.64949	2728.64676	2730.71168	2730.70888	2730.80731	2730.80453					

^aAbbreviations used: Eq. as equatorial and Ax. as axial. ^bRef. 6. The parameters denoted with an asterisk(*) were held fixed at the given value during the iterative process (see text of Ref. 6). ^cRef. 5.

large when compared to the value obtained by vibrational⁵ investigation. Such a large value from microwave is probably caused from the fixed value 111° of the H_αC_αBr angle during the r_α parameter determination. In the present theoretical study these angles are obtained from optimized parameters as 12.5, 17.2, 17.1, and 14.5° for the equatorial and 7.3, 14.7, 7.3, and 10.0° for the axial conformers at the LANL1DZ, MP2/6-311+G(d,p), BLYP/6-311+G(d,p), and B3LYP/6-311+G(d,p) levels, respectively.

Even though the values of the puckering angle difference between the two conformers obtained from the previous vibrational study⁵ and the theoretical calculations using the MP2/6-311+G(d,p) level have discrepancy of about 3°, the puckering angles of the two conformers in both studies are in good agreement. When we consider the uncertainty of reduced mass, this agreement of the puckering angle difference between the experimental and theoretical studies shows that BLYP/6-311+G(d,p) level can give a reliable conformational structure for the bromocyclobutane. For the energy difference between the two conformers of bromocyclobutane the previous vibrational study⁵ gives us the values of ~350 cm⁻¹ and 361±20 cm⁻¹ for the gas from the relative intensity and the potential function, respectively. The values obtained by *ab initio* calculations at the LANL1DZ, MP2/6-311+G(d,p), BLYP/6-311+G(d,p), B3LYP/6-311+G(d,p) levels are 386, 599, 614, and 610 cm⁻¹, respectively. These values also show the equatorial conformation is more stable than the axial. Therefore the energy difference and the puckering angle difference between the two conformers obtained from *ab initio* calculations can be valuable in the conformational studies of monohalocyclobutanes.

Also, *ab initio* calculation at MP2/6-311+G(d,p) level can provide an excellent guide to study the difference of the structural parameters among the conformers.

Acknowledgement. Authors wish to express their gratitude to the Institute of Basic Science of Changwon National University for the kind support given to this work.

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A Sequence-Selective Peptide-Binding Receptor

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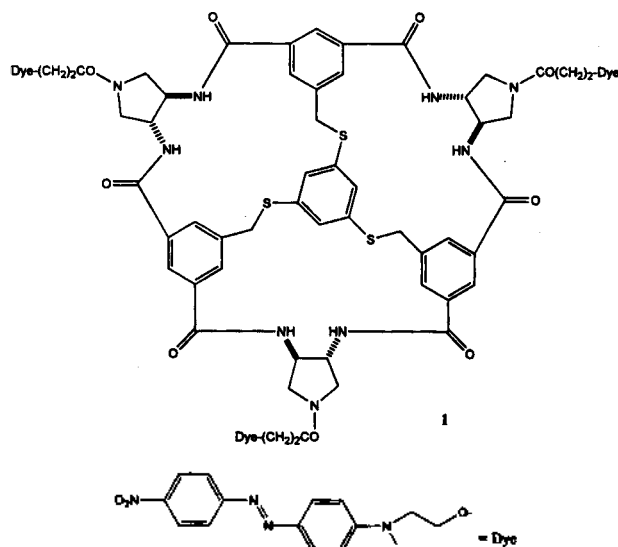
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Received September 12, 1997

One of the remarkable features of many biological receptors, such as enzymes and antibodies, is their ability to recognize and selectively bind multi-residue peptide sequences. To discriminate between a vast array of different, and often closely related molecules in a biological medium, biological receptors use well-defined binding sites, with different sizes and arrays of functional groups, which are constructed by various combinations of the structurally related building blocks such as α -amino acids.

Recently, synthetic receptors have begun to reproduce such ability.¹ Among those are a class of cyclooligomeric receptors derived from trimesic acid (A) and chiral 1,2-diamines (B).² These molecules showed high enantio- and residue-selectivities in the binding of amino acids and small peptides. Furthermore, the peptide binding properties of these readily accessible receptors were markedly different, when the way in combinations of A and B are different. Obviously, there exist a number of way in which A and B can be combined. Here, to expand the scope of the peptide-binding selectivity of this class of receptors, a C₃ symmetric bowl-shaped receptor (1) is described.

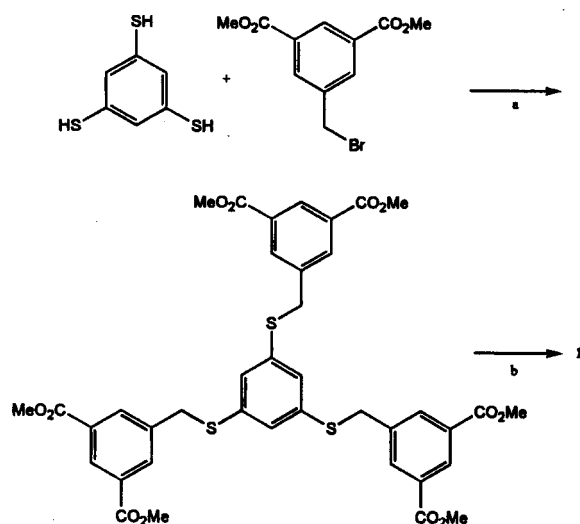
In receptor 1, three molecules of A and B are linked



through a 1,3,5-benzenetricaptane. As a result, 1 has a conformationally well-defined hydrophobic cavity composed of four *m*-substituted benzenes and periphery of hydrogen bond donors/acceptors. Therefore, receptor 1 might be expected to bind peptides selectively by hydrogen bondings and hydrophobic interactions.³

Synthesis of 1 begins with 1,3,5-benzenetricaptane as shown in Scheme 1. A triple alkylation with bromomethylbenzene 3,5-dicarboxylic acid dimethylester provided the hexamethylester 2. Ester hydrolysis and subsequent EDC coupling with pentafluorophenol led to the cyclization precursor. The final step was an intermolecular macrolactamization which used hexakis (pentafluorophenyl) ester and (3R,4R)-N-(Disperse Red I)succinyl- pyrrolidine diamine di-TFA salts to close the macrocyclic ring. This cyclization provided the intensely red receptor 1 in 32% yield.

To survey the binding properties of receptor 1, a solid phase color assay was employed with an encoded combinatorial library⁴ of 50,625 acylated tetrapeptide substrates (R-AA3-AA2-AA1).⁵ Substrate library was screened for



Scheme 1. (a) DIPEA, THF (77%). (b) i. NaOH, ii. C₆F₅OH/EDC (45%) and then Dye-linked pyrrolidine diamine diTFA salt/DIPEA in THF (32%).