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DFT study of the mechanism and stereochemistry of electrophilic transannular addition reaction of bromine to 6-oxa-heptacyclo[9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]docosan-14,18,20-triene-12,17-dicarboxylic anhydride

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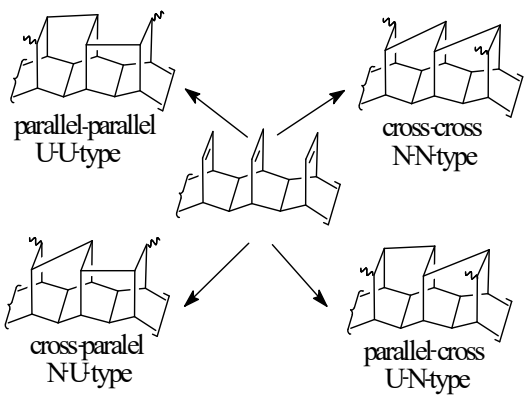
The geometry and the electronic structure of 6-oxa-heptacyclo[9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}] docosan-14,18,20-triene-12,17-dicarboxylic anhydride (HDTD) have been investigated by DFT methods. The study shows that the norborneyl double bond of the HDTD molecule is endo pyramidalized and the central and bicyclo[2,2,2]octenyl double bonds are exo pyramidalized. The structure and stability of the cation intermediates and products of the reaction have been investigated by DFT methods. The most stable cation intermediate is U-N-type ion and the reaction takes place over this cation. The cation centre of U-N-type ion mutually interacts with the unshared electron pair of the oxygen atom of the tetrahydrofuran ring on the exo face and is sterically hindered by the tetrahydrofuran ring. The nucleophilic attack of bromide anion (Br^-) on the cation centre of U-N-type ion occurs on the endo face and as a result the exo,endo-dibromide isomer of U-N-type product is obtained, which is 6.913 kcal mol^{-1} more stable than the exo,exo-isomer.

Keywords: Theoretical chemistry, Density functional calculations, Electrophilic transannular addition, Transannular addition, Juxtaposed double bonds, Intramolecular skeletal rearrangement

Rigid polycyclic molecules having isolated double bonds located in the laticyclic topology[1] and spatially in close proximity have provided suitable frameworks for the study of orbital interactions[2-4] and transannular reactions[5]. The attack of an electrophile to polycyclic strained alkene having three parallel, face-to-face (juxtaposed) double bonds in spatial proximity usually leads to the transannular bridge formation in either cross (N-type) or parallel (U-type) manner or both[6,7]. The face-to-face double bonds among which the number of σ bonds is four (linked with four σ bonds) may be bonded either in parallel (U-type) or cross (N-type)[8] manner. Therefore, in polycyclic strained alkenes, three parallel face-to-face (juxtaposed) double bonds may be linked in the manner of cross-cross (N-N-type), cross-parallel (N-U-type), parallel-parallel (U-U-type) and parallel-cross (U-N- type) (Scheme 1). In electrophilic addition reaction of bromine to 6-oxa-heptacyclo [9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]docosan-14,18,20-triene-12,17-dicarboxylic anhydride (HDTD) U-N-type product[7] and to 6,16-dioxaoctacyclo[9.9.2.2^{3,9}.2^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}] hexacosa-21,23,25-triene (DOHT) N-N-type product is obtained[6,7].

In order to investigate the inner mechanism and dynamic stereochemistry of these reactions in detail, it is crucial to determine the structure and stability of the intermediates (cyclic-bridged, N-N-, N-U-, U-U- and U-N-type cations) formed during the course of the reaction and investigate their skeletal isomerization. The direction of the flow of these



Scheme 1

reactions is ascertained by the direction of the skeletal isomerization of the cyclic bridge halogenium cation formed as a result of the heterolytic splitting of the alkene…halogen molecular charge-transfer (CT) complex. The intramolecular skeletal isomerization is realized so as to form the more stable skeletal structure. It is feasible for the cyclic bridged halogenium cation to transform into N-N-, N-U-, U-U- and U-N-type bridged cations as a result of the transannular cross-cross (N-N-type), cross-parallel (N-U-type), parallel-parallel (U-U-type) and parallel-cross (U-N-type) linkage of the double bonds. Therefore, the stability of N-N-, N-U-, U-U- and U-N-type cations into which the cyclic bridged halogenium cation isomerizes, is important in order to ascertain the direction of the addition reaction. Also, the investigation of the structure of cationic centres of N-N-, N-U-, U-U- and U-N-type ions and the possibility of the attack of halogenide anion (X^-) towards these centres is of great significance for the determination of the direction of the addition reaction and the stereochemistry of the products.

The structure and nature of the alkene play an important role in the electrophilic addition reaction of halogens to three parallel face-to-face (juxtaposed) double bonded strained alkenes. The investigation of geometric and electronic structure of alkenes by calculating the pyramidalization of the double bonds and other geometric parameters determines the relationship between the structure of the alkenes and their behaviour in electrophilic addition reactions. It is crucial to investigate the structure of the strained alkenes and calculate the reactivity indices ("relative electrophilicity" and "relative nucleophilicity") with the intention of locating their preferable reactive sites and centers[9]. In general, the stereochemical regularities of addition reactions of halogens to unsaturated strained systems are the subjects of detailed investigation. Stereoselectivity of these reactions depends on the electronic structure of the double bonds of strained olefins to a large extent. The study of the stability and stereochemistry of the different configurations of the reaction products is fundamental so as to interpret the many characteristics of the electrophilic addition reactions.

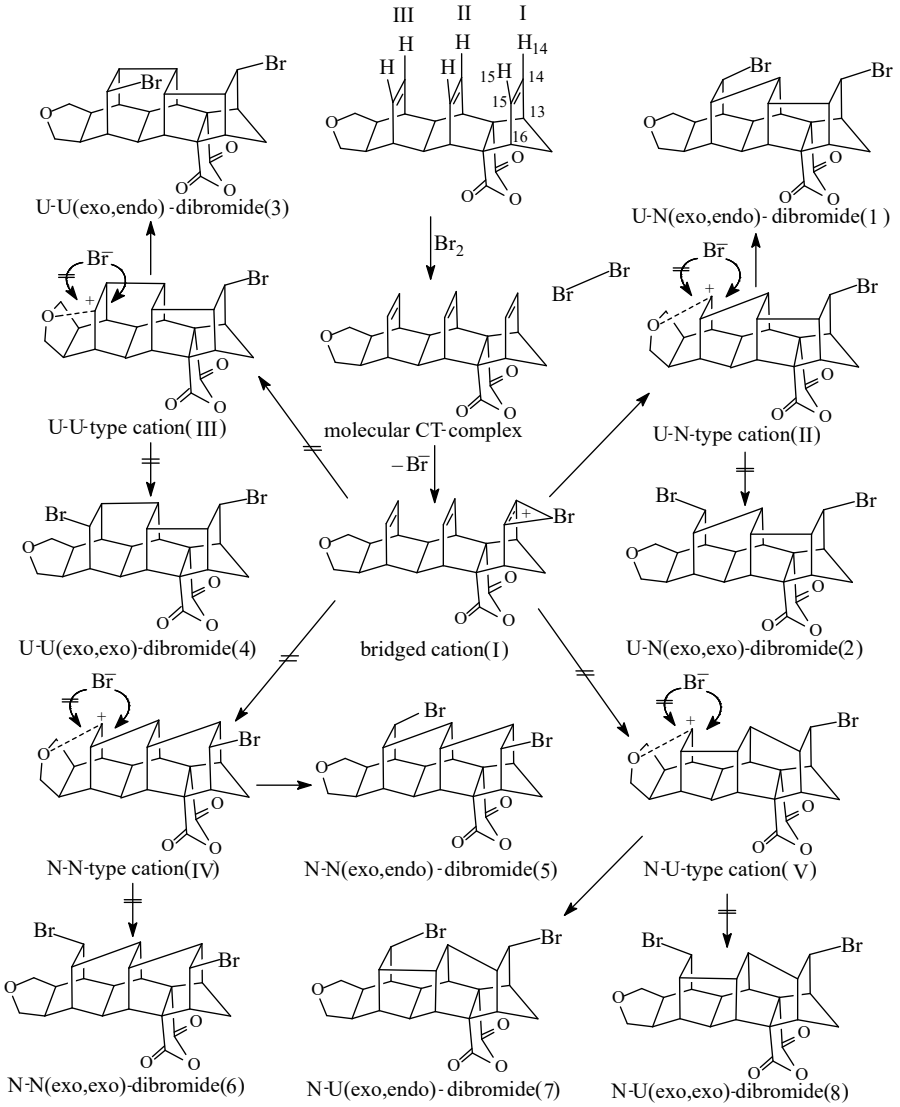
The addition reactions of halogens to alkenes with rigid structure and their intermediates have been investigated by the methods of quantum chemistry[10-19]. In our previous studies, the addition of chlorine and bromine to many polycyclic olefins with rigid structure have been studied theoretically[20-28]. As a follow-up to these investigations, the mechanism and stereochemistry of the electrophilic addition of bromine to 6-oxa-heptacyclo[9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]docosan-14,18,20-triene-12,17-dicarboxylic anhydride (HDTD) have been investigated (Scheme 2). In this work, the electropilic addition of bromine to HDTD molecule has been studied theoretically. The structures and stabilities of the reaction cationic intermediates (bridged, N-N-, N-U-, U-U- and U-N-type cations) and products have been investigated by DFT methods. Also, the geometry and the electronic structure of the HDTD molecule have been computed by DFT methods. While the U-N-type exo,endo-dibromide product is obtained in the electrophilic addition of bromine to HDTD molecule[7], however, the exo,exo-dibromide isomer of U-N-type product and other dibromide (Scheme 2) were not. An explanation for this has also been proposed.

Computational Methods

The geometry and the electronic structure of the 6-oxa-heptacyclo[9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]docosan-14,18,20-triene-12,17-dicarboxylic anhydride (HDTD) were investigated by DFT/B3LYP (density functional theory with B3LYP, the hybrid Becke's three parameter functional and Lee-Yang-Parr exchange-correlation potential)[29,30] method using the 6-311G(d,p) and 6-311++G(d,p)[31] basis sets. The predicted cationic intermediates and products formed in the addition reaction were investigated using the B3LYP/6-311G(d,p) method. By using the optimized geometries of cations and products by B3LYP/ 6-311G(d,p) method, their single point energies were calculated at the B3LYP/6-311++G(2d, 2p)[31] level. Solvent effects were calculated at the same theory level as the optimizations were performed by single-point calculations on the optimized structures using the CPCM (conducting polarized continuum model)[32,33] method (with UAKS cavities[34]) in chloroform (ε=4.807). All stationary points were characterized by calculating the vibrational frequencies and zero point vibrational energies were added for all species. The calculations have been performed with Gaussian 03[35] software.

Results and Discussion

Full geometric optimization of the HDTD molecule was obtained by DFT/B3LYP method with the 6-311G(d) and 6-311++G(d,p) basis sets and the structure of the molecule was also investigated in detail. Considering the results of each method, the



Scheme 2

Table 1 — Calculated double bond lengths (Å), distances (Å) between two double bonds and out-of-plane bending angle (deg.) of HTDT molecule

Method	Double bond (**I**)			Double bond (**II**)			Double bond (**III**)	
	$r_{C=C}$ (Å)	$R_{I\text{-}II}$ (Å)	Ψ (°)	$r_{C=C}$ (Å)	$R_{II\text{-}III}$ (Å)	Ψ (°)	$r_{C=C}$ (Å)	Ψ (°)
B3LYP/6-311G(d,p)	1.335	2.962	6.243	1.330	3.077	1.106	1.331	0.236
B3LYP/6-311++G(d,p)	1.336	2.964	6.207	1.330	3.079	1.075	1.332	0.171

pyramidalization parameters[36,37] of the molecule were evaluated with the aim of determining the structural deformation of double bonds. The HDTD molecule has three paralel [norbornenyl double bond (**I**), central double bond (**II**) and bicyclo[2,2,2]octenyl double bond (**III**)] (Scheme 2) face-to-face aligned double bonds. The calculated values of the out-of-plane bending angle (ψ) (out-of-plane angle between the planes C13C14C15C16 and H14C14C15H15 or ψ which is defined as $\psi = 180° - |D|$, D is the dihedral angle C13C14C15H15 as shown in Scheme 2[37-39] were calculated according to the results of each method. The distance (R) (distance between midpoint of opposing C=C double bonds) and the orientation angle (θ) (dihedral angle between two planes containing four unsaturated carbon atoms in the minimum energy structure of the HDTD molecule)[40] were determined. These results are given in Table 1.

Table 2 — Calculated relative energies of cations

Cations	Relative energy (kcal mol^{-1})		
	B3LYP/ 6311G(d,p)	B3LYP/6311++G(2d,2p) //B3LYP/6-311G(d,p)	CPCM-B3LYP/6311++G(2d,2p) //B3LYP/6-311G(d,p)
U-N-type (II)	0.0	0.0	0.0
U-U-type (III)	2.888	2.948	3.072
N-N-type (IV)	4.083	4.138	4.144
N-U-type (V)	6.906	7.083	7.459

The θ angle between the double bonds of the HDTD molecule is approximately zero.

According to the results, norbornenyl double bond (**I**) of the HDTD molecule was endo pyramidalized, on the other hand the central double bond (**II**) and bicyclo[2,2,2]octenyl double bond (**III**) were exo pyramidalized. Among the double bonds, the most pyramidalized one (the one with the most structural deformation) is norbornenyl double bond (**I**) (Table 1). The norbornenyl double bond is more strained and more reactive toward addition reactions than the bicyclo[2,2,2]octenyl double bond[41]. When the pyramidalization degree of the double bond of olefins increases, their chemical reactivites also increase[42]. Analysis of frontier orbital (HOMO) of the HDTD molecule showed that the electron density ($q_{\mu,\ HOMO}$) in exo face of norbornenyl double bond (**I**) is high. The attack of bromine to the HDTD molecule occurs on the sterically less hindered exo face of the norbornenyl double bond (**I**) which has more electron density. As known, olefin-halogen molecular CT-complex is formed in the first step of electrophilic addition to olefins of halogens[11, 13-15, 33, 43]. The polarization of bromine and the subsequent heterolytic splitting of HDTD**…**Br_2 molecular CT-complex results in the formation of the bridged cation **I** (Scheme 2). It is possible for the bridged cation **I** to transform into N-N-, N-U-, U-U- and U-N-type cations as a result of intramolecular skeletal isomerization (Scheme 2). These cations are the possible intermediates of the addition reactions of bromine to HDTD molecule in gas phase and in solution.

Generally, the electrophilic addition reaction of halogens to alkenes realizes over the more stable cations. Hence, the investigation of the structure, stability and their mutual transformation is important so as to develop theoretical ideas about their addition reactions and learn the mechanism and stereochemistry of these reactions. The structures and relative stabilities of these cations were determined by carrying out geometrical optimization using the B3LYP/6-311G(d,p) methods and the total energies were also calculated. By using the optimized geometries of cations at the B3LYP/ 6-311G(d,p) level, their single point energies have been computed using B3LYP/6-311++G(2d,2p) and CPCM-B3LYP/6-311++G(2d,2p) methods. The calculated relative energies are given in Table 2.

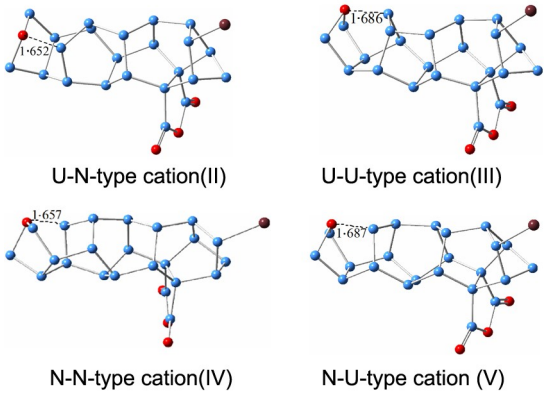


Fig. 1 — The optimized geometries of cations [B3LYP/ 6-311G(d,p)]. (Distances are in Å).

According to the results of each method, the N-N-, N-U-, U-U- and U-N-type cations (Scheme 2) are more stable than the bridged-bromonium cation **I**. The skeletal isomerization of the bridged-bromonium cation into N-N-, N-U-, U-U- and U-N-type cations is thermodynamically feasible. The most stable cation among N-N-, N-U-, U-U- and U-N-type cations is U-N-type cation (Table 2) Therefore, the addition reaction of bromine to HDTD molecule should occur over U-N-type cation. Thus, the direction of the reaction is determined by the direction of the intramolecular skeletal rearrangement of the bridged-bromonium ion **I** into U-N-type ion so as to form the skeletal structure. The stability of the skeletal structure formed as a result of the intramolecular skeletal isomerization of bridged-bromonium ion **I** depends primarily on the types and stability of the new cyclic structures included in the molecular system as a result of the isomerisation. Cross (N-type) linkage of norbornenyl (**I**) and central (**II**) double bonds causes deformation in the planar structure of the anhydride ring (Fig. 1) and hence reduction in the

stabilities of N-N- and N-U-type cations. The analysis of the electronic and geometric structures of N-N-, N-U-, U-U- and U-N-type cations indicates a mutual interaction between the cation centre in these ions and the unshared electron pairs of the oxygen atom of tetrahydrofuran ring (Fig. 1). The interaction, which takes place for the cations, causes the ions to become more stable by bringing about specific changes in the electronic and geometric structure of the ions. In these cations, the distance ($R_{O\text{-}C}^{+}$) between the oxygen atom of the tetrahydrofuran ring and the cation centre decreased. For U-N-type cation, the $R_{O\text{-}C}^{+}$ internuclear distance was 1.652 Å [(B3LYP/6-311G(d,p)]. Hence, the cation centre of the skeletal rearrangement ions were hindered sterically by the tetrahydrofuran ring on the exo face (Fig. 1). Therefore, for the determination of the stability of skeletal rearrangement of ions, the skeletal structure of the cation and the interaction between the cationic center and oxygen atom of tetrahydrofuran ring are important.

The electrophilic addition reaction of bromine to HDTD molecule takes place over the more stable U-N-type cation into which the bromonium ion isomerizes through parallel-cross mechanism. Since the cation centre of the U-N-type ion mutually interacts with the unshared electron pair of the oxygen atom of the tetrahydrofuran ring on the exo face, and is sterically hindered by the tetrahydrofuran ring, the nucleophilic attack occurs on the endo face and as a result, exo,endo-dibromide isomer of the U-N-type product is obtained. As can be seen, the electronic and steric factors are important for the determination of the direction of the attack of the bromide anion (Br^{-}) towards the cationic centre of U-N-type cation. The stability of U-N-type ion and the structure of its cationic centre are effective on the determination of the direction of addition reaction and the stereochemistry of products.

By fully optimizing the geometric structures of the exo,exo- and exo,endo-isomers of U-N-type reaction product and of other dibromides (Fig. 2) by B3LYP/6-311G(d,p) method, their total energies were calculated and their stereochemistry were investigated. The single point energies of dibromides were calculated by using B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p) and CPCM-B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p) methods. The calculated relative energies are given in Table 3. According to the results of each method, the exo,endo-isomer of the U-N-type dibromide molecule, is more stable than the exo,exo-isomer. Therefore, thermodynamically, the formation of exo,endo-isomer of U-N-type product is more feasible. The most stable dibromide among those dibromides investigated is U-N(exo,endo)-dibromide (Fig. 2).

The energy diagram of the electrophilic transannular addition reaction of bromine to the HDTD molecule obtained from B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d) and CPCM-B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p) methods is given in Fig. 3. As can be seen from the energy diagram, the reaction takes place over the most stable U-N-type cation and finally an U-N(exo,endo)-dibromide is obtained. Thus, the reaction occurs by

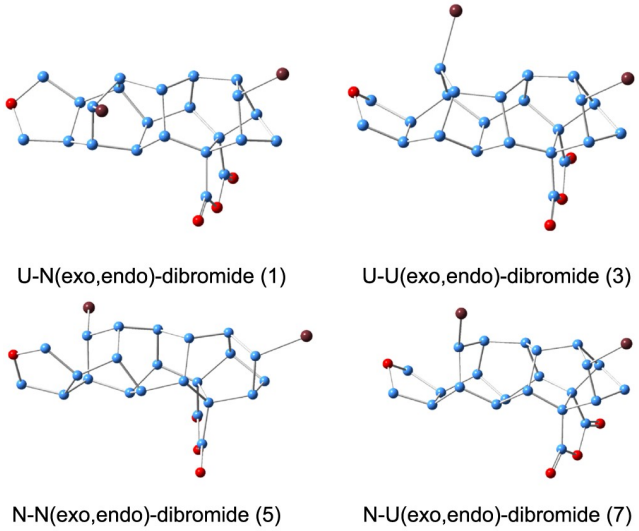


Fig.2 — The optimized geometries of products [B3LYP/6-311G(d,p)].

Table 3 —The calculated relative energies of products

Dibromides	Relative energy (kcal mol^{-1})		
	B3LYP/6311G(d,p)	B3LYP/6311++G(2d,2p) //B3LYP/6-311G(d,p)	CPCM-B3LYP/6311++G(2d,2p) //B3LYP/6-311G(d,p)
U-N(exo,endo)	0.0	0.0	0.0
U-N(exo,exo)	6.985	6.913	5.726
U-U(exo,endo)	2.614	3.254	3.297
N-N(exo,endo)	2.672	3.438	3.348
N-U(exo,endo)	6.386	7.125	7.464

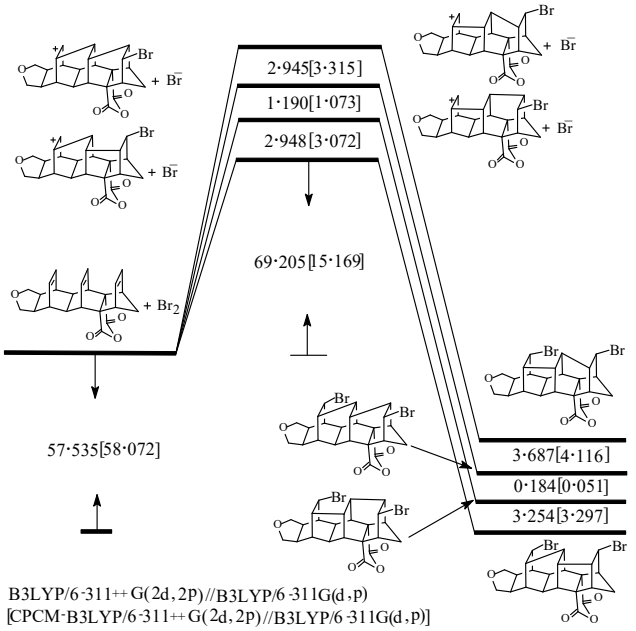


Fig. 3 — The energy diagram of HDTD-Br2 system (kcal mol^{-1}).

the formation of the most stable intermediate (U-N-type cation). At the same time, thermodynamically the most stable reaction product is U-N(exo,endo)-dibromide. In addition, the energy barrier between the reactants (HDTD+Br_2) and the lowest energy ionic intermediates (intermediates with low energy) (U-N-type cation + Br^-) is 69.205 kcal mol^{-1} in the gas phase and is 15.169 kcal mol^{-1} in the solvent medium (chloroform). Hence, in comparison to the gas phase, the energy barrier is lower in solvent medium (chloroform), and the reaction takes place easily.

Conclusions

Norbornenyl double bond (**I**) of the HDTD molecule was endo pyramidalized, however the central double bond (**II**) and bicyclo[2,2,2]octenyl double bond (**III**) were exo pyramidalized. The most pyramidalized double bond (the one with more structural deformation) is norbornenyl double bond (**I**). The norbornenyl double bond is more strained and more reactive toward addition reactions than the bicyclo[2,2,2]octenyl double bond. The attack of bromine to the HDTD molecule realizes on the sterically less hindered exo face of the norbornenyl double bond (**I**) with more electron density. The N-N-, N-U-, U-U- and U-N-type cations are more stable than the bridged-bromonium cation. The most stable cation among N-N-, N-U-, U-U- and U-N-type cations is U-N-type cation. The electrophillic addition reaction of bromine to HDTD molecule takes place over the more stable U-N-type cation into which the bridged-bromonium ion isomerized by paralel-cross mechanism. Since the cation centre of the U-N-type ion mutually interacts with the unshared electron pair of the oxygen atom of the tetrahydrofuran ring on the exo face, and is sterically hindered by the tetrahydrofuran ring, the nuclephilic attack of the bromide anion (Br^-) realizes on the endo face and as a result, exo,endo-dibromide isomer of the U-N-type product is obtained. The exo,endo-isomer of the U-N-type dibromide molecule, is more stable than the exo,exo-isomer. The theoretical results are in agreement with those obtained by the experimental investigation of the addition of bromine to 6-oxa-heptacyclo[9.6.2.2^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]docosan-14,18,20-triene-12,17-dicarboxylic anhydride[7].

References

1 Goldstein M J & Hoffmann R, *J Am Chem Soc*, 93 (1971) 6193.
2 Hoffmann R, Imamura A & Hehre W J, *J Am Chem Soc,* 90 (1968) 1499.
3 Hoffmann R, *Acc Chem Res,* 4 (1971) 1.
4 Grimme W, Wortmann J, Frowein D, Lex J, Chen G & Gleiter R, *J Chem Soc Perkin Trans,* 2 (1998) 1893.
5 Gleiter R & Schafer W, *Acc Chem Res,* 23 (1990) 369.
6 Lin C T, Wang N J, Tseng H Z & Chou T C, *J Org Chem,* 62 (1997) 4857.
7 Lin C T, Hsu H C & Chou T C, *J Org Chem,* 64 (1999) 7260.
8 Abbasoglu R, Magerramov A & Asamaz Y, *Acta Chim Slov,* 56 (2009) 237.
9 Roy R K, Krishnamurti S, Geerlings P & Pal S, *J Phys Chem A,* 102 (1998) 3746.
10 Chiappe C, Rubertis A D, Lemmen P & Lenoir D, *J Org Chem,* 65 (2000) 1273.
11 Chiappe C, Rubertis A D, Detert H, Lenoir D, Wannere C & Schleyer R P, *Chem Eur J,* 8 (2002) 967.
12 Rathere R, Lindeman S V, Zhu C J, Mori T, Schleyer R P & Kochi J K, *J Org Chem,* 67 (2002) 5106.
13 Lenoir D & Chiappe C, *Chem Eur J*, B9 (2003) 1037.
14 Herges R, Papafflippopoulos A, Hess K, Chiappe C, Lenoir D & Detert H, *Angew Chem Int Ed,* 44 (2005) 1412.
15 Chiappe C, CPomelli C S, Lenoir D & Wattenbach C, *J Mol Model,* 12 (2006) 631.
16 Wang S C & Tantillo D J, *Eur J Org Chem,* 3 (2006) 738.
17 Balcı M, Güney M, Daştan A & Azizoglu A, *J Org Chem,* 72 (2007) 4756.
18 Islam S M & Poirier R A, *J Phys Chem A,* 112 (2008) 152.
19 Kong J, Roy D, Lenoir D, Zhang X, Zou J & Schleyer P R, *Org Let,* 20 (2009) 4684.
20 Abbasoglu R, *J Mol Model,* 12 (2006) 991.
21 Abbasoglu R, *J Mol Model,* 13 (2007) 425.
22 Abbasoglu R, *J Mol Model,* 13 (2007) 1215.
23 Abbasoglu R & Magerramov A, *Acta Chim Slov,* 54 (2007) 882.
24 Abbasoglu R, Uygur Y & Magerramov A, *Indian J Chem,* 47B (2008) 90.
25 Abbasoglu R, *J Mol Model,* 15 (2009) 397.
26 Abbasoglu R & Magerramov A, *Indian J Chem,* 48A (2009) 1091.

27 Abbasoglu R & Yasar A, *Turk J Chem,* 34 (2010) 127.
28 Abbasoglu R, *J Mol Model,* 16 (2010) 781.
29 Lee C, Yang W & Parr R G, *Phys Rev B,* 37 (1988) 785.
30 Becke A D, *J Chem Phys*, 98 (1993) 5648.
31 Krishnan R, Binkley J S, R Seeger & Pople J A, *J Chem Phys*, 72 (1980) 650.
32 Barone V & Cossi M, *J Phys Chem A,* 102 (1998) 1995.
33 Tomasi J, Mennucci B & Cami R, *Chem Rev*, 105 (2005) 2999.
34 Takano Y & Houk K N, *J Chem Theory Comput,* 1(1) (2005) 70.
35 *Gaussian 03, Revison B03,* Gaussian, Pittsburgh, PA, 2003.
36 Borden W T, *Chem Rev,* 89 (1989) 1095.
37 Ermer O, Bell P & Mason S A, *Angew Chem Int Ed Engl*, 28 (1989) 1239.
38 Margtic D, Williams V R & Warrener N R, *J Org Chem,* 68 (2003) 9186.
39 Vazquez S & Camps P, *Tetrahedron,* 61 (2005) 5147.
40 Osawa E, Aigami K & Inamoto Y, *J Org Chem,* 42 (1977) 2621.
41 Huisgen R, Ooms P H J, Mingin M & Allinger N L, *J Am Chem Soc,* 102 (1980) 3951.
42 Watson W H, *Stereochemistry and Reactivity of Systems Containing π Electrons,* (Verlag Chemie Int, Florida, USA) 1983, pp. 75-104.
43 Legon A C & Thumwood J M A, *Phys Chem Chem Phys,* 3 (2001) 1397.