Methyl 1,3-Diphenylbicyclo[1.1.0]butane-2-*exo*-carboxylate. New Example of the Thermal Inversion of Bicyclobutane System

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Received February 16, 2012

Abstract—A fact of a reversible thermal inversion of *exo-* and *endo-*isomers of methyl 1,3-diphenylbicyclo[1.1.0] butane-2-carboxylate was established experimentally. The equilibrium constant of the process at 126°C is 14.2 with *endo-*isomer prevailing. Using DFT/PBE/L22 method the geometry of the isomers was optimized and also the geometry of the previously studied related *exo,exo-* and *endo,endo-*isomers of dimethyl 1,3-diphenylbicyclo[1.1.0] butane-2,4-dicarboxylate. The energy barrier of these mutual conversions was estimated.

DOI: 10.1134/S1070428012080027

Up till now a single case is described of a reversible thermal inversion of the bicyclobutane system which has been observed at 120–140°C in compounds I and II [1–3]. This process requires a rupture of the central C^{1} – C^{3} bond.



For the isomerization $Ia \rightleftharpoons Ib$ the equilibrium constanst (*K* 1.40 ± 0.07) and activation parameters ($\Delta H^{\ddagger} 26 \pm 2 \text{ kcal mol}^{-1}, \Delta S^{\ddagger} 9 \pm 4 \text{ e.u.}$) were evaluated using NMR spectroscopy [3].

The absence of other examples of bicyclobutane system inversion is due to the proceeding of all known cases of the thermal isomerization of the bicyclobutane compounds by the more feasible route to the formation of 1,3-butadiene derivatives via a concerted rupture of two side C–C bond with the retention of the central C^{1} – C^{3} bond [4]. Various calculation methods estimate the inversion barrier of the bicyclo[1.1.0]butane proper from 30 to 90 kcal mol⁻¹. The calculation by the method GVB/6-31G(d) estimated the value of the barrier at 50.0 kcal mol⁻¹[5] exceeding by 10 kcal mol⁻¹ the activa-

tion energy of the bicyclobutane-butadiene isomerization [6]. Unlike the bicyclobutanes with tetrahedral carbon atoms in the positions 2 and 4, which are just the object of this study, the bicyclobutane with a trigonal carbon atom in the position 2, namely 1,3-di(*tert*-butyl)bicyclo[1.1.0] butan-2-one undergoes the inversion already at 30°C, whose barrier measured experimentally by dynamic ¹H NMR spectroscopy is 16.7 kcal mol⁻¹[7].

Obviously the phenyl substituents in the nodal positions of bicyclobutanes I and II facilitate the opening of the C^{1} – C^{3} bond at the expense of the benzyl resonance favoring the inversion process compared with the isomerization into the butadiene derivative, which actually occurs with these compounds only at a higher temperature (180°C) [1].

Looking for the other bicyclobutane derivatives capable of the thermal inversion we turned to compound **IIIb**. It was first synthesized in [8] by the cleavage of tricyclopentanone **IV** with sodium methylate, and later it was obtained in [9] at the thermal decomposition of a derivative of 2,3-diazabicyclo[3.1.0]-hex-2-ene (**V**). The configuration was assigned to compound **IIIb** based on the Masamune method of its synthesis. Stereoisomer **IIIa** was unknown.

We prepared monoester **IIIb** in the crystalline state by Komendantov procedure and investigated its thermal



stability. Boiling the sample in octane (30 min, 126°C) led to the formation of a mixture of the initial bicyclobutane **IIIb** and its diastereomer **IIIa** in the ratio 93.4 : 6.6. Compound **IIIa** was isolated by column chromatography on silica gel as an oily substance that failed to crystallize. The thermolysis of bicyclobutane **IIIa** under the same conditions resulted in the same mixture of compounds **IIIa**, **IIIb** in the same ratio. Thus the equilibrium constant K of the isomerization **IIIa** \rightleftharpoons **IIIb** proved to be 14.2 \pm 0.2, by an order of magnitude larger than the isomerization constant **Ia** \rightleftharpoons **Ib**.



Stereoisomeric bicyclobutanes IIIa, IIIb were characterized by the ¹H and ¹³C NMR spectra. Therewith the comparison of their ¹H NMR spectra confirmed the adequacy of the configuration assignment. In particular, only in the spectrum of the endo-isomer IIIb the signals of exo-protons H² and H⁴ were split due to the long-range spin-spin coupling with a constant $^{4}J4.3$ Hz (*W*-rule [10]). In contrast, all the ring protons of the *exo*-isomer IIIa give rise to singlets because of a small (0-1.0 Hz) geminal coupling constant characteristic of bicyclobutanes and the lack of long-range spin-spin coupling. The assignment performed is consistent with the strong difference in the chemical shifts of H² protons of the stereoisomers: In compound IIIa the endo-proton H² occurs in the region of the magnetic shielding of te opposite three-carbon ring, and in compoundand IIIb the exo-proton H² suffers a deshielding due to the rapproachement of the phenyl substituents.

Therefore the interconversions of compounds **IIIa**, **IIIb** that we have performed are a new example of the thermal reversible *exo*,*endo*-isomerization in the bicy-clobutane series.

In order to reveal the features of the structure of bicyclobutanes Ia, Ib and IIIa, IIIb and to estimate the

relative stability of stereoisomers the geometry optimization of these structures and for the sake of comparison also of a model structure of the known [11] 1,3-diphenylbicyclo[1.1.0]butane (VI) was performed by DFT method. The perspective appearance of the most feasible conformations of the compounds is presented in Fig. 1. The search for the structures was carried out using molecular mechanics methods by the program ChemAxon MarvinBeans [12]. The selected characteristics of the bicyclobutanes in question are given in the table. It turned out that the planes of the phenyl rings in compound VI are strictly orthogonal to the plane passing through the atoms $C^{5}C^{3}C^{1}C^{5'}$. We regarded this position as standard and characterized the positions of the phenyl rings at the atoms C^1 and C^3 in compounds Ia, Ib and IIIa, IIIb by the angles of the deviation from the standard plane φ_1 and φ_2 respectively. We also present in the table the corresponding parameters of compounds Ia, Ib that we have borrowed from the experimental data obtained by XRD analysis of single crystals of these compounds [13]. The geometry characteristics calculated for the gas phase are in general close to those experimentally measured indicating the sufficient level of the quantum-chemical calculations and makes it possible to discuss the details of the structure and find the difference in the structures I and III. Some distinctions may be attributed to the features of the crystal packing of the molecules.

The most important feature of structures **Ib** and **IIIb** is the orientation of the phenyl rings close to that in bicyclobutane **VI** as show the small vlues of angles φ_1 and φ_2 (see the table). Therewith any steric interactions are absent in these compounds both between the phenyl groups proper and between the phenyl groups and *exo*-H^{2,4} atoms. Just this orientation of the phenyl rings is the most favorable for the conjugation between them transferred by the "banana" C¹–C³ bond and consisting of the overlapping of nearly pure *p*-atomic orbitals [14].





Fig. 1. Perspective view of molecules Ia, Ib, IIIa, IIIb, VI. Hydrogens atoms are not shown.

The experimental confirmation of the existence of the conjugation between two phenyl groups in compounds **Ib**, **IIb**, **IIIb**, **IV** was obtained by their UV spectra possessing a strong absorption in the long-wave region (~270 nm, $lg\epsilon \sim 4.0$) [3, 8, 15–17] close to the absorption region of the stilbene chromophore.

In compounds **Ia** and **IIIa** the phenyl rings are turned to the opposite sides with respect to the plane $C^{I}C^{3}C^{5}C^{5'}$ impeding their conjugation through the central bicyclobutane bond $C^{I}-C^{3}$. The absence of the conjugation between the phenyl rings in compounds **Ia** and **IIIa** is indicated by the lack of the long-wave absorption in the UV spectrum [15–17]. The reason of this orientation consists in the stric interactions between the *ortho*-hydrogens of the phenyl groups and the *exo*-methoxycarbonyl groups.

Another feature distinguishing the *endo*- and *exo*isomers of compounds under consideration is the considerable difference in the values of the α angles. The bicyclobutane fragment in *exo*-isomers **Ia** and **IIIa** is somewhat flattened as compared with compound **VI** whereas in the *endo*-isomers **Ib**, **IIIb** it is more convoluted. Therewith in diesters **Ia**, **Ib** the deviations from the standard are considerably larger than in monoesters **IIIa**, **IIIb**. This is evidently due to essentially greater steric interactions involving two methoxycarbonyl groups in compounds **Ia**, **Ib** than in monoesters **IIIa**, **IIIb** (see the table).

The changes in the length and order of the bond C^{1} -C³are also of interest. In exo-isomer IIIa and especially in the exo, exo-isomer Ia these values are essentially smaller than in compound VI, whereas in the endo, endo-isomer Ib and especially in the endo-isomer IIIb the deviations from the standard are insignificant. The side bonds in the bicyclobutanes of the "b" configuration are notably shorter of the same bonds in the diastereomers "a" (see the table). Methoxycarbonyl groups in compounds Ia, IIIa, IIIb are materially normal to the planes of the cyclopropane rings. In endo-isomer Ib the methoxycarbonyl groups are turned to opposite dides with respect to each other and form an angle of ~53° to the planes of the threemembered rings (see angles β and γ in the table). This orientation of the groups in compound Ib is the result of their strong reciprocal repulsion, and it destabilizes the molecule. At the same time in the monoester IIIb

Selected g chemical	geometrical para calculations DF	meters, total - T/PBE/L22 a	(E) and relat and of XRD	ive (ΔE) energ analysis [13] ^a	ies of bicycloł	butanes I, III,	VI, VII and t	ransition state	s TS1–TS4	ł accordii	ng to the	data of c	uantum-
Ctenotreo	; ;	ZPE, a.u.	ΔE ,		Interatomic d	listances, Å (b	yond orders)		An	gle betw	een plan	es, deg ^b	
DILUCIULE	<i>ь</i> , а.u.	(kcal mol ⁻¹)	kcal mol ⁻¹	C1–C2	C2-C3	C3-C4	$C^{I-C^{4}}$	C1-C3	α	β	λ	φ1	φ_2
Ia	-1072.974946	0.324059	0	1.515 (0.87)	1.533 (0.87)	1.515 (0.87)	1.533 (0.87)	1.465 (0.86)	112.7	93.1	93.2	56.3	55.8
		(203.3501)		[1.517]	[1.527]	[1.498]	[1.522]	[1.455]	[113.4]	[90.5]	[86.6]	[72.8]	[52.3]
Ib	-1072.973923	0.323817	0.49	1.494 (0.92)	1.507 (0.91)	1.494 (0.92)	1.507 (0.91)	1.567 (0.68)	127.1	53.0	54.0	1.1	1.3

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1.2

1.2

I

90.06

177.6

1.519(0.98) 1.519(0.98) 1.514(1.00) 1.514(1.00) 1.514(1.00) 1.987(0.29)

30.66

0.280839

-845.195679

TS2

(176.2291)

0.0

0.0

122.8

[20.3]

[6.0]

[60.7]

[49.6]

[127.2]

[1.558]

[1.506]

[1.497]

[1.505]

0.2

0.6

78.3

78.0

172.4

1.517 (0.98) 1.515 (0.98) 1.517 (0.98) 1.975 (0.11)

1.515 (0.98) [1.484]

27.87

0.31993

-1072.926403

TS1

(200.7985)

203.1981)

0

0.283176

-845.246869

IIIa

(177.6959)

31.5

29.0

I

90.6

118.2

1.517(0.89) 1.518(0.89) 1.504(0.89) 1.504(0.89) 1.504(0.89) 1.505(0.79)

0.7

0.9

Ι

92.5

125.2

1.507(0.92) | 1.509(0.92) | 1.503(0.94) | 1.503(0.94) | 1.542(0.73)

3.29

0.282644

-845.241096

dIII

(177.3617)

T T I I

179.9

1.517 (1.00) 1.517 (1.00) 1.517 (1.00) 1.517 (1.00) 1.999 (0.28)

32.08

-617.461240

TS3

(150.1852)

0

0.241786

-617.514818

7

(151.7233)0.239335

1.501(0.92) 1.501(0.92) 1.501(0.92) 1.501(0.92) 1.548(0.72)

0.1

0.1

I

L

I

I

121.7

1.500(0.92) 1.500(0.92) 1.500(0.92) 1.500(0.92) 1.492(0.84)

0

0.083923 (52.6623)

-155.803732

ΠΛ

I

Ι

I

I

179.8

1.508 (0.97) 1.508 (0.97) 1.508 (0.97) 1.508 (0.97) 2.058 (0.05)

45.95°

0.077680

-155.724253

TS4

(48.7452)

^b Angles between planes are as follows: $\alpha C^{2}C^{3}/C^{1}C^{4}C^{3}$, $\beta C^{1}C^{2}C^{2}nC^{2}C^{carb}O^{1}$, $\gamma C^{1}C^{4}C^{3}/C^{4}C^{carb}O^{1}$ $^{\circ}$ For the singlet transition state the barrier is 70 kcal mol⁻¹ ^a Data of XRD experiment are given in brackets.

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in good agreement with the experimental data. We applied the DFT method to the study of the energy profile of the experimentally observed inversion of the bicyclobutane system in compounds I and III, and of the hypothetical inversion in compound VI and in unsubstituted bicyclobutane VII. The structural features of the corresponding transition states TS1-TS4 were revealed. The energy barriers were evaluated along IRC procedure. The results are presented in the table. In the transition states TS1-TS3 the planes of the phenyl rings turned out to be orthogonal to the plane formed by the atoms C⁵C³C¹C⁵. This structure is favorable for the conjugation of the rings through the weakened central bicyclobutane bond C^{1} - C^{3} as is seen from the distribution of the electron density of HOMO of the carbon atoms of these intermediates (Fig. 2). In all likelihood the inversion in bicyclobutanes I, III, VI proceeds without a compleate cleavage of the central C^{1} - C^{3} bond as show the values of the interatomic distances $C^{1}-C^{3}$ and the nonzero order of this bond in the corresponding transi-

tion states (see the table). On the contrary, the transition

state TS4 is a biradical as shows the localization of the

electron density of HOMO exclusively on the atoms C¹

14 kcal mol⁻¹ exceeds the energy of TS3 which confirms

the considerable assistance to the thermal inversion of the

bicyclobutane system of the introduction of the phenyl

groups into the nodal positions of the bicyclobutane.

The calculation indicates also that the introduction of the

methoxycarbonyl groups into the positions 2 and 4 of the

1,3-diphenylbicyclobutane also results in the decrease of

the inversion barrier, namely, the energies of TS1 and TS2

are less by the energy than TS3 by 4.8 and 2.0 kcal mol⁻¹

According to the calculation the energy of TS4 by

and C³ (Fig. 2), cf. [18].

respectively.

with the endo-proton H⁴ is significantly less. Therefore it is possible to conclude that the relative stability of monoester **IIIb** should be higher than that of diester **Ib**. In each pair of diastereomers the endo-isomer "b"

the destabilizing steric interaction of the CO₂Me group

proved to be more stable than the exo-isomer "a" (see the table). However the energy difference of the diastereomers of diester I ($\Delta E 0.49$ kcal mol⁻¹) is notably less than that of the diastereomers of monoester III (ΔE 3.29 kcal mol⁻¹)

TS3 TS4

Fig. 2. Electron density distribution of HOMO in the transition states TS1-TS4 according to quantum-chemical calculation. The shown part of molecular orbital is described with the wave function with the positive sign.

spectrometer Bruker AC-300 (300.130 and 75.468 MHz respectively) in CDCl₃. The conditions of analytical TLC were as follows: adsorbent Silufol UV-254, eluent hexane-ethyl ether, 5:1, development in iodine chamber. The column chromatography was performed using silica gel 40/100µ.

The search for the most stable conformations of compounds Ia, Ib, IIIa, IIIb, VI was carried out applying the methods of molecular mechanics along the program ChemAxon MarvinBeans [12]. The obtained structures were further optimized using MOPAC2009 program [19] in the RM1 approximation [20]. The final calculation of structures and also the optimization of the geometry of the stationary points (minima and transition states) on the potential energy surface and the IRC procedure was performed by DFT method (functional PBE [21], basis L22 [22]) using PRIRODA software [23]. The correspondence of the maximum point to the transition state was confirmed by the presence of one imaginary frequency in the Hessian [53.66*i* (TS1), 124.37*i* (TS2) cm⁻¹]. The calculation and visualization of the electron density of the molecular orbital was done along MOLEKEL program [24].

Methyl-1,3-diphenyl-2-endo-bicyclo[1.1.0]butanecarboxylate (IIIb) was obtained by procedure [9], mp 74–75°C (mp 75°C [9]), R_f 0.25. ¹H NMR spectrum, δ, ppm: 2.70 d (1H, endo- H^4 , ²J 1.4 Hz), 2.96 d.d (1H, exo-H⁴, ²J 1.4, ⁴J 4.3 Hz), 3.78 s (3H, OMe), 4.04 d (1H,

EXPERIMENTAL

METHYL 1,3-DIPHENYLBICYCLO[1.1.0]BUTANE-2-exo-CARBOXYLATE.





exo-H², ⁴*J* 4.3 Hz), 7.11–7.28 m (10H, 2Ph). ¹³C NMR spectrum, δ, ppm: 31.4 (C^{1,3}), 35.1 (C⁴), 46.7 (C²), 51.7 (OMe); 125.3 (4C), 126.2 (2C), 128.3 (4C), 133.8 w (C_{arom}); 170.8 w (C=O).

Reversible thermal isomerization of compounds IIIa, IIIb. A solution of 30 mg of *endo*-bicyclobutanea IIIb in 1.0 ml of octane was boiled under an argon atmosphere for 30 min. The solvent was evaporated in a vacuum, the ratio of isomers **IIIa, IIIb** in the residue was determined from the ¹H NMR spectrum. The experiment was repeated three times, and the equilibrium constant $K(endo/exo) = 14.2 \pm 0.2$ was determined. The same value was obtained in similar experiments with *exo*isomer **IIIa**; here in each run ~10 mg of the substance was used. The longer heating (75 min) did not change the ratio of the *endo-* and *exo-*isomers.

Methyl-1,3-diphenyl-2*-exo*-bicyclo[1.1.0]butanecarboxylate (IIIa) was isolated by chromatographic separation of the product of the thermolysis of *endo*isomer IIIb. Oily substance, R_f 0.29. ¹H NMR spectrum, δ , ppm: 1.32 s (1H, *endo*-H⁴), 2.12 s (1H, *exo*-H⁴), 2.21 s (1H, *endo*-H²), 3.63 s (3H, OMe), 7.27–7.36 m (10H, 2Ph). CIERTP SIMP ¹³C NMR spectrum, δ , ppm: 28.8 (C^{1,3}), 33.2 (C⁴), 44.9 (C²), 51.4 (OMe); 126.7 (2C), 128.1 (4C), 128.6 (4H), 132.7 w (C_{arom}); 167.6 w (C=O). Found, %: C 81.92; H 6.22. C₁₈H₁₆O₂. Calculated, %: C 81.79; H 6.10.

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