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CLARIFICATION OF STEREOCHEMISTRY ASPECTS FOR *N*-HYDROXY-5-NORBORNENE-2,3-DICARBOXIMIDE DERIVATIVES AND ELUCIDATION OF THEM BY EXPERIMENTAL AND THEORETICAL INVESTIGATIONS, INCLUDING THE SYNTHESIS OF *N,N'*-BIS-*(5-EXO*-NORBORNENE-2,3-DICARBOXYIMIDYL) CARBONATE

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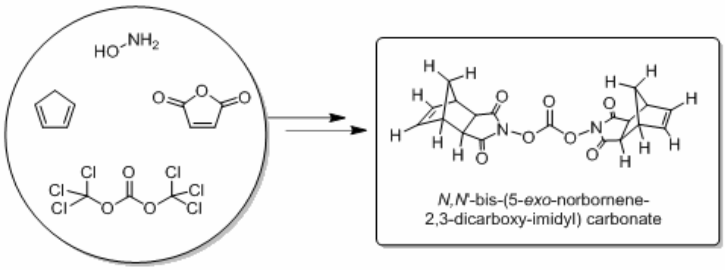
Ambiguities about the stereochemistry of *N*-hydroxy-5-norbornene-2,3-dicarboximide and *N, N'*-bis-(5-norbornene-2,3-dicarboxyimidyl) carbonate and confusing naming of *N*-hydroxy-5-norbornene-2,3-dicarboximide and its corresponding anhydride by literature and chemical sellers were addressed. This considered the stereochemistry itself as well as the description thereof. The unclear points could be elucidated by scientific deliberations and by practical and theoretical experiments. *N, N'*-bis-(5-*exo*-norbornene-2,3-dicarboxyimidyl) carbonate was synthesised for the first time and for comparison, the *exo* and *endo* isomer of *N*-hydroxy-5-norbornene-2,3-dicarboximide and *N, N'*-bis-(5-*endo*-norbornene-2,3-dicarboxy-imidyl) carbonate were manufactured. The molecular structures of *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide and *N, N'*-bis-(5-*endo*-norbornene-2,3-dicarboxy-imidyl) carbonate have been investigated by X ray crystallography. The stereochemistry assignments of corresponding *exo*-*endo* isomers pairs were studied by various NMR experiments and the thermodynamical heat of formation were calculated by theoretical methods. The *exo*-*endo* isomers pairs can be differed easily by the chemical shifts of special atoms. For the ^{13}C-NMR experiment is this salient atom the methylene bridge carbon and in the case of ^{1}H-NMR experiment this role fulfilled by the protons which defines the *exo*-*endo* isomerism. Using theoretical concepts, we could illustrate that the *exo* carbonate is thermodynamically more stable than its corresponding *endo* isomer. For the *exo* and *endo* isomers of *N*-hydroxy-5-norbornene-2,3-dicarboximide and their corresponding anhydrides, the *exo* isomers were just slightly favoured. These results underlined the experimental facts that the equilibration of them ends in a rate of nearly fifty-fifty.



INTRODUCTION

The symmetrical *N, N'*-bis-(5-norbornene-2,3-dicarboxyimidyl) carbonate (**1**) is represented by two different stereoisomers: the *exo* (**1a**) and the *endo* (**1b**) isomer (Figure 1). In 1980 Ogura and Takeda presented a synthesis of the *N,N'*-bis-(5-norbornene-2,3-dicarboxyimidyl) carbonate (**1**) in a German patent.[1] However, no information about the *endo*/*exo* configuration of *N,N'*-bis-(5

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norbornene-2,3-dicarboxyimidyl) carbonate (**1**) or its starting materials was mentioned. It must be assumed that the authors prepared the *endo*-carbonate **1b**. Their synthesis of **1b** starts with 5-norbornene-2,3-dicarboxylic anhydride (**2**), which results from a Diels-Alder reaction of maleic anhydride and cyclopentadiene. It is commonly known that the Diels-Alder reaction favours the *endo* isomer **2b** by kinetical control (Figure 1). Therefore, the authors must have used the 5-*endo*-norbornene-2,3-dicarboxylic anhydride (**2b**) as starting material for the synthesis of the *N,N'*-bis-(5-*endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**), having the *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**3b**) as intermediate. To the best of our knowing, the synthesis of *N,N'*-bis-(*5-exo*-norbornene-2,3-dicarboxy-imidyl) carbonate (**1a**) is still not described in the literature. Therefore, this synthesis was our main synthetic aim of the present work.

Synthetically the *exo* carbonate **1a** and the *endo* carbonate **1b** should be easily obtained from the corresponding *N*-hydroxy-5-*exo*-norbornene-2,3-dicarboximide (**3a**) and *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**3b**). Ogura and Takeda described in their patents[1,2] the synthesis of the *N,N′*-disuccinimidyl-, *N,N′*-diphthalimidyl-, and *N,N′*-bis-(5-norbornen-2,3-dicarboxyimidyl) carbonate using phosgene and the corresponding *N*-hydroxy imides and the use of them as reagents for the preparation of active amino acid esters. The *N,N'*-bis-(5-*endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**) and *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**3b**) have important applications in the peptide synthesis domain. Carbonate **1b** is a useful alternative for *N,N′*-disuccinimidyl-, and *N,N′*-diphthalimidylcarbonate in the preparation of special reactive amino acids esters.[1-4] Crystallographic studies on symmetric carbonates have been made on *N,N′*-disuccinimidyl carbonate[5,6], bis(*o*-nitro-phenyl) carbonate[7], bis(*p*-nitro-phenyl) carbonate[8] and *N,N′*-carbonyl-disuccinimide.[9] Crystallographic data cannot be found either for the *N,N'*-bis-(*5-exo*-norbornene-2,3-dicarboxy-imidyl) carbonate (**1a**) or for the *N,N'*-bis-(*5-endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**).

A decade after the work of Ogura and Takeda[1,2] was published, triphosgene was introduced by Ghosh *et al*. for the synthesis of symmetrical carbonates as an alternative of gaseous phosgene and liquid diphosgene.[10] It was shown that this phosgene analogue could be used for the carbonate synthesis without any disadvantage for the coupling reaction. While Ghosh *et al*. used dichloromethane as solvent and triethylamine as base, Pereira *et al*. presented an improved protocol for the synthesis of *N,N′*-disuccinimidylcarbonate using triphosgene, tetrahydrofuran and tri-n-butyl-amine, because of the better solubility of the reactants in that mixture.[11] This protocol is still state-of-the-art and was used for the synthesis of *N,N′*-disuccinimidyl-, and *N,N′*-diphthalimidyl-carbonate from e.g. Lee *et al*.[12] and Simon *et al*.[6,13] Also in our group, triphosgene is used routinely as an inexpensive and safe material.[14–16]

Recently, a synthesis for the *endo* form **1b** was described[17], based on the protocol of Pereira *et al*.[11] But the authors did not discuss the possibility that the synthesis of the *endo* isomer is described already in the previous published work of Ogura and Takeda.[1,2] An advantage to the Ogura protocol was the use of solid triphosgene instead of gaseous phosgene, which makes the handling of the synthesis easier and safer.

The intermediate *N*-hydroxy-5-*exo*-norbornene-2,3-dicarboximide (**3a**) can be obtained from 5-*exo*-norbornene-2,3-dicarboxylic anhydride (**2a**) and compound **3b** is synthesised from the *endo*-anhydride **2b**.[18,19] The *endo* anhydride **2b** is the kinetic product of the Diels-Alder reaction of maleic anhydride and cyclopentadiene (Figure 1). As usual for the Diels-Alder reaction, it is formed predominantly the *endo* product.[20-23] The *exo* anhydride **2a** cannot be produced by this method but it is accessible by isomerisation at elevated temperatures. Several studies about the *endo-exo* isomerization for the conversion of 5-*endo*-norbornene-2,3-dicarboxylic anhydride (**2b**) into its *exo* isomer **2a** have been made over the time.[24-26] The *endo-exo* isomerization occurs bellow *retro*-Diels-Alder reaction temperature.[26,27] The transformation results in an *exo-endo* rate between 50:50 to 60:40, which affords labour-intensive purification for the 5-*exo*-norbornene-2,3-dicarboxilic anhydride (**2a**). The right *endo-exo* assignments have been established by IR and NMR examinations.[1,2,28-30] The *endo-exo* transformation is also makeable for the *endo-N*-hydroxy imide **3b**.

Since the *exo*-carbonate **1a** has not been described in the literature until now, we wanted to present a synthesis protocol. This molecule has been investigated by variety of spectroscopical methods. The differences between the *endo-exo* isomers have been pointed out. Furthermore, the following aspect should be clarified: The anhydrides **2** and the *N*-hydroxy imides **3** are also represented just by their *exo* (**2a**/**3a**) and their *endo* (**2b**/**3b**) isomers (Figure 1), but there is also a quality sold where neither the stereochemistry is given nor it is mentioned that it is a mixture of isomers.

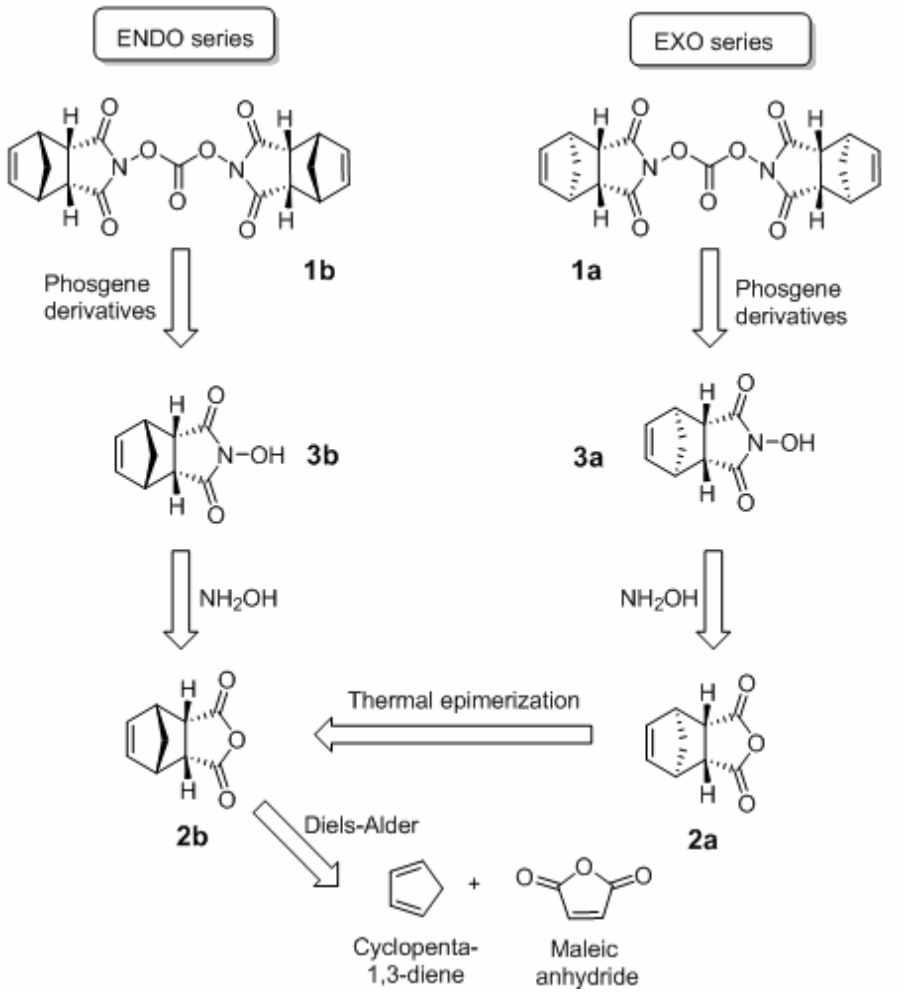

Fig. 1 – Retrosynthetic analysis for *N,N'*-bis-(5-*exo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1a**) and *N,N'*-bis-(5-*endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**).

RESULTS AND DISCUSSION

The *endo* isomer **3b** and the *exo* isomer **3a** of *N*-hydroxy-5-norbornene-2,3-dicarboximide have been obtained as white solids according to the literature.[19] The synthesis started from the commercially available *exo* and *endo* anhydrides, **2a** and **2b**, using hydroxyl amine and sodium carbonate as reagents in tetrahydrofuran.

Kotto and *Koskimies* recorded the ^{1}H-NMR and ^{13}C-NMR experiments for the *exo*-/*endo*-5-norbornene-2,3-dicarboxylic anhydrides **2a** and **2b**.[31] They found that the chemical shifts of the protons of the carbons 2 and 3 showed the highest difference between the *exo* and the *endo* isomer (Figure 2). The signal of the *exo* isomer is by a value of around 0.5 ppm shifted downfield (Table 1). This shifting switched the order of the signals from the protons H1/H4 and H2/H3. The differences of the chemical shifts for the other protons were not as significant. In the case of the carbon experiment the main difference between the *exo* and *endo* isomer is found for carbon 7. The signal of the *exo* isomer is by a value of around 8.5 ppm shifted downfield (Table 2).

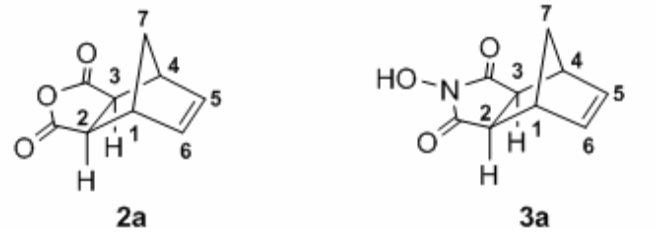

Fig. 2 – Numbering of 5-*exo*-norbornene-2,3-dicarboxyanhydride (2a) and *N*-hydroxy-5-*exo*-norbornene-2,3-dicarboximide (3a).

Table 1

^{1}H-NMR data (in ppm) measured in deuterated DMSO

	Carbonates		Anhydrides[31]		*N*-Hydroxy-imides	
	1a (*exo*)	**1b** (*endo*)	**2a** (*exo*)	**2b** (*endo*)	**3a** (*exo*)	**3b** (*endo*)
H-1 and H-4	3.38-3.30	3.59-3.51	3.39-3.47	3.47-3.55	3.11-3.07	3.25-3.21
H-2 and H-3	2.72-2.65	3.37-3.31	3.03	3.56-3.62	2.60-2.57	3.28-3.25
H-5 and H-6	6.36-6.32	6.16-6.08	6.33	6.30	6.31-6.27	6.07-6.03
H-7_{exo}	1.38	1.60	1.65	1.77	1.36	1.57
H-7_{endo}	1.13	1.54	1.42	1.59	1.13	1.48

Table 2

^{13}C-NMR data (in ppm) measured in deuterated DMSO

	Carbonates		Anhydrides[31]		*N*-Hydroxy-imides	
	1a (*exo*)	**1b** (*endo*)	**2a** (*exo*)	**2b** (*endo*)	**3a** (*exo*)	**3b** (*endo*)
C-Carbonyl	170.06	168.92	171.7	171.5	173.52	172.91
C-1 and C-4	44.17	43.80	46.8	46.1	44.03	43.85
C-2 and C-3	41.97	42.05	48.8	47.1	43.64	42.10
C-5 and C-6	137.43	134.67	137.8	135.5	137.18	134.37
C-7	40.44	50.82	44.1	52.7	40.12	51.01

This trend could be observed also for the *N*-hydroxy imides **3a** and **3b**. The ^{1}H-NMR spectra of the *exo*-/*endo*-*N*-hydroxy imides **3a** and **3b** were compared with the spectra of the *exo*-/*endo*-anhydrides **2a** and **2b**. The order of the signals is conserved for both types of isomers, the *endo* series and the *exo* series. The signals for the imides **3a** and **3b** are shifted to the high field. Again, the switch in the order of the signals H1/H4 and H2/H3 is shown by the *N*-hydroxy imides **3a** and **3b**, like it is observable for the anhydrides **2a** and **2b**. In the ^{13}C-NMR spectra of the imides the carbonyl carbons are found at lower fields than for the anhydrides. The differences of the chemical signals are more significant for carbon 7 of the imides **3a** and **3b** than for the anhydrides **2a** and **2b**.

A side aspect of interest was the fact that the anhydrides **2** and also the *N*-hydroxy imides **3** are sold basically in three different classifications: as *exo* isomer, as *endo* isomer and as a quality where the stereo configuration is not specified. Therefore, commercially available samples of 5-norbornene-2,3-dicarboxylic anhydride (**2**) and *N*-hydroxy-5-norbornene-2,3-dicarboximide (**3**) with unspecified stereochemical configuration were purchased from chemical suppliers. For both samples, the spectroscopical data were recorded and compared with our self-made *exo*-/*endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximides (**3a**/**3b**) and the purchased anhydrides (**2a**/**2b**). The conclusion was that both compounds with unspecified stereochemistry showed exclusively the specific signals for their corresponding *endo* isomer. In the case of the *N*-hydroxy imides **3**, the unspecified sample and our synthesised sample were compared with a commercially available *endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximides (**3b**). All three samples had the same spectroscopical data. As final proof, the unspecified sample of *N*-hydroxy imide **3** led exclusively to the *endo* carbonate **1b**. This fact makes sense since the compounds **2** and **3** are assessable via *endo*-favouring Diels-Alder reaction of maleic anhydride and cyclopentadiene. Nevertheless, the purities of the unspecified samples were remarkable. We bought *N*-hydroxy-5-norbornene-2,3-dicarboximides (**3**) as unspecified substance and *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximides (**3b**) as *endo*-declared isomer.

Interestingly, both substances had the same CAS-number [21715-90-2], although it can be found in the chemical abstract service for the *endo*-imide **3b** the CAS-number [39743-84-5].

The *exo* isomer and the *endo* isomer of the *N,N′*-bis-(5-norbornene-2,3-dicarboxyimidyl) carbonate **1a** and **1b** have been obtained like white solids according to the literature. Either the *exo*-/*endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximides **3a** and **3b** have been activated by trimethylsilyldiethylamine and transformed by phosgene in a tetrahydrofuran/toluene mixture,[1,2] or they have been dissolved in tetrahydrofuran and converted by solid bis(trichlormethyl) carbonate and tri-n-butylamine.[6,12,17]

The ^{1}H-NMR and ^{13}C-NMR of the *exo*-/*endo*-carbonates **1a** and **1b** reflects the symmetry of the molecules. The two norbornene subunits of the carbonates show for the equal protons and carbons the same chemical shifts. Overall, the chemical shifts (^{1}H- and ^{13}C-NMR) of the carbonates **1a** and **1b** are very similar to the precursors **3a** and **3b**. The carbonyl groups of the imide function have a higher difference in the chemical shift, which reflects the influence by the new established carbonate group. Furthermore, the carbonates **1a** and **1b** have a signal in the ^{13}C-NMR experiment which represents the carbonate carbon.

For further evidence of the structures of **1a**, **1b**, **3a** and **3b**, 2D spectra (HH-Cosy, HSQC, HMBC) and NOE experiments were recorded. The results confirmed the suggested structures. The carbonates **1a** and **1b** show just cross signals for the norbornene units. The *N*-hydroxy imides **3a** and **3b** present needed cross peaks (Figure 3).

The *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**3b**) has been crystallized from an acetone/ hexane equimolar mixture. The solid-state structure of the *endo* isomer was established by X-ray diffraction analysis (Figure 4); the *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**3b**) crystallises in the centrosymmetric space group $P2_1/c$ with one molecule in the asymmetric unit, with a = 11.9042(2) Å, b = 7.72924(10) Å, c = 9.3889(2) Å, β = 109.836(2)°, V = 812.63(2) Å^3, Z = 4, Dc = 1.464 Mg/m^3, λ = 1.54184 Å, μ(MoK_α) = 0.935 mm^{-1}, F(000) = 376. The OH group displays a short and linear intermolecular hydrogen bridge O3–H3···O1 1.75(2) Å, 175.1(18)°, operator: –x+1, y–0.5, –z+1.5. The hydrogen of the hydroxy group is involved in a classical hydrogen bond H(O3)···O1 which is short and linear with a distance of 1.75 Å. A second hydrogen bond H1···O1 is weaker and longer with a distance of 2.51 Å. This hydrogen bond is rather angled, probably attributed by the steric hinderance of the central ring, leading to ribbons of hydrogen bonded rings (Figure 5).

The *N,N′*-bis-(5-*endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**) has been crystallized from an acetone/hexane equimolar mixture. The solid-state structure of the *endo* isomer was established by X-ray diffraction analysis (Figure 6); the *N,N′*-bis-(5-*endo*-norbornene-2,3-dicarboxyimidyl) carbonate (**1b**) crystallises in the non-centrosymmetric space group Fdd2 with half a molecule in the asymmetric unit, with a = 23.389(2) Å, b = 22.532(2) Å, c = 6.3910(5) Å, V = 3368.1(5) Å^3, Z = 8, Dc = 1.516 Mg/m^3, λ = 1.54184 Å, μ(MoK_α) = 0.996 mm^{-1}, F(000) = 1600. The second half generates by a twofold axis along C10–O4. The interplanar angle between the five-membered ring N1–C8–C2–C3–C9 and the central unit O3–C10–O4–O3A is 78.46(4)°. The packing diagram shows that the molecules are linked through classical hydrogen bonds H4···O1, H2···O2, and H7A···O2 to form layers perpendicular to plane (110). It is seen clearly the doubled *cis*-conformation of the carbonate unit (Figure 7).

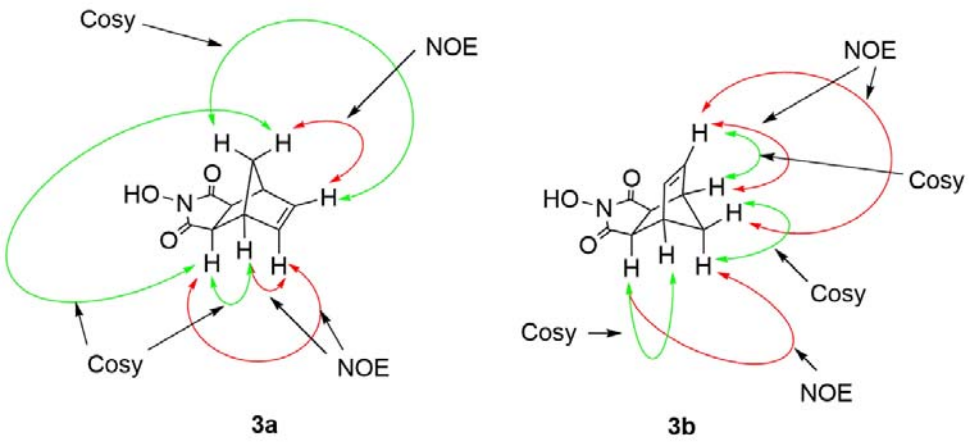

Fig. 3 – Strong NOE and HH-Cosy contacts for *N*-hydroxy imides 3a and 3b.

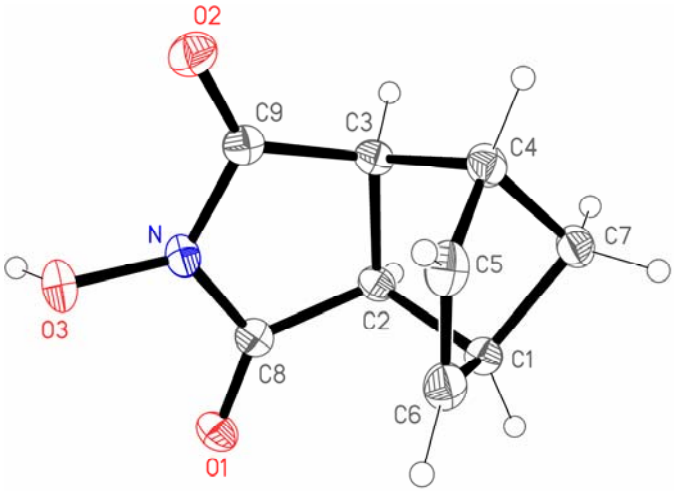

Fig. 4 – Molecular structure of *N*-hydroxy-*5-endo*-norbornene-2,3-dicarboximide (3b). Atoms are drawn as 50% thermal ellipsoids. Selected bond lengths [Å]: O2-C9 1.2079(14), O3-N 1.3806(12); selected angles [°]: C8-C2-C1 113.93(9), C9-C3-C4 113.82(9); selected dihedral angles [°]: C3-C9-N-O3 172.60(9), C3-C9-N-C8 0.96(12).

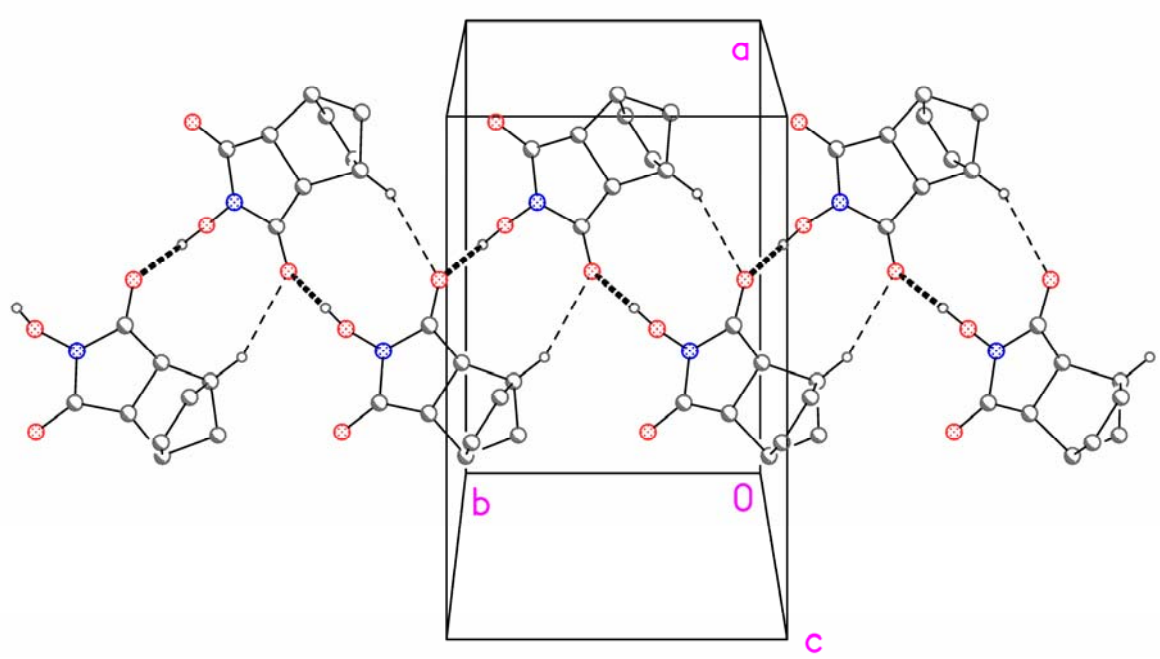

Fig. 5 – Packing diagram of compound 3b viewed perpendicular to the *ab* plane.
Dashed lines indicate the classical hydrogen bond H(O3)-O1 1.75 Å and the "weak" hydrogen bond H1-O1 2.51 Å.

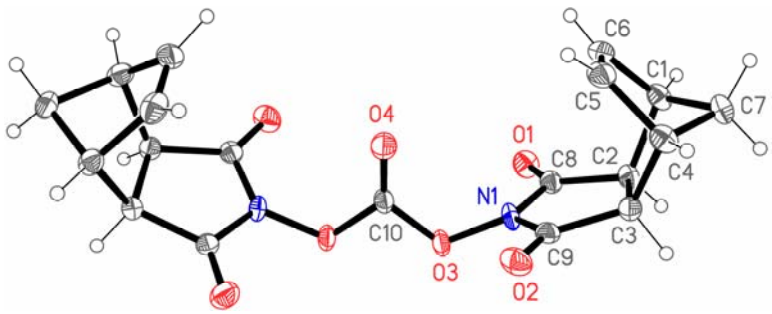

Fig. 6 – Molecular structure of *N,N'*-bis(*5-endo*-norbornene-2,3-dicarboxyimidyl) carbonate (1b). Atoms are drawn as 50% thermal ellipsoids. Selected bond lengths [Å]: O2-C9 1.2022(15), O3-N 1.3924(13), N1-C9 1.3941(16), C1-C7 1.5419(17); selected angles [°]: C4-C7 1.5433(13), C8-C2-C1 115.65(10), C9-C3-C4 116.40(11); selected dihedral angles [°]: O4-C10-O3-N1 -2.52(11), C10-O3-N1-C9 84.69(13), O3-N1-C8-C2 -166.63(10), C9-N1-C8-C2 4.63(15).

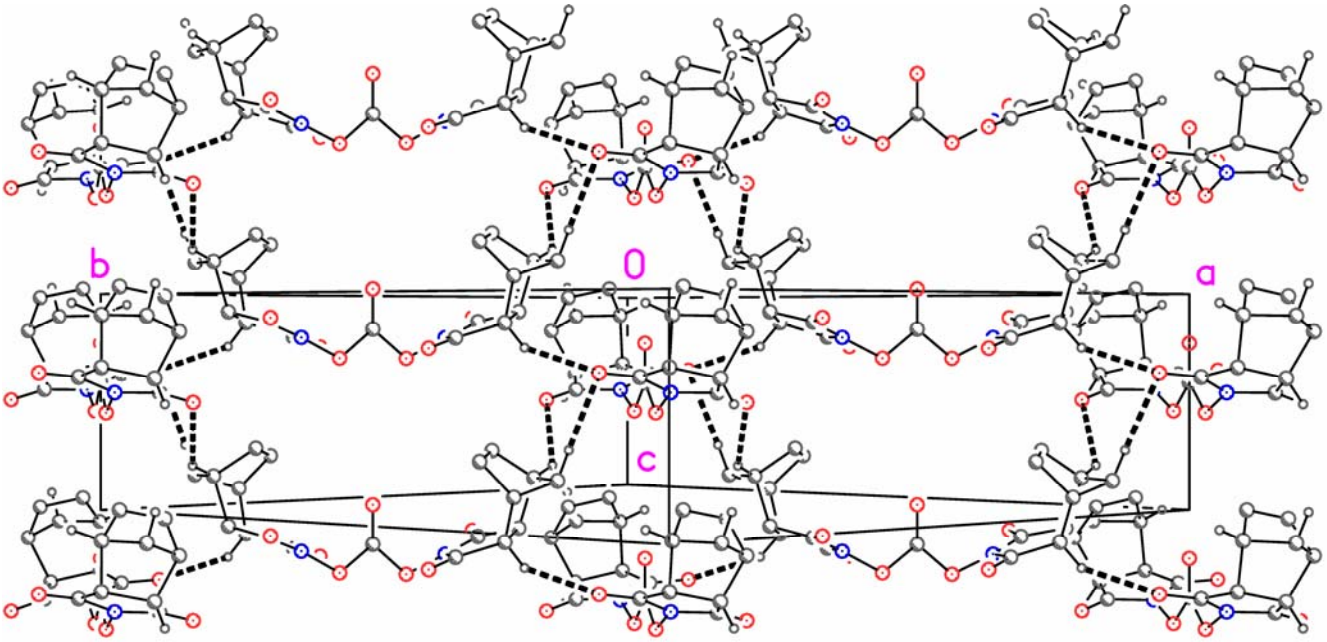

Fig. 7 – Packing diagram of compound 1b viewed perpendicular to the plane (110). Dashed bonds indicate the hydrogen bonding interactions [Å]: H4-O1 2.47, H2-O2 2.37, H7A-O2 2.53.

Table 3

Energy differences between the *endo*/*exo* isomers

Compound	$\Delta(E°_{endo} - E°_{exo})$ / kcal mol^{-1}	$\Delta(H°_{endo} - H°_{exo})$ / kcal mol^{-1}	$\Delta(G°_{endo} - G°_{exo})$ / kcal mol^{-1}
Anhydrides (**2a, 2b**)	0.9	0.9	0.8
N-OH (**3a**, **3b**)	0.7	0.7	0.7
Carbonates* (**1a**, **1b**)	2.7	2.7	2.5

* both isomers have been considered in their Z/Z conformation

Table 4

Energy differences between the different conformations of *endo* carbonate

Conformer	$\Delta(E°_{Z/Z} - E°)$ / kcal mol^{-1}	$\Delta(H°_{Z/Z} - H°)$ / kcal mol^{-1}	$\Delta(G°_{Z/Z} - G°)$ / kcal mol^{-1}
E/Z	-0.5	-0.5	-0.6
E/E	-2.4	-2.4	-4.2

THEORY

Since in the Diels-Alder reaction only the kinetically favoured 5-*endo*-norbornene-2,3-dicarboxylic anhydride (**2b**) will be formed, the corresponding *exo* isomer is accessible *via* a thermal epimerization of **2b** (Scheme 1). Experimentally, this thermal epimerization reaction is incomplete and always stops for neat conditions at a ratio of about 53:47 in favour of the *exo* compound (**2a**), suggesting that thermodynamically both isomers should have very similar energies. In order to shed light on this experimental result, we have performed additional theoretical calculations by means of density functional theory (DFT) methods at the B97-D/6-311G(d,p) level of theory, confirming that within the error limits both isomers are equal in energies (Table 3). The same energetic trend also holds true for the analogous *N*-hydroxy imides **3a** and **3b**, which we have calculated for comparison.

Based on our crystallographic data of the *endo* carbonate (**1b**) we calculated the energy differences between the *endo* and *exo* isomers in their Z/Z conformations revealing that the *exo* isomer is clearly the thermodynamically more stable isomer (2.5–2.7 kcal mol^{-1}). In addition, we have also looked at the energy differences for the respective E/Z and E/E conformations of **1b** (Table 4). While the energies for the *endo*-Z/Z and *endo*-E/Z conformers are almost identical within the DFT error limits (± 1 kcal mol^{-1}), the *endo*-E/E conformer is energetically much less preferred. Compared to the *endo*-Z/Z conformer the energy difference was calculated to by -2.4 kcal mol^{-1} for $\Delta E°$ and $\Delta H°$, whereas for $\Delta G°$ the difference is -4.2 kcal mol^{-1}.

Our calculations have shown that the respective in all cases the *exo* compounds are energetically slightly preferred over the *endo* isomers. While for the anhydride and the *N*-hydroxy imide the energy differences are within the theoretical error limits, this trend was significantly more pronounced for the Z/Z carbonates.

EXPERIMENTAL

All reagents were purchased from commercial sources (Sigma-Aldrich, Acros or ABCR) and used without further purification. Solvents were of analytical grade.

^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature on a Bruker Avance III 400 operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. 2D-spectra and NOE experiments were recorded at room temperature on a Bruker Avance III 500 operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts (δ) are reported relative to tetramethylsilane. In the case of multiplets, the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Mass spectra were recorded on a Finnigan MAT 8400-MSS and Finnigan MAT 4515. Column chromatography was carried out using Merck silica gel 60 (70–200 mesh).

Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of the diffractometer (Oxford Diffraction Nova). Intensity data were recorded at low temperature using mirror-focussed Cu-K_α radiation (λ = 1.54184 Å). Absorption corrections were based on multi-scans. The structures were refined anisotropically on *F*2 using the program SHELXL-97.[32] The OH-hydrogen was located in a difference synthesis and refined freely. Other hydrogens were refined using a riding model starting from calculated positions. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository numbers CCDC-1589365 (**1b**), and CCDC-1589366 (**3b**). (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

All computations were performed using the density functional method B97-D[33] as implemented in the Gaussian09 program.[34] For all main group elements (C, H, N and O) the all-electron triple-ζ basis set (6-311G**) was used.[35]

PROCEDURES

General Procedure A. The following protocol based on a procedure of Zinner and Düerkop.[19] Hydroxyl amine hydrochloride (833 mg, 12 mmol) and sodium carbonate (636 mg, 6 mmol) are dissolved in water (20 mL) and allowed to stir at room temperature. After 10 min the 5-norbornene-2,3-dicarboxylic anhydride (1.97 g, 12 mmol) is added, and the reaction mixture is stirred for another three hours at room temperature. Some solid material forms, which are filtered off, washed carefully with water (40mL) and dried under reduced pressure. The substance is used without further purification.

General Procedure B. The following protocol based on a procedure of Ogura and Takeda.[1,2] Trimethylsilyl-diethylamine (1.45 g, 1.9 mL, 10 mmol) is mixed with *N*-hydroxy-5-norbornene-2,3-dicarboximide (1.43 g, 8 mmoL). The resulting mixture is heated to 55°C for three hours using reflux facilities. Afterwards the developed Diethylamine and unreacted Trimethylsilyldiethyl-amine is removed under reduced pressure. The residue is taken up in tetrahydrofuran (30mL) and cooled to 0°C using an ice-bath. At this temperature a solution of phosgene in toluene (20mL, 15wt%, 30 mmol) is added. The reaction mixture is stirred for four hours under temperature control. Then the reaction mixture is allowed to warm up to ambient temperature. The solvents and the excess of phosgene is removed under reduced pressure. It remains a solid residue. This is washed twice with Acetone (each 50mL) and recrystalized from Acetonitrile. It remains a crystalline product which is used without further purification.

General Procedure C. The following protocol based on procedures from Simon *et al.*[6,13] , Pereira *et al.*[11] and Lee *et al.*[12] using the work up protocol from a recently presented synthesis of compound **1b**.[17] *N*-hydroxy-5-2,3-dicarboximide (717 mg, 4 mmol) is dissolved in tetrahydrofuran (8 mL) and cooled to 0°C using an ice-bath. Bis(trichloromethyl) carbonate (593 mg, 2 mmol) is added under stirring and allowed to stir for 15 minutes. To this reaction mixture is dropped a mixture of tri-(n-

butyl)-amine and tetrahydrofuran (1mL amine; 2 mL tetrahydrofuran) maintaining the temperature between 0 and 4°C. The reaction is stirred overnight. Then the tetrahydrofuran is removed under reduced pressure. The residue is taken up in ethylacetate (10mL) and washed with citric acid buffer, saturated sodium hydrocarbonate solution and brine. The organic phase was dried over sodium sulphate and the solvent is stripped under reduced pressure. The resulting solid is recrystallized from acetonitrile and is used without further purification.

Synthesis of (3aR,4R,7S,7aS)-2-hydroxy-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (N-hydroxy-5-exo-norbornene-2,3-dicarboximide) **(3a)** The substance is produced according to *general procedure A* using norbornene-*exo*-2,3-dicarboxylic anhydride (**2a**). Yield: 72 % (1.54 g, 8.6 mmol), GC-MS: *m*/*z* = 179 (5), 114 (10), 91 (15), 66 (100); $\delta_{\mathbf{H}}$ (DMSO, 400 MHz): 7.62 (bs, -O*H*), 6.31-6.27 (m, 2H, H-5, H-6), 3.11-3.07 (m, 2H, H-1, H-4), 2.60-2.57 (m, 2H, H-2, H-3), 1.36 (d, *J* = 9.73Hz, 1H, H-7_{exo}), 1.13 (d, *J* = 9.73Hz, 1H, H-7_{endo}); $\delta_{\mathbf{C}}$ (DMSO, 100 MHz): 173.52 (C=O, 2 C), 137.18 (CH, C-5, C-6), 44.03 (CH, C-1, C-4), 43.64 (CH, C-2, C-3), 40.12 (*C*H_2, C-7); H,H-Cosy, HMBC, HSQC, NOESY and NOE´s were made.

Synthesis of (3aR,4S,7R,7aS)-2-hydroxy-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (N-hydroxy-5-endo-norbornene-2,3-dicarboximide) **(3b)** The substance is produced according to *general procedure A* using norbornene-*exo*-2,3-dicarboxylic anhydride (**2a**). Yield: 66 % (1.41 g, 7.9 mmol), GC-MS: *m*/*z* = 179 (5), 114 (10), 91 (15), 66 (100); $\delta_{\mathbf{H}}$ (DMSO, 400 MHz): 10.50 (s, -O*H*), 6.07-6.03 (m, 2H, H-5, H-6), 3.28-3.25 (m, 2H, H-2, H-3), 3.25-3.21 (m, 2H, H-1, H-4), 1.57 (d, *J* = 8.65Hz, 1H, H-7_{exo}), 1.48 (d, *J* = 8.65Hz, 1H, H-7_{endo}); $\delta_{\mathbf{C}}$ (DMSO, 100 MHz): 172.91 (C=O, 2 C), 134.37 (CH, C-5, C-6), 51.01 (*C*H_2, C-7), 43.85 (CH, C-1, C-4), 42.10 (CH, C-2, C-3); H,H-Cosy, HMBC, HSQC, NOESY and NOE´s were made.

Synthesis of bis((3aR,4R,7S,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl) carbonate (N,N'-bis(5-exo-norbornene-2,3-dicarboxy-imidyl) carbonate) **(1a).** The substance is produced according to *general procedure B and C* using *N*-hydroxy-5-*exo*-norbornene-2,3-dicarboximide (**1a**). Yields: B: 74% (1.16 g, 3.0 mmol), C: 54% (417 mg, 1.1 mmol. The spectroscopical data were for both products practically identical. The data differed just in the second decimal place by values less than 0.02 ppm which is within the measuring span. $\delta_{\mathbf{H}}$ (DMSO, 400 MHz): 6.36-6.32 (m, 4H, H-5, H-6, H-5´, H-6´), 3.38-3.30 (m, 4H, H-1, H-4, H-1´, H-4´), 2.72-2.65 (m, 4H, H-2, H-3, H-2´, H-3´), 1.38 (d, *J* = 9.95Hz, 2H, H-7_{exo}, H-$7'_{exo}$), 1.13 (d, *J* = 9.95Hz, 2H, H-7_{endo}, H-$7'_{endo}$); $\delta_{\mathbf{C}}$ (DMSO, 100 MHz): 170.06 (C=O, 4 C), 148.13 (C=O, 1 C, carbonate), 137.43 (CH, C-5, C-6, C-5´, C-6´), 44.17 (CH, C-1, C-4, C-1´, C-4´), 41.97 (CH, C-2, C-3, C-2´, C-3´), 40.44 (*C*H_2, C-7, C-7´); H,H-Cosy, HMBC, HSQC, NOESY and NOE´s were made.

Synthesis of bis((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl) carbonate (N,N'-bis(5-endo-norbornene-2,3-dicarboxy-imidyl) carbonate) **(1b).**

The substance is produced on the one hand according to *general procedure B* using *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**1a**) and on the other hand according to *general procedure B and C* using *N*-hydroxy-5-norbornene-2,3-dicarboximide (**1**), where the stereochemistry was not specified. Yields: B (*endo*): 67% (1.03 g, 2.7 mmol), B (without) 83% (1.28 g, 3.3 mmol), C (without): 55% (387 mg, 1.0 mmol). The spectroscopical data were for all products practically identical. The data differed just in the second decimal place by values less than 0.02 ppm which is within the measuring span. Spectroscopical data, starting with *N*-hydroxy-5-*endo*-norbornene-2,3-dicarboximide (**1a**): $\delta_{\mathbf{H}}$ (DMSO, 400 MHz): 6.16-6.08 (m, 4H, H-5, H-6, H-5´, H-6´), 3.59-3.51 (m, 4H, H-1, H-4, H-1´, H-4´), 3.37-3.31 (m, 4H, H-2, H-3, H-2´, H-3´), 1.60 (d, *J* = 8.85Hz, 2H, H-7_{exo}, H-$7'_{exo}$), 1.54 (d, *J* = 8.85Hz, 2H, H-7_{endo}, H-$7'_{endo}$); $\delta_{\mathbf{C}}$ (DMSO, 100 MHz): 168.92 (C=O, 4 C), 148.64 (C=O, 1 C, carbonate), 134.67 (CH, C-5, C-6, C-5´, C-6´), 50.82 (*C*H_2, C-7, C-7´), 43.80 (CH, C-1, C-4, C-1´, C-4´), 42.05 (CH, C-2, C-3, C-2´, C-3´); H,H-Cosy, HMBC, HSQC, NOESY and NOE´s were made. Spectroscopical data, starting with stereochemically *unspecified* *N*-hydroxy-5-norbornene-2,3-dicarboximide (**1**): $\delta_{\mathbf{H}}$ (DMSO, 400 MHz): 6.14-6.07 (m, 4H, H-5, H-6, H-5´, H-6´), 3.58-3.51 (m, 4H, H-1, H-4, H-1´, H-4´), 3.36-3.29 (m, 4H, H-2, H-3, H-2´, H-3´), 1.60 (d, *J* = 8.85Hz, 2H, H-7_{exo}, H-$7'_{exo}$), 1.54 (d, *J* = 8.85Hz, 2H, H-7_{endo}, H-$7'_{endo}$); $\delta_{\mathbf{C}}$ (DMSO, 100 MHz): 168.94 (C=O, 4 C), 148.65 (C=O, 1 C, carbonate), 134.69 (CH, C-5, C-6, C-5´, C-6´), 50.82 (*C*H_2, C-7, C-7´), 43.81 (CH, C-1, C-4, C-1´, C-4´), 42.07 (CH, C-2, C-3, C-2´, C-3´).

CONCLUSIONS

The stereochemical properties of *N,N'*-bis-(5-norbornene-2,3-dicarboxyimidyl) carbonate (**1**) could be clarified. Ogura and Takeda did not indicate in their patents[1,2] the stereochemistry of compound **1** regarding the *endo*/*exo* isomerism for the norbornyl core. Based on experimental and theoretical analysis of their starting materials, it can be concluded that they synthesised the *endo*-isomer, the *N,N'*-bis-(5-*endo*-norbornene-2,3-dicarboxy-imidyl) carbonate (**1b**). In this context, the stereo-declaration of commercially available 5-norbornene-2,3-dicarboxylic anhydrides (**2**) and *N*-hydroxy-5-norbornene-2,3-dicarboximides (**3**) were also investigated. It was found that samples without any information about the *endo*/*exo* isomerism contained practically exclusively the *endo*-form. The *exo*-forms are accessible via a work-full and therefore an expansive way, containing an incomplete isomerisation and several crystallisation steps. The confusing naming of 5-norbornene-2,3-dicarboxylic anhydrides (**2**) and *N*-hydroxy-5-norbornene-2,3-dicarboximides (**3**) by literature and chemical sellers were pointed out. Furthermore, the molecular structures of the *N*-hydroxy-*5-endo*-norbornene-2,3-dicarboximide (**3b**) and *N,N'*-bis-(5-*endo*-norbornene-2,3-dicarboxy-imidyl) carbonate (**1b**) were proved without any doubt by X-ray spectroscopy. Also, the *exo* isomers **1a** and **3a** of them were synthesised and fully characterized. It should be lined out that the pairs of *exo*-*endo* isomers can easily differ by the chemical shifts of special atoms. For the ^{13}C-NMR experiment is this special atom C7. Here the signal moves by around 10 ppm. In the case of ^{1}H-NMR experiments fulfilled this role the H2/H3 protons. Using theoretical concepts, we could illustrate that the *exo* carbonate **1a** is more stable than its corresponding *endo* isomer **1b**. The isomerisation of the *endo* anhydride **2b** to the *exo* anhydride **2a** ends in a nearly 50-50 equilibrium. This experimental fact could be underlined through a calculation of their energies. The *exo* isomer is slightly favoured, but respecting the error limits both isomers are equal in energies. Overall, we presented with the *N,N'*-bis-(5-*exo*-norbornen-2,3-dicarboxyimidyl)carbonate (**1a**) a new representative for bis-imidyl carbonates with clarified stereochemical properties which differs from the others by its chemical behaviour. Therefore, this molecule should be taken up in the list of reagents which are used to build up active amino acids esters, like *N,N'*-disuccinimidyl-, *N,N'*-diphthalimidyl-, and *N,N'*-bis-(*5-endo*-norbornen-2,3-dicarboxyimidyl) carbonate.

Table 5

Crystallographic data

	3a	**1a**
Empirical Formula	$C_9H_9NO_3$	$C_{19}H_{16}N_2O_7$
Formula Weight	179.17	384.34
T/K	100(2)	100(2)
Wavelength λ/Å	1.54184	1.54184
Crystal System	Monoclinic	orthorhombic
Space Group	$P2_1/c$	$Fdd2$
a/Å	11.9042(2)	23.389(2)
b/Å	7.72924(10)	22.532(2)
c/Å	9.3889(2)	6.3910(5)
α (°)	90	90
β (°)	109.836(2)	90
γ (°)	90	90
Volume [Å^3]	812.63(2)	3368.1(5)
Z	4	8
Reflections Collected	29200	8379
Independent reflections	1694 [R_{int} = 0.0396]	1638 [R_{int} = 0.0235]
ρ_C/g cm^{-3}	1.464	1.516
μ/mm^{-1}	0.935	0.996
$R(F_O)$, [$I > 2\sigma(I)$]	0.0333	0.0256
Rw (F_O^2)	0.0855	0.0674
Goodness of fit on (F^2)	1.051	1.107
Absolute structure parameter		0.18(15)
$\Delta\rho$/eÅ^{-3}	0.292/–0.215	0.213/–0.138

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