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Note

H-Bond-Driven Supramolecular Architectures of the *Syn* and *Anti* Isomers of the Dioxime of Bicyclo[3.3.1]nonane-3,7-dione

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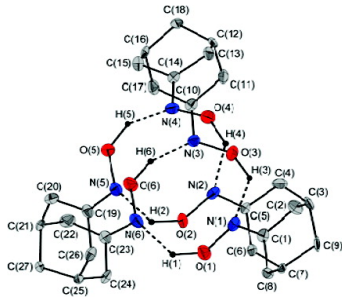

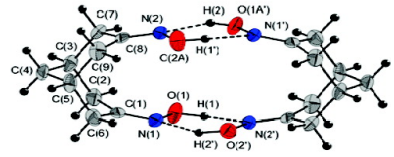

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JOC*Note*

H-Bond-Driven Supramolecular Architectures of the *Syn* and *Anti* Isomers of the Dioxime of Bicyclo[3.3.1]nonane-3,7-dione

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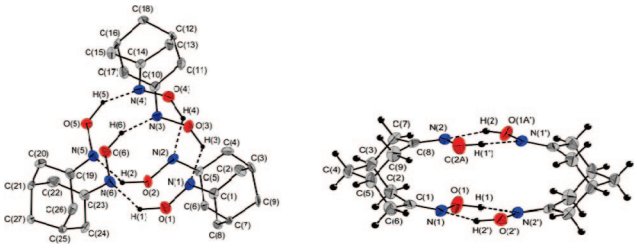


The formation and high stability of the H-bond-driven supramolecular architectures of the s*yn* and *anti* isomers of the dioxime of bicyclo[3.3.1]nonane-3,7-dione were investigated by single crystal X-ray diffraction, NMR, FTIR, and molecular modeling. Self-assembly of the achiral *syn* isomer into a cyclic trimer (supramolecular wheel) and of the chiral *anti* isomer into homochiral cyclic dimers was observed.

Self-assembly processes are based on noncovalent bonds, the driving forces of supramolecular chemistry.[1] The construction of supramolecular architectures with molecular species requires the formation of these intermolecular connections, usually by stacking interactions (CH−π, $\pi-\pi$ or p−π) or by hydrogen bonds.[2] The role of hydrogen bonds in supramolecular and biological compounds can be illustrated through examples like the association between complementary nucleobases (e.g., the adenine−thymine aggregates denominated as the Watson−Crick motif, **I**, Chart 1)[3] and the formation of large host molecules via these specific interactions (e.g., adenine−uracyl interactions, AU; **II**, Chart 1).[4]

CHART 1. Supramolecular Aggregates with the Nucleobase Motif, Based on Hydrogen Bonding Formations

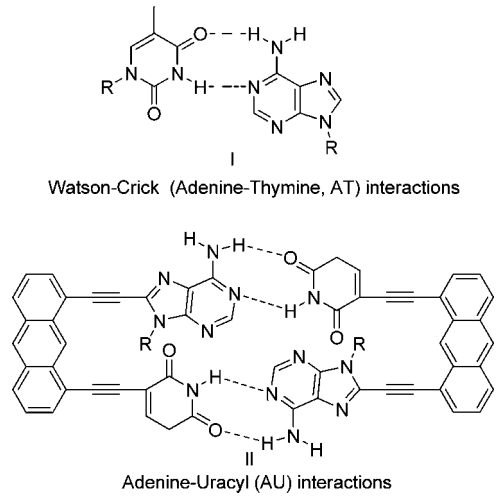
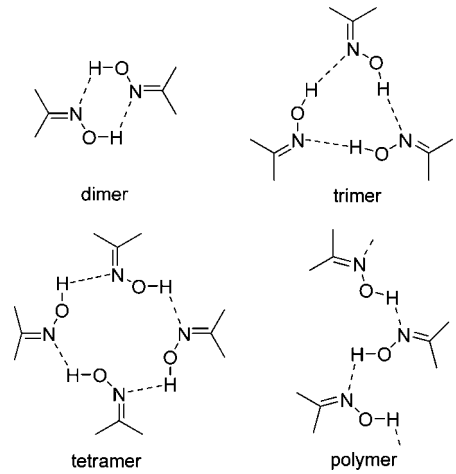


CHART 2. Possible Hydrogen Bond Aggregates with the Oxime Motif



In recent papers,[5] the importance of the hydrogen bonding of oximes in the building of supramolecular architectures was highlighted. The versatility of the oxime system is due to the possibility of building dimers, trimers, tetramers, or polymers via hydrogen bonds (Chart 2).[5b,c]

The spectacular formation of a capsule via the H-bond-driven dimerization of a cyclic trioxime, and of its supramolecular

† "Babes-Bolyai" University.

‡ National Institute for Research and Development of Isotopic and Molecular Technologies.

(1) For textbooks, see: (a) Voegtle, F. *Supramolekulare Chemie*; Teubner: Stuttgart, Germany, 1992. (b) Lehn, J.-M. *Supramolecular Chemistry*; Verlag Chemie: Weinheim, Germany, 1995. (c) Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: New York, 2000; pp 69−136. (d) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: New York, 2000p pp 463−558.

(2) (a) Nishio, M. *Tetrahedron* **2005**, *61*, 6923–6950. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426. (c) Custelcean, R. *Chem. Commun.* **2008**, 295–307.

(3) Kyogoku, Y.; Lord, R. C.; Rich, A. *Biochim. Biophys. Acta* **1969**, *179*, 10–17.

(4) Sessler, J. L.; Wang, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1726–1729.

(5) (a) Bruton, E. A.; Brammer, L.; Pigge, F. C; Aakeröy, C. B.; Leinen, D. S. *New J. Chem.* **2003**, *27*, 1084–1094. (b) Infantes, L.; Motherwell, S. *Struct. Chem.* **2004**, *15*, 173–184. (c) Nyui, T.; Nogami, T.; Ishida, T. *CrystEngComm* **2005**, *7*, 612–615. (d) Mazik, M.; Bläser, D.; Boese, R. *J. Org. Chem.* **2005**, *70*, 9115–9122. (e) Eppel, S.; Bernstein, J. *Acta Crystallogr.* **2008**, *B64*, 50–56. (f) Aakeröy, C. B.; Salmon, D. J.; Smith, M. M.; Desper, J. *Cryst. Growth Des.* **2006**, *6*, 1033–1042. (g) Strenge, A.; Rademacher, P. *Eur. J. Org. Chem.* **1999**, *161*, 1–1617.

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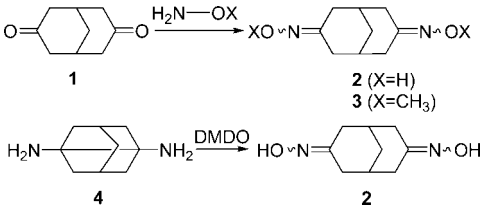
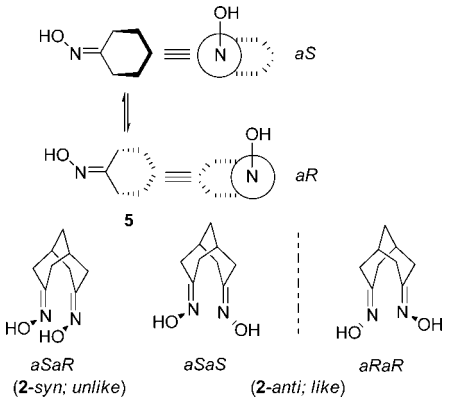
SCHEME 1



SCHEME 2



host−guest system by the inclusion in the capsule of a CH_4 molecule, has recently been reported.[6]

Considering the high ability of oximes to participate in hydrogen bonding, it was considered of interest to investigate the formation of supramolecular aggregates via H-bonds, starting from the dioximes of bicyclo[3.3.1]nonane-3,7-dione. These compounds exhibit a rigid skeleton and show isomers bearing different orientations of the OH groups.

The dioxime (**2**) of bicyclo[3.3.1]nonane-3,7-dione (**1**) has already been synthesized (Scheme 1), either by the standard condensation procedure[7a] or by dimethyldioxirane (DMDO) oxidation of the corresponding tricyclic-diamine **4**[7b,c] (Scheme 1). In these procedures, mixtures of *syn* and *anti* isomers of dioxime **2** were obtained. The *syn* and *anti* isomers of **2** are defined by taking into account the orientation of the OH groups belonging to the oxime moieties. If these groups have the same orientation, the isomer is named *syn*; if they have opposite orientations, the structure is considered to be the *anti* isomer (Scheme 2).

The *syn* isomer was isolated by crystallization from ethanol out of the mixture of isomers obtained in the condensation procedure.[7a] The mixture of isomers obtained by oxidation[7b,c] (^{13}C NMR spectra calculated a ratio of *syn*/*anti* = 3/7; the spectrum of the *syn* isomer is more complex) was used in further reactions without separation. The dimethyl derivative (**3**) was obtained (Scheme 1) by the condensation reaction of diketone **1** with H_2N-OCH_3 and the *syn* and *anti* isomers were isolated by flash chromatography.[7c] Molecular modeling and photoelectron spectroscopy investigations of dioxime **2** and of dimethyl derivative **3** revealed a preference for the chair conformation for the six-membered rings and for transannular interactions between the oxime groups.[7c]

(6) Scarso, A.; Pellizzaro, L.; De Lucchi, O.; Linden, A.; Fabris, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 4972–4975.

(7) (a) Strenge, A.; Rademacher, P. *Eur. J. Org. Chem.* **1999**, 1601–1609. (b) Camps, P.; Muñoz-Torrero, D.; Muñoz-Torrero, V. *Tetrahedron Lett.* **1995**, *36*, 1917–1920. (c) Camps, P.; Muñoz-Torrero, D. *Tetrahedron Lett.* **1994**, *34*, 3187–3190.

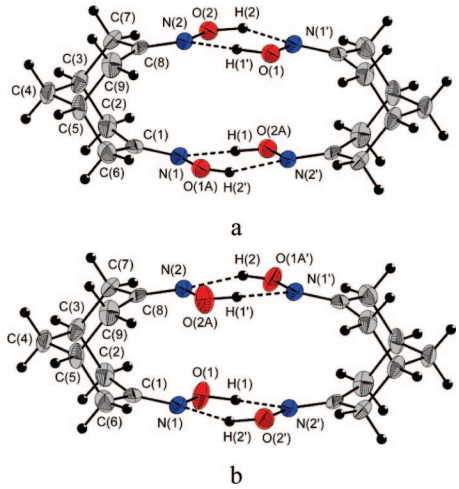


FIGURE 1. ORTEP diagrams for the cyclic dimers of **2**-*anti* (a: *aRaR*−*aRaR*; b: *aSaS*−*aSaS* associations).

In this work, the *syn* and *anti* isomers of dioxime **2** (obtained by the condensation procedure)[5g] were isolated by column chromatography and characterized as single compounds. The formation of spectacular supramolecular architectures—built up for each isomer through stereospecific H-bond interactions—was revealed. The static and dynamic stereochemistry of the isolated isomers was also investigated.

The stereochemistry of dioxime **2** should be discussed, considering the peculiar axial chirality of the cyclohexanone oxime (**5**, Scheme 2); this is similar to the previously described case of alkylydenecyclohexane derivatives.[8] The dioxime of bicyclo[3.3.1]nonane-3,7-dione (**2**) exhibits two chiral axes (the C═N bonds; Scheme 2); thus, the *syn* isomer is an achiral *unlike* form (*aRaS*), while the *anti* isomer is chiral and exhibits separable enantiomers (*like* isomers: *aSaS* and *aRaR*). Due to the rigid structure of the bicyclo[3.3.1]nonane skeleton, a conformational equilibration of these stereoisomers cannot take place.

The ratio between *syn* and *anti* isomers in the crude product was measured from NMR spectra (the ratio of *syn*/*anti* = 1/1.4). To establish the equilibrium ratio and to determine the kinetic parameters, we investigated the *syn* ⇄ *anti* equilibrium via isomerization processes carried out in the NMR tube ($CDCl_3$, pH 3.17; see the Supporting Information). Two independent experiments, starting either from the pure *syn* or from the pure *anti* isomer, were carried out and both gave an equilibrium *syn*/*anti* ratio of 1/1.44 (this value is similar to that obtained in the synthesis of the dioxime **2**). The k_{obs1} value (*syn* ⇄ *anti*) was found to be 5.26×10^{-3} min^{-1} (see the Supporting Information). The enantiomers of the *anti* isomer were discriminated (t_{Ranti} = 12.443 and t'_{Ranti} = 13.762 min) on HPLC, using a chiral column (Chiralcel OJ-H; see the Supporting Information) and hexane−isopropanol (9/1) as eluent.

Solid State Structural Investigations. The molecular structures for the *syn* and *anti* isomers were obtained by single crystal X-ray diffractometry. These investigations revealed the H-bonding associations of the molecules and the formation of spectacular supramolecular aggregates. The *anti* isomer gives a cyclic dimer through four hydrogen bond interactions (Figure 1). The association of these molecules is homochiral and involves either *aRaR* (a) or *aSaS* (b) configurations (the dimers

(8) Grosu, I.; Balog, M.; Mager, S. *Rev. Roum. Chim.* **2005**, *50*, 333–339.

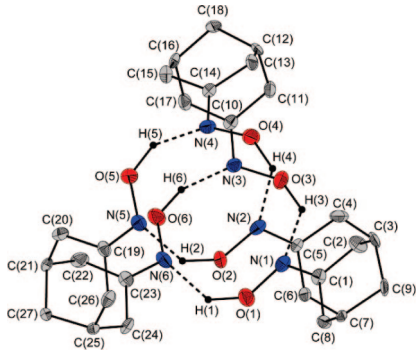


FIGURE 2. ORTEP diagram for the cyclic trimer of the achiral **2**-*syn* isomer.

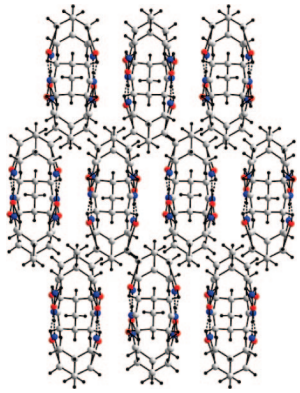


FIGURE 3. View of the lattice (along the *c* crystallographic axis) of **2**-*syn*.

are built up by highly enantiospecific recognition processes). The crystal structure is a homogeneous solution of the two enantiomeric dimers (it is a pseudoracemate). When the X-ray structure was solved, an average structure was obtained with 1/1 contributions from structures a and b. The *syn* isomer forms a supramolecular wheel via a cyclic trimer built up through six hydrogen bonds (Figure 2). The position of the oxime hydrogen atoms could not be precisely determined. In fact, these hydrogen atoms are shared by the O and N atoms of the molecules involved in the hydrogen bonds. The distances from the hydrogen atoms to the oxygen atoms are longer than the usual covalent bonds and the distances to the nitrogen atoms are shorter than the usual hydrogen bonds. The distances from the oxygen atoms to the neighboring nitrogen atoms of the partner molecules in the trimer are in the range of $d = 2.706-2.771$ Å.

The same distances (from nitrogen to oxygen atoms of the groups involved in the hydrogen bonds) in the dimers are in the range of $d = 2.731-2.794$ Å. These low values suggest strong hydrogen bond interactions and high stability of the cyclic structures.

The investigations of the lattice for **2**-*syn* revealed a layered structure with tight channels along the a crystallographic axis (Figure 3).

Molecular modeling at the ab initio level (see the Supporting Information) was used to investigate the structures of the supramolecular associations of *syn* and *anti* isomers of **2**. The calculations revealed the formation of only the cyclic trimer for the *syn* structure. The stabilization of the trimer via H-bonds was evaluated at $\Delta G° = 59.08$ kcal/mol ($\Delta E°$/dioxime molecule $= 19.69$ kcal/mol). The calculated distances from the H atoms of the OH groups to the N atoms of the associated molecules are in the range of $d = 1.835-1.839$ Å.

For the *anti* isomer, the energy modifications brought by the formation of the cyclic dimer ($\Delta G° = 30.43$ kcal/mol; $\Delta E°$/dioxime molecule $= 15.21$ kcal/mol) and of the cyclic trimer were also calculated ($\Delta G° = 54.57$ kcal/mol; $\Delta E°$/dioxime molecule $= 18.19$ kcal/mol). The distances from the H atoms of the OH groups to the N atoms of the associated molecules exhibit the same value for the dimer ($d = 1.928$ Å) and cover the range of $d = 1.803-1.897$ Å for the trimer (see the Supporting Information). Despite the higher calculated stability for the trimer, the *anti* isomer crystallizes in the dimer form, maybe due to the contribution of other packing forces.

For both the *syn* and *anti* structures, solid state FTIR investigations only recorded the O−H absorption bands corresponding to the H-bond associated molecules. The lower frequency values ($\upsilon = 3109-3190$ cm^{-1}) for the *syn* isomer than for the *anti* one ($\upsilon = 3281-3328$ cm^{-1}) reveal, as expected, stronger hydrogen bonding in the cyclic trimer (*syn*) than in the cyclic dimer (*anti*).

Structural Aspect in Solution. The NMR data (^{1}H and ^{13}C) of the separated isomers are listed in the Supporting Information. The FTIR spectra of **2**-*syn* and **2**-*anti* in aprotic solvent (10.0 mM; $CHCl_3$) exhibit only absorption bands corresponding to the H-bond associated molecules ($\upsilon_{syn} = 3110/3202$ cm^{-1}; $\upsilon_{anti} = 3164/3295$ cm^{-1}). To break the H-bond associations, so as to obtain the absorption of the isolated molecules, spectra were recorded in 1:1 solutions of tetrachloroethylene (C_2Cl_4)/$CHCl_3$, and the samples were diluted up to 0.156 mM.

The bands corresponding to the dioxime monomers ($\upsilon_{syn} = 3696$ cm^{-1}; $\upsilon_{anti} = 3684$ cm^{-1}) could be observed by decreasing the concentrations of the investigated solutions. The intensities of the bands corresponding to the free dioximes increase with dilution, and at 0.156 mM, the monomer/associated molecules ratio was found to be 0.3 for the *syn* isomer and 0.2 for the *anti* isomer, respectively.

In summary, we report herein the formation of stable H-bond-driven supramolecular aggregates of *syn* and *anti* isomers of dioxime **2** of bicyclo[3.3.1]nonane-3,7-dione (**1**). The formation of a supramolecular wheel (via six H-bonds in the case of *syn* isomer) and a homochiral cyclic dimer (via four H-bonds in the *anti* case) was revealed by single crystal X-ray diffractometry, molecular modeling, and FTIR. The enantiomers of the *anti* isomer were discriminated on chiral HPLC, and the kinetic and thermodynamic parameters of the *syn* ⇄ *anti* equilibrium were calculated from NMR experiments.

Experimental Section

Bicyclo[3.3.1]nonane-3,7-dione was synthesized by using the procedure described in the literature[9] and it was purified by flash chromatography on silica gel. Solvents such as dichloromethane and ethyl acetate were distilled prior to use in synthesis and separations.

The synthesis of **2** was performed by using an improved procedure of a method already described in the literature:[5g]

A solution of hydroxylamine hydrochloride (3.64 g, 52.4 mmol) and sodium acetate (2.79 g, 34.0 mmol) in water (40 mL) was added dropwise to a well-stirred solution of bicyclo[3.3.1]nonane-3,7-dione (1.00 g, 6.6 mmol) in ethanol (33 mL). Immediately a white precipitate occurred. The reaction mixture was stirred at room

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temperature for 24 h, then the white solid was filtered off then solved in dichloromethane (50 mL) and washed twice with water (2 × 10 mL). Ethanol from filtrate was evaporated in vacuum and after addition of water (20 mL), the aqueous solution was extracted four times with 50 mL of dichloromethane. The organic layers were combined and dried over Na_2SO_4. Filtration and evaporation in vacuum of the solvent led to a mixture of *syn* and *anti* diastereoisomers in a ratio of 1/1.4 (0.9 g, 75% yield).

The crude product was submitted to separation by flash chromatography on silica gel and eluted with ethyl acetate (R_f(*syn*) 0.21 and R_f(*anti*) 0.38), to obtain the pure 0.29 g of *anti* (32%) and 0.23 g of *syn* (26%) isomers, respectively. Crystals suitable for X-ray diffraction were obtained from a double layered ethyl acetate-pentane mixture.

***syn*-Bicyclo[3.3.1]nonane-3,7-dione-3,7-dioxime (2-*syn*):** yield 26%, white crystals; mp 240 °C; purified by flash chromatography (silica gel, ethyl acetate) R_f 0.21. Calculated for $C_9H_{14}N_2O_2$: C 59.32, H 7.74, N 15.37. Found: C 59.05, H 7.45, N 15.60. ^{1}H NMR (DMSO-d_6) δ 1.76−1.85 (overlapped peaks, 4 H, 1-H, 5-H, 9-H_2), 2.15−2.32 (overlapped peaks, 6 H, 2-H_{ax}, 2-H_{eq}, 4-H_{ax}, 6-H_{ax}, 8-H_{ax}, 8-H_{eq}), 2.99 (d, 2 H, J = 15.3 Hz, 4-H_{eq}, 6-H_{eq}), 10.10 ppm (broad signal, 2H, =NOH). ^{13}C NMR (DMSO-d_6) δ 27.7 (C^1), 29.6 (C^5), 30.3 ($C^{2,8}$), 32.6 (C^9), 36.8 ($C^{4,6}$), 154.1 ($C^{3,7}$). FT-IR (KBr): 3190, 3109, 2914, 2854, 1667, 1488, 1430, 1358, 1212, 1067, 983 cm^{-1}.

***anti*-Bicyclo[3.3.1]nonane-3,7-dione-3,7-dioxime (2-*anti*):** yield 32%, white crystals; mp 230 °C; purified by flash chromatography (silica gel, ethyl acetate) R_f 0.38. Calculated for $C_9H_{14}N_2O_2$: C 59.32, H 7.74, N 15.37. Found: C 59.09, H 7.95, N 15.62. ^{1}H NMR (DMSO-d_6) δ 1.77 − 1.88 (overlapped peaks, 4 H, 1-H, 5-H, 9-H_2), 2.07−2.25 (overlapped peaks, 6 H, 2-H_{ax}, 4-H_{ax}, 4-H_{eq}, 6-H_{ax}, 8-H_{eq}, 8-H_{ax}), 3.00 (d, 2 H, J = 15.3 Hz, 2-H_{eq}, 6-H_{eq}), 10.11 ppm (broad signal, 2H, =NOH). ^{13}C NMR (DMSO-d_6) δ 29.1 ($C^{1,5}$), 29.6 ($C^{4,8}$), 32.7 (C^9), 37.6 ($C^{2,6}$), 154.1 ($C^{3,7}$). FT-IR (KBr) 3328, 3281, 2939, 2912, 2866, 1669, 1475, 1434, 1343, 1281, 1064, 934 cm^{-1}.

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Supporting Information Available: Procedures and characterization of the *syn* and *anti* isomers of **2**, general experimental data, determination of the kinetic and thermodynamic data for the *syn* ⇄ *anti* equilibrium, the data of the chromatographic investigations of **2**, results of molecular modeling and FTIR investigations, copies of ^{1}H and ^{13}C NMR spectra, cif files, and a table of the parameters for the crystallographic determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting information for the paper:

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by

Nicoleta Toşa, Attila Bende, Richard Attila Varga, Anamaria Terec, Ioan Bratu and Ion Grosu*

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1. General experimental data

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra, COSY, HMQC, and HMBC were recorded in DMSO-d_6 at *rt* on a 300 MHz spectrometer. The X-ray crystallographic data were collected at *rt*, using graphite-monochromated MoKα radiation. The structural data were deposited at the Cambridge Crystallographic Data Center, deposition numbers CCDC 678197 (*anti*) and CCDC 678198 (*syn).*

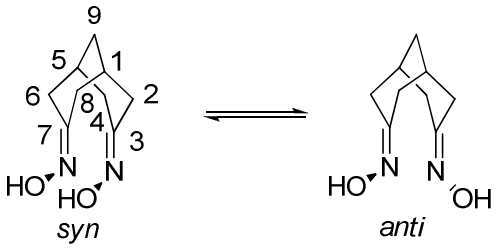
FT-IR measurements were performed in the range 4000 to 350 cm^{-1} on a single beam spectrometer with a 2 cm^{-1} resolution, and 256 scans were performed to collect each spectrum. Solutions for FT-IR measurements were prepared by successive dilution from a concentrated solution (10 mM) made from a weighted amount of dioxime. Solutions were prepared just before use in order to minimize evaporation of the solvents. The isomers were studied in a C_2Cl_4-$CHCl_3$ (1:1 v/v) solution over a concentration range 0.156 – 10 mM at room temperature. For each sample a solvent blank was run first.

Melting points are uncorrected.

Thin layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F_{254} using UV and vanillin visualization. Preparative column (flash) chromatography was performed on silica gel (40-63 μm).

2. Data of the NMR investigations of the *syn*⇆*anti* equilibrium of **2**.

Under acidic conditions the *syn* and *anti* isomers of dioxime **2** are in a running equilibrium (scheme 1; similar equilibria were observed for other dioximes, too):[1]



Scheme 1

This equilibrium was investigated using ^{1}H NMR spectra. The experiments were based on the differences of the chemical shifts for the equatorial protons at positions 2,4,6,8 belonging to the *syn* ($\delta_{2e,8e}$ = 3.48 ppm) and to the *anti* isomers ($\delta_{4e,8e}$ = 3.36 ppm). The experiments were run starting from either the pure *syn* or *anti* isomers and were based on the recording of the ^{1}H NMR spectra of the same sample over several periods of time and on the measuring in these spectra of the ratios between the isomers using the intensities of their specific signals (Figures

1 and 2). The collecting of data (Table 1) was made at shorter intervals at the beginning of the process and for the calculation of ratios mean values of the integrals were used.

The reaction was considered to be of first order and the pH (3.17) of the solvent was fitted (with F_3C-COOH) to obtain a convenient "time scale" for the process.

The experimental results (calculated with relations **1** and **2**) are shown in Figures 3 and 4 and in Table 2.

$$\ln \frac{x_e}{x_e - x} = (k_1 + k_{-1}).t \qquad (1)$$

$$\frac{k_1}{k_{-1}} = K \qquad (2)$$

In equations (**1**) and (**2**) k_1 and k_{-1} are the forward and reverse reaction rate constants, K is the equilibrium constant, x_e is the initial concentration of the starting isomer, x is the concentration of the same isomer at the "t" time.

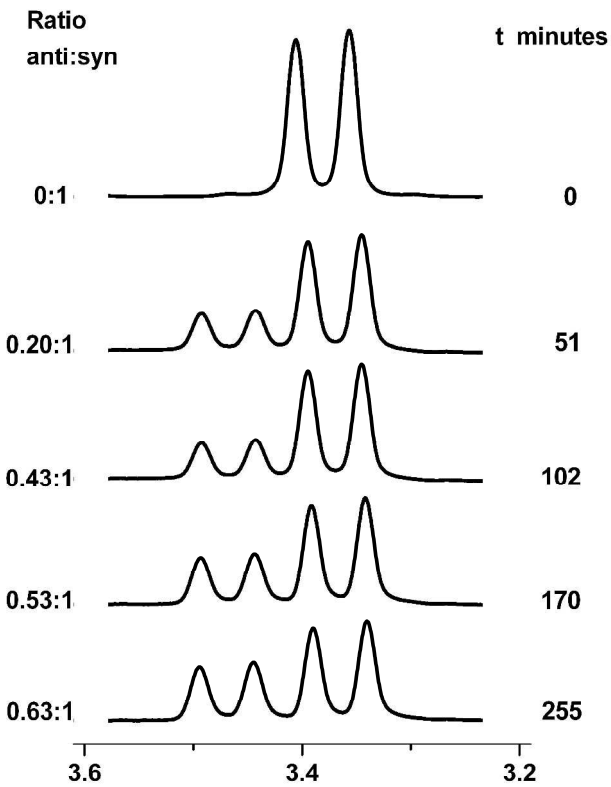


Figure 1. NMR investigation of the *anti*⇆*syn* isomerization of **2**.

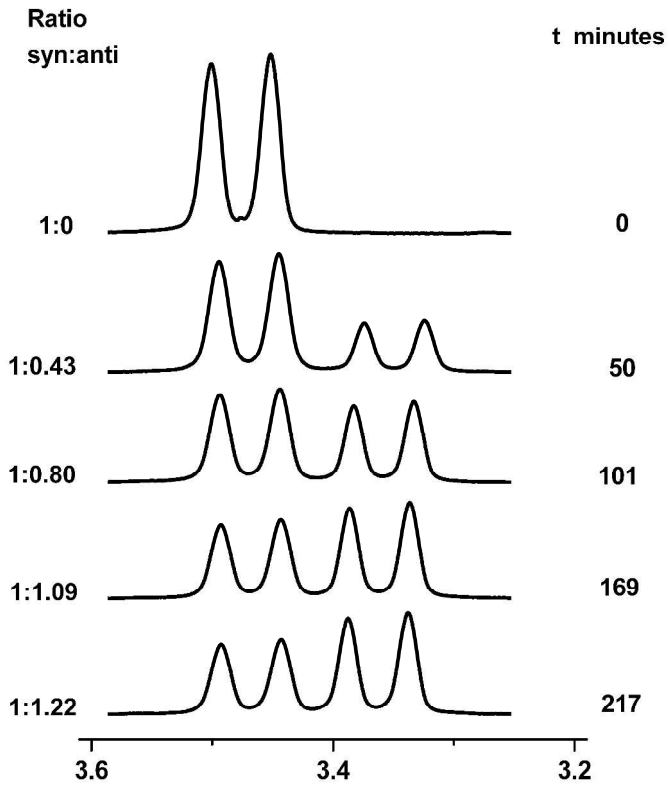


Figure 2. NMR investigation of the *syn*⇆*anti* isomerization of **2**.

Table 1 Data (time/ratio of isomers) of the kinetic measurements for the *syn*⇆*anti* equilibrium in **2**.

	Syn⇆*anti*		*Anti*⇆*syn*	
Nr.	**2a** *syn*			**2a** *anti*
	Time (min)	Ratio *syn*/*anti*	Time (min)	Ratio *anti*/*syn*
1	0	1:0	0	1:0
2	7	1:0.096	17	1:0.038
3	16	1:0.159	34	1:0.157
4	28	1:0.254	51	1:0.200
5	50	1:0.427	68	1:0.250
6	68	1:0.560	85	1:0.320
7	84	1:0.675	102	1:0.418
8	101	1:0.796	119	1:0.447
9	118	1:0.891	136	1:0.467
10	135	1:0.958	153	1:0.481
11	152	1:1.033	170	1:0.532
12	169	1:1.088	187	1:0.540
13	183	1:1.150	204	1:0.550
14	200	1:1.162	221	1:0.578
15	217	1:1.218	272	1:0.640
16	At equilibrium	1:1.437	At equilibrium	1:0.696

The k_1 and k_{-1} values were determined taking into account the slope of the linear fit equation (based on the least-squares method) for the data of isomers equilibration and the graphics were obtained using Origin program (Figures 3 and 4).

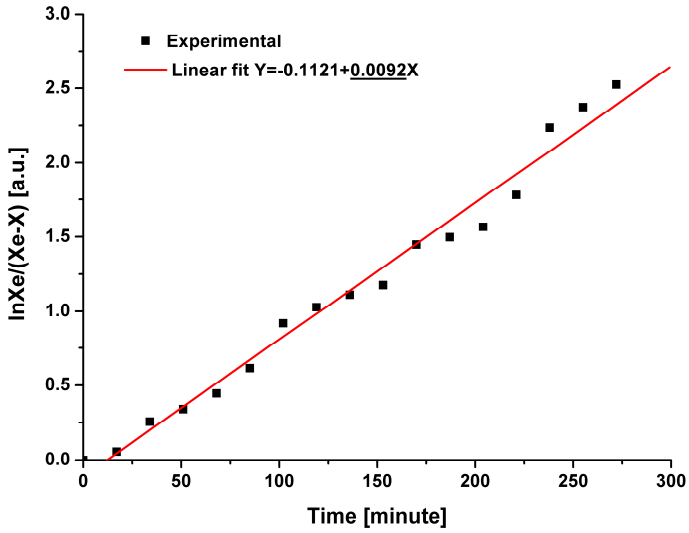


Figure 3. The graphical representation of the *anti*⇆*syn* isomerization of **2**

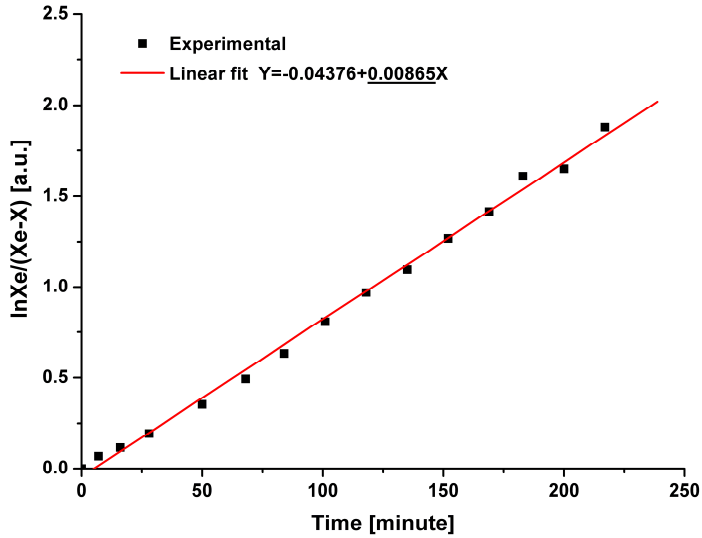


Figure 4. The graphical representation of the *syn*⇆*anti* isomerization of **2**

Table 2 Kinetic parameters (k_1; k_{-1}) for isomerization of **2** starting from *syn* and *anti* isomers

Starting isomer	Initial concentration ($mol \cdot l^{-1}$)	*K*	$k_1 x10^{-3}$ min^{-1}	$k_{-1} x10^{-3}$ min^{-1}
syn	8.8 $x10^{-3}$	1.4373	5.10	3.549
anti	8.8 $x10^{-3}$	0.69574	3.774	5.425

3. Data of the chiral HPLC investigation of dioxime **2**

In order to establish the chiral behavior of *syn* and *anti* isomers of **2**, a mixture of these isomers was subjected to a HPLC separation using a chiral stationary phase.

The chiral separation was performed on an AGILENT HPLC equipped with a 4.6 mm Ø×250 mm Chiralcel OJ-H column, using hexane–2-propanol (90:10) as eluent (flow rate 1mL/minute) and UV detection at 254 nm. The three separated peaks (Figure 5) correspond to the *anti:* t_{R1} = 12.443 min, t_{R2} = 13.762 min and *syn*: t_{R3} = 15.011 min isomers.

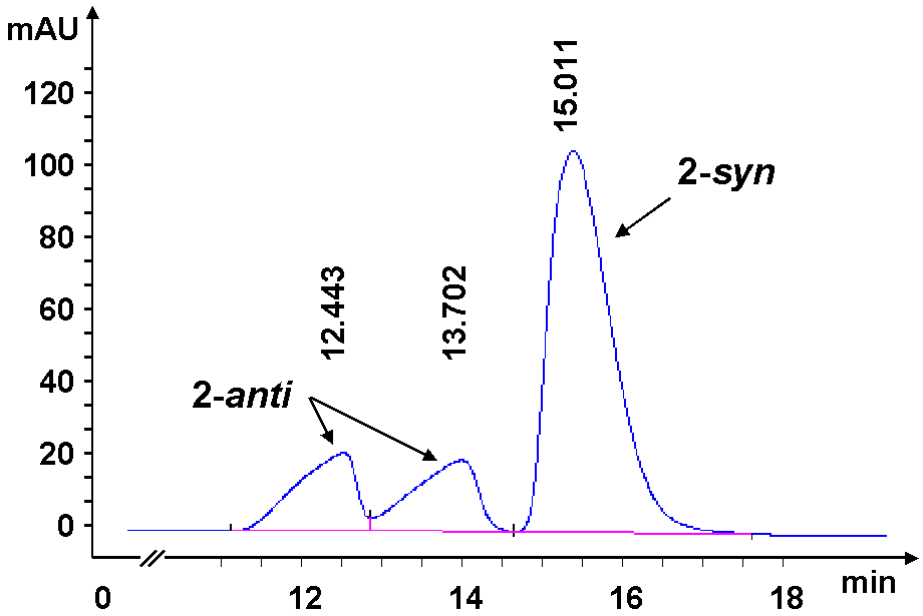


Figure 5. Chromatogram obtained during the chiral HPLC resolution of the mixture of stereoisomers of compound **2**.

4. Parameters of the crystallographic determinations for compounds **2**-*syn* and **2**-*anti*

The details of the crystal structure determination and refinement for ***syn*** and ***anti*** isomers of dioxime **2** are given in Table 3. Data were collected at room temperature (297 K). The structures were refined with anisotropic thermal parameters. The hydrogen atoms were refined with a riding model and a mutual isotropic thermal parameter. For structure solving and refinement a software package SHELX-97 was used.[2,3] The drawings were created with Ortep[4] and Diamond programs.[5]

For both compounds the positions of the hydrogen atoms bonded to the oxygen atoms were found from the electron density maps and the structures were refined considering O-H distances of 0.98 Å in the case of **2**-*anti* and values of the O-H distances in the range 1.10-1.17 Å for **2**-*syn*

isomer. In the molecular structure of **2**-*syn* the positions of hydrogen atoms involved in the hydrogen bonds could not be determined properly. These hydrogen atoms are in fact shared by the oxygen and nitrogen atoms involved in the association (for similar situations see reference 6). In order to show in the ORTEP diagram classic O-H----N based structures unusual lengths for the O-H bonds were admitted (d = 1.10-1.17 Å) and this fact had as consequence the alteration of the ls_shift/su_max parameter which exhibits the value 5.84 instead of 0.

Table 3. Parameters of the crystallographic determinations for *syn* and *anti* isomers of compound **2**.

Compound	***Syn***	***anti***
Empirical formula	$C_9H_{14}N_2O_2$	$C_{18}H_{28}N_4O_4$
Formula weight	182.22	364.44
Temperature (K)	297(2)	297(2)
Wavelength, Å	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P21/c	Pbca
a, Å	12.7815(15)	11.7089(17)
b, Å	11.2772(13)	11.4168(17)
c, Å	20.068(2)	14.228(2)
α °	90	90
β °	107.626(2)	90
γ °	90	90
Volume, $Å^3$	2756.8(6)	1902.0(5)
Z	12	4
Density (calculated) mg/m^3	1.317	1.273
Absorption coefficient, mm^{-1}	0.094	0.091
F(000)	1176	784
Crystal size/mm	0.26 x 0.21 x 0.20	0.23 x 0.20 x 0.15
Theta range for data collection/ (°)	1.67 to 25.00	2.86 to 24.99
Index ranges	-15<=h<=15, -13<=k<=13, -23<=l<=23	-13<=h<=13, -13<=k<=13, -16<=l<=16
Reflections collected	25920	12624
Independent reflections	4859 [R(int) = 0.0534]	1673 [R(int) = 0.0604]
Refinement method	Full matrix least-square on F^2	Full matrix least-square on F^2
Data/restraints/parameters	4859 / 0 / 377	2743 / 0 / 170
Goodness-of-method on F^2	1.172	1.284
Final R indices [I>2σ(I)]	R1 = 0.1394, wR2 = 0.3519	R1 = 0.1282, wR2 = 0.1829
R indices (all data)	R1 = 0.1558, wR2 = 0.3651	R1 = 0.1385, wR2 = 0.1873
Largest diff. peak and hole, eA^{-3}	0.991 and -0.370	0.213 and -0.215

5. Results of the molecular modeling for the supramolecular architectures of *syn* and *anti* isomers of **2**

The geometry optimization of *syn* and *anti* isomers of bicyclo[3.3.1]nonane-3,7-dione-3,7-dioxime were performed using the Gaussian 03 program package[7] considering the B3LYP density functional theory method with 6-31G** basis set (including polarization functions for all atoms).

Results of the geometry optimizations

Anti-isomer

2-*anti* (dimer): Figure 6

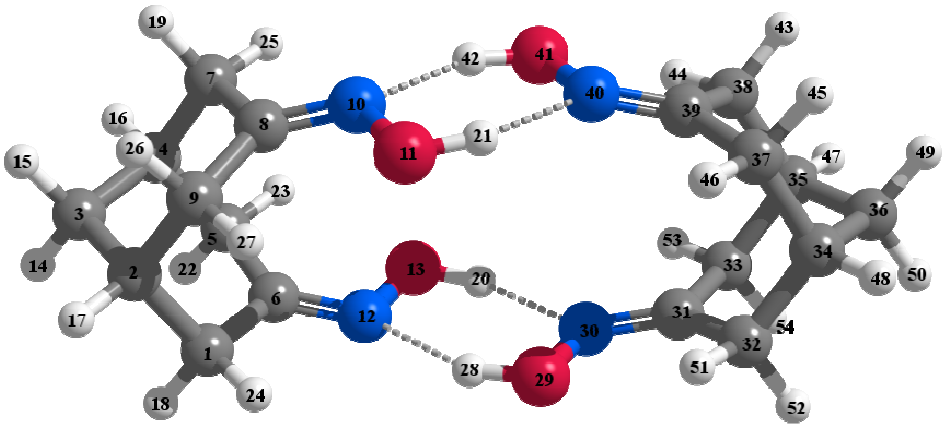


Figure 6. Balls and sticks representation of the optimized structure of the homochiral dimer (*aRaR, aRaR*) of **2**-*anti*.

Intermolecular interaction energy: ΔE_{AB} = 30.43 kcal/mol ($\Delta E_{AB}/N_{molec}$ = 15.22 kcal/mol)

$C_1 – C_2$ distance = 10.505 Å
$H_1 \ldots N_2$ = 1.928 Å
$H_2 \ldots N_1$ = 1.928 Å
$H_3 \ldots N_4$ = 1.928 Å
$H_4 \ldots N_3$ = 1.928 Å
$N_1 \ldots N_2$ = 3.038 Å $N_1 \ldots N_3$ = 3.439 Å
$N_3 \ldots N_4$ = 3.038 Å $N_2 \ldots N_4$ = 3.440 Å
$O_1 \ldots O_2$ = 3.248 Å
$O_3 \ldots O_4$ = 3.248 Å

2-*anti*‘ (trimer): Figure 7

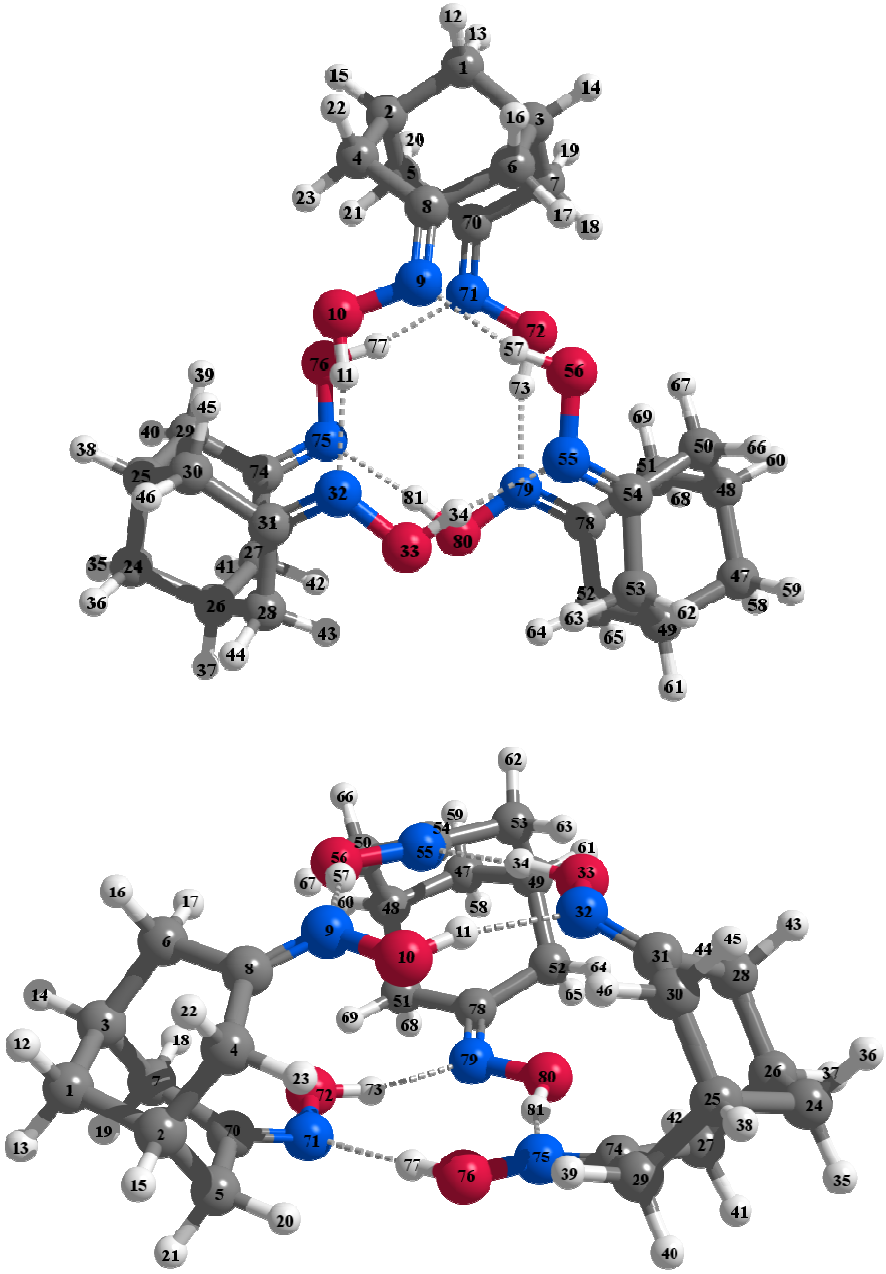


Figure 7. Balls and sticks representations of the optimized structure of the homochiral trimer (*aRaR, aRaR, aRaR*) of **2**-*anti*.

Intermolecular interaction energy: ΔE_{ABC} = 54.57 kcal/mol ($\Delta E_{ABC}/N_{molec}$ = 18.19 kcal/mol)

$C_1 – C_2$ distance = 9.675 Å
$C_2 – C_3$ distance = 10.076 Å $\overline{C-C} = 9.901$ Å
$C_3 – C_1$ distance = 9.952 Å

$H_1 \ldots N_2$ = 1.845 Å	$H_4 \ldots N_5$ = 1.842 Å
$H_2 \ldots N_3$ = 1.897 Å	$H_5 \ldots N_6$ = 1.859 Å
$H_3 \ldots N_1$ = 1.822 Å	$H_6 \ldots N_4$ = 1.803 Å

$N_1 \ldots N_2$ = 3.532 Å	$N_4 \ldots N_5$ = 3.577 Å
$N_2 \ldots N_3$ = 3.604 Å	$N_5 \ldots N_6$ = 3.518 Å

$N_3 \ldots N_1 = 3.589$ Å
$O_1 \ldots O_2 = 3.766$ Å
$O_2 \ldots O_3 = 3.806$ Å
$O_3 \ldots O_1 = 3.772$ Å
$N_1 \ldots N_4 = 3.709$ Å
$N_2 \ldots N_5 = 3.660$ Å
$N_3 \ldots N_6 = 3.691$ Å

$N_6 \ldots N_4 = 3.546$ Å
$O_4 \ldots O_5 = 3.741$ Å
$O_5 \ldots O_6 = 3.798$ Å
$O_6 \ldots O_4 = 3.781$ Å

$V_{molec} = 1770.67$ Å^3

2-*syn* (trimer) Figure 8

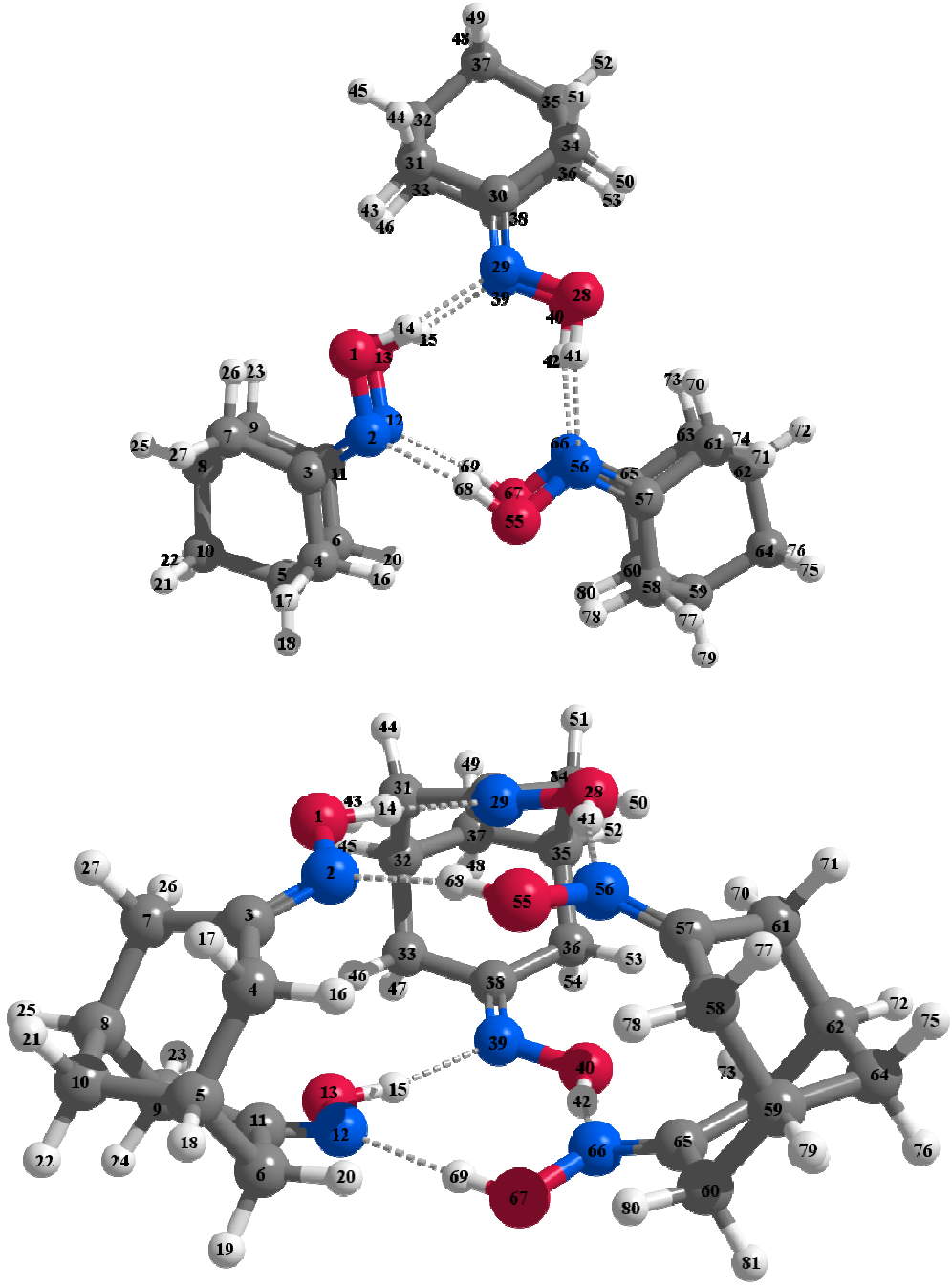


Figure 8. Balls and sticks representations of the optimized structure of the achiral trimer of **2**-*syn*.

Intermolecular interaction energy: ΔE_{ABC} = 59.08 kcal/mol ($\Delta E_{ABC}/N_{molec}$ = 19.69 kcal/mol)

$C_1 – C_2$ distance = 9.824 Å
$C_2 – C_3$ distance = 9.837 Å $\overline{C-C} = 9.829$ Å
$C_3 – C_1$ distance = 9.826 Å

$H_1 \ldots N_2$ = 1.836 Å	$H_4 \ldots N_5$ = 1.837 Å
$H_2 \ldots N_3$ = 1.839 Å	$H_5 \ldots N_6$ = 1.838 Å
$H_3 \ldots N_1$ = 1.838 Å	$H_6 \ldots N_4$ = 1.835 Å
$N_1 \ldots N_2$ = 3.496 Å	$N_4 \ldots N_5$ = 3.495 Å
$N_2 \ldots N_3$ = 3.496 Å	$N_5 \ldots N_6$ = 3.492 Å
$N_3 \ldots N_1$ = 3.488 Å	$N_6 \ldots N_4$ = 3.491 Å
$O_1 \ldots O_2$ = 3.794 Å	$O_4 \ldots O_5$ = 3.794 Å
$O_2 \ldots O_3$ = 3.793 Å	$O_5 \ldots O_6$ = 3.790 Å
$O_3 \ldots O_1$ = 3.795 Å	$O_6 \ldots O_4$ = 3.793 Å
$N_1 \ldots N_4$ = 3.735 Å	
$N_2 \ldots N_5$ = 3.730 Å	
$N_3 \ldots N_6$ = 3.734 Å	

V_{molec} = 1766.78 $Å^3$

6. Copies of ^1H and ^{13}C NMR spectra of *syn* and *anti* isomers of **2**.

Copies of ^1H and ^{13}C NMR spectra in DMSO-d_6 of *syn* and *anti* isomers of **2** are shown in figures 9-12

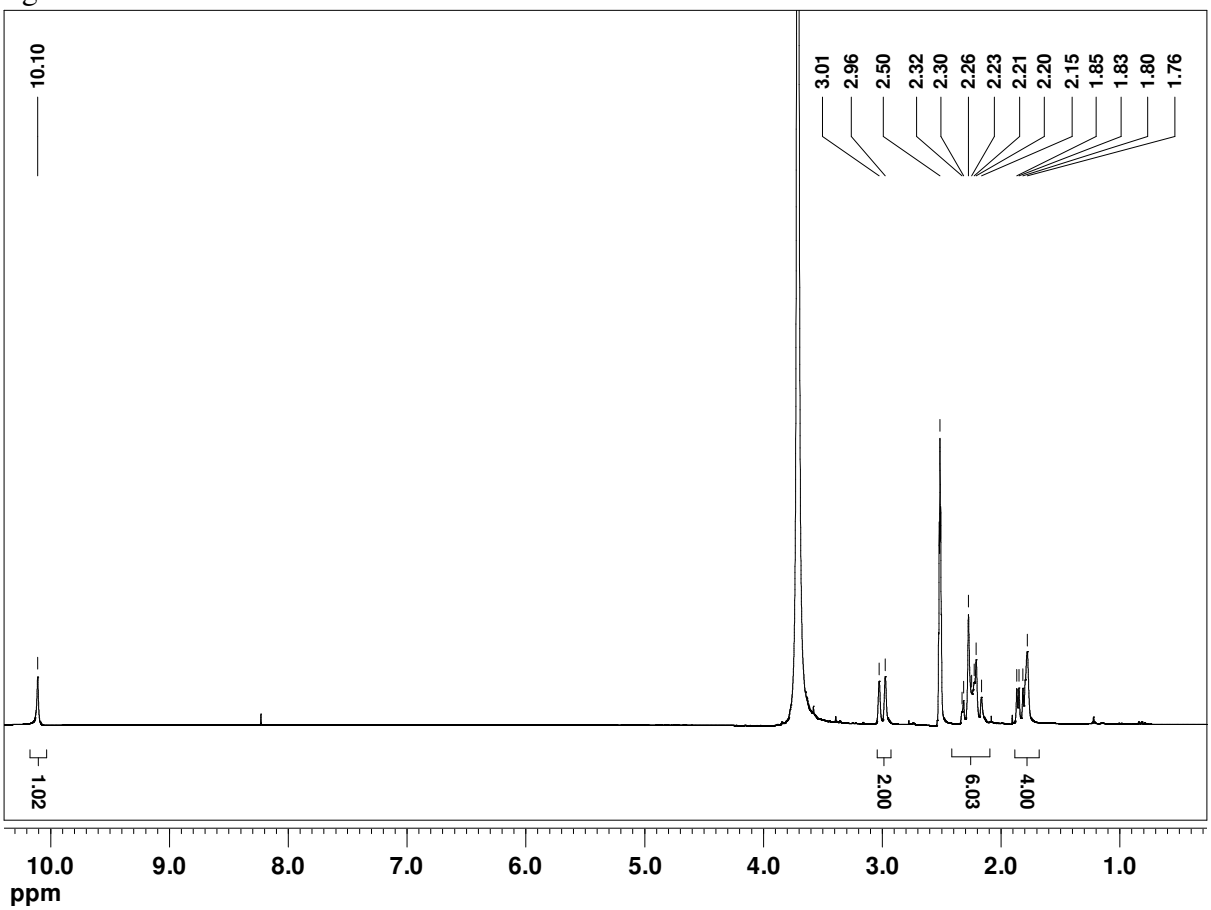


Figure 9. ^1H NMR spectrum of **2**-*syn*.

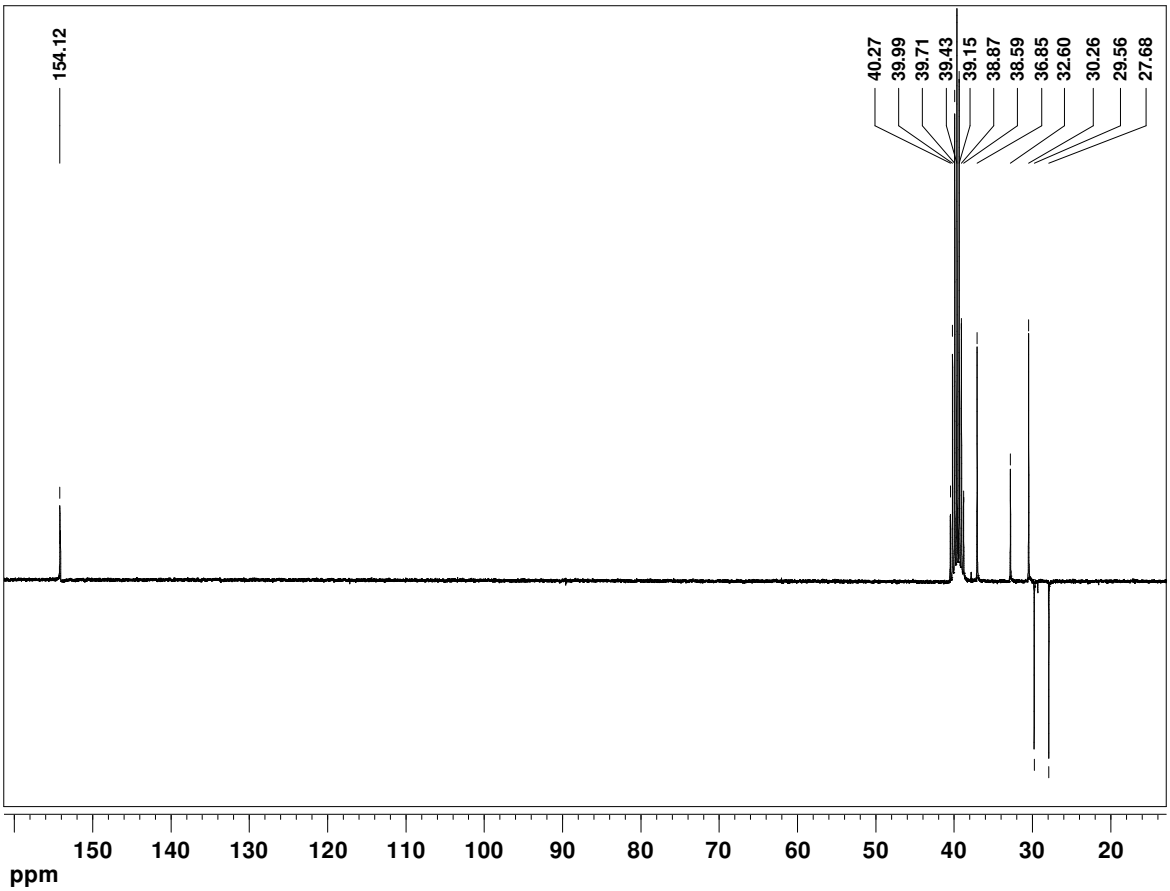


Figure 10. ^{13}C NMR spectrum of **2**-*syn.*

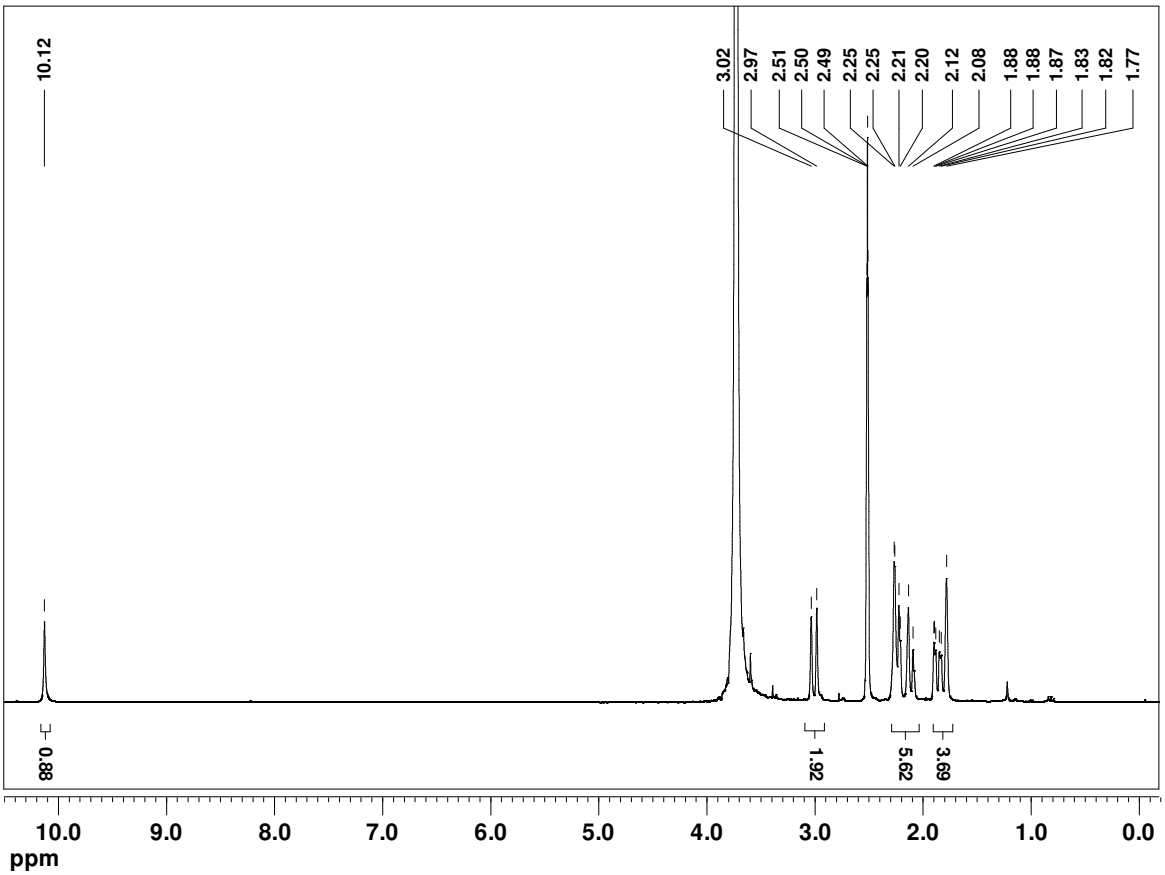


Figure 11. ^{1}H NMR spectrum of **2**-*anti.*

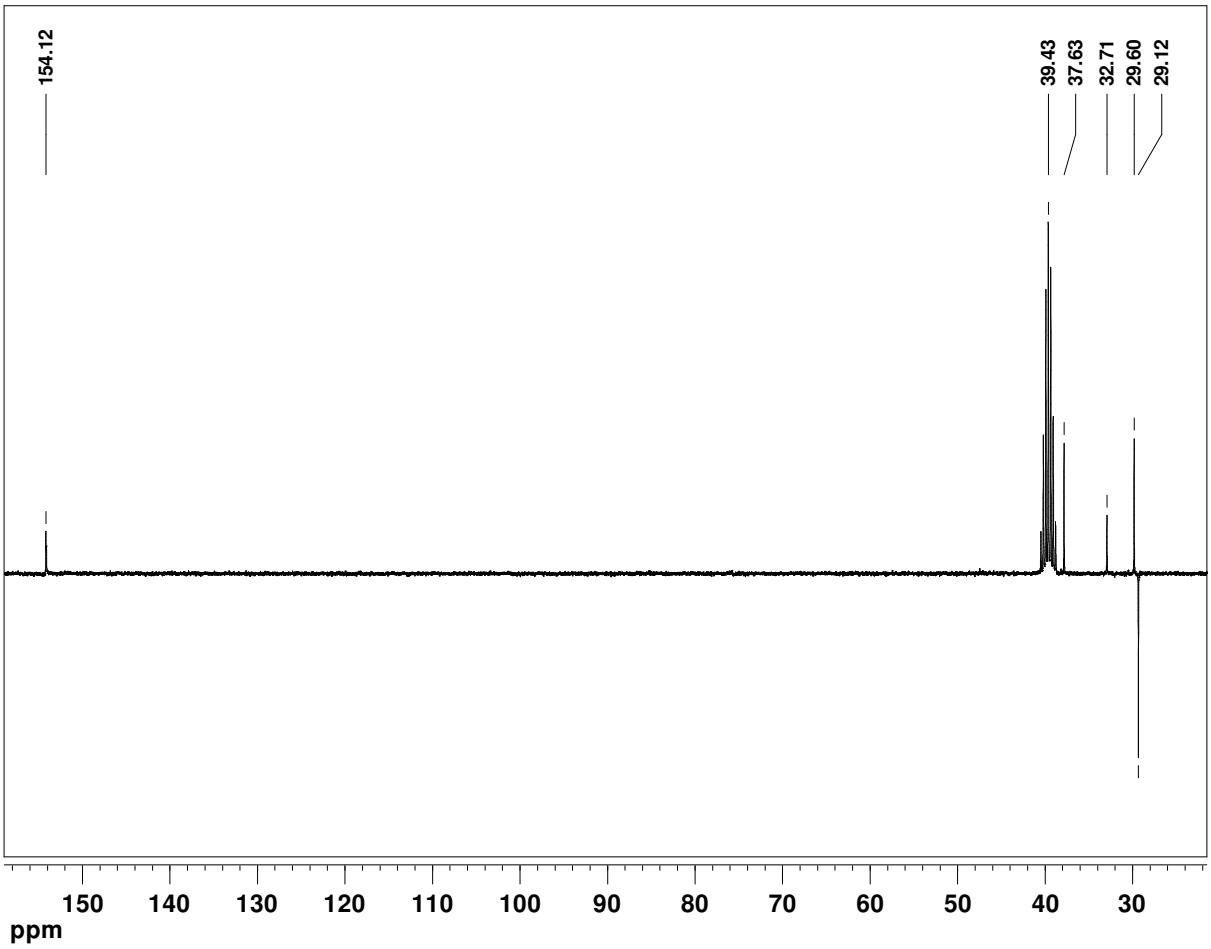
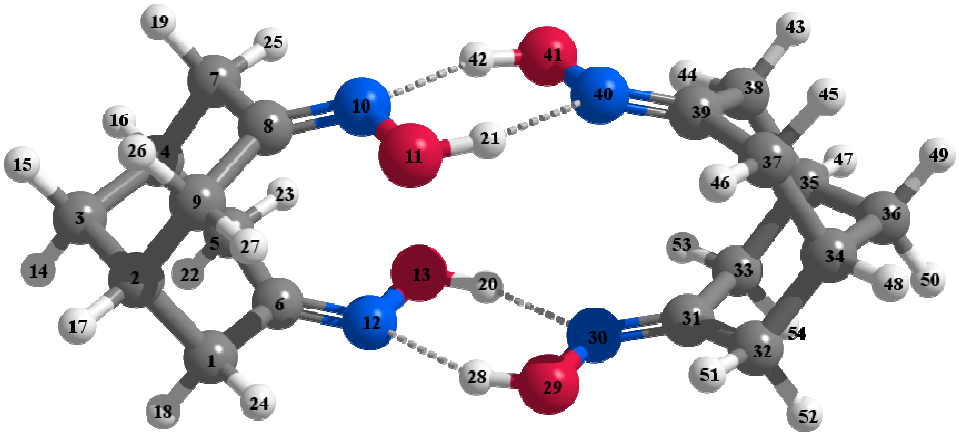


Figure 12. ^{13}C NMR spectrum of **2**-*anti*.

7. Cartesian coordinates of the B3lyp/6-31G(d) optimized structures of **2**-*anti* (dimer), **2**-*anti'*(trimer) and **2**-*syn* (trimer)

Compound: dimer of **2**-*anti*



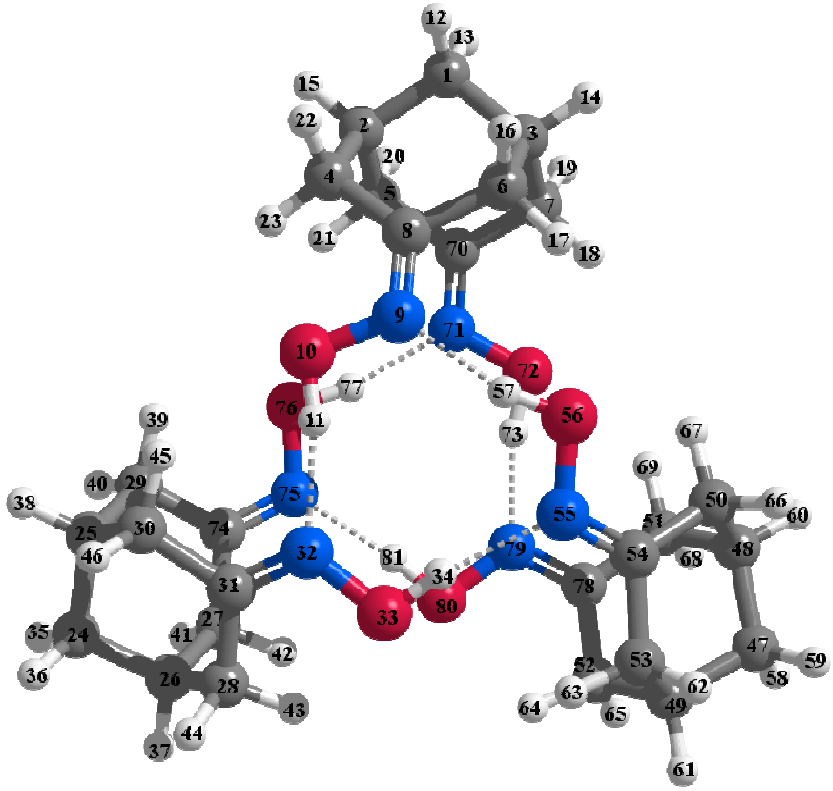
Cartesian coordinates:

54

Atom	X	Y	Z
C	-3.49844	1.06506	1.45786
C	-4.36987	-0.18259	1.23693

C	-5.25237	0.00074	0.00046
C	-4.37025	0.18316	-1.23643
C	-3.52217	1.45429	-1.07309
C	-2.74547	1.43981	0.21250
C	-3.50014	-1.06542	-1.45760
C	-2.74651	-1.44003	-0.21259
C	-3.52299	-1.45453	1.07310
N	-1.51101	-1.71209	-0.15905
O	-0.86781	-1.67358	-1.37326
N	-1.51017	1.71268	0.15868
O	-0.86661	1.67469	1.37272
H	-5.90075	0.86743	0.12742
H	-5.90170	-0.86528	-0.12620
H	-4.99866	0.31066	-2.11584
H	-4.99802	-0.30962	2.11660
H	-4.14859	1.89935	1.72757
H	-4.15142	-1.89921	-1.72606
H	0.06790	1.74442	1.11863
H	0.06687	-1.74263	-1.11964
H	2.83990	1.58363	-1.90837
H	4.19457	2.31445	-1.06637
H	2.80495	0.91862	2.27665
H	-2.80732	-0.92009	-2.27714
H	4.19619	-2.31403	1.06610
H	-2.84076	-1.58473	1.90828
H	-0.06670	1.74456	-1.11946
O	0.86792	1.67461	-1.37304
N	1.51104	1.71267	-0.15881
C	2.74641	1.44000	-0.21225
C	3.52272	1.45399	1.07356
C	3.49993	1.06550	-1.45737
C	4.36977	0.18216	1.23702
C	4.37027	-0.18291	-1.23645
C	5.25233	-0.00067	0.00050
C	3.49857	-1.06572	1.45761
C	3.52236	-1.45423	-1.07343
C	2.74557	-1.44005	0.21208
N	1.51022	-1.71275	0.15815
O	0.86674	-1.67506	1.37224
H	0.06783	-1.74448	1.11831
H	4.19490	-2.31426	-1.06672
H	2.84017	-1.58356	-1.90879
H	4.14883	-1.90000	1.72696
H	2.80502	-0.91967	2.27643
H	4.99876	-0.31013	-2.11585
H	4.99793	0.30905	2.11671
H	5.90082	-0.86729	0.12722
H	5.90142	0.86556	-0.12589
H	2.84032	1.58377	1.90868
H	4.19574	2.31365	1.06702
H	4.15092	1.89947	-1.72602
H	2.80695	0.92006	-2.27677

Compound: trimer of **2**-*anti'*



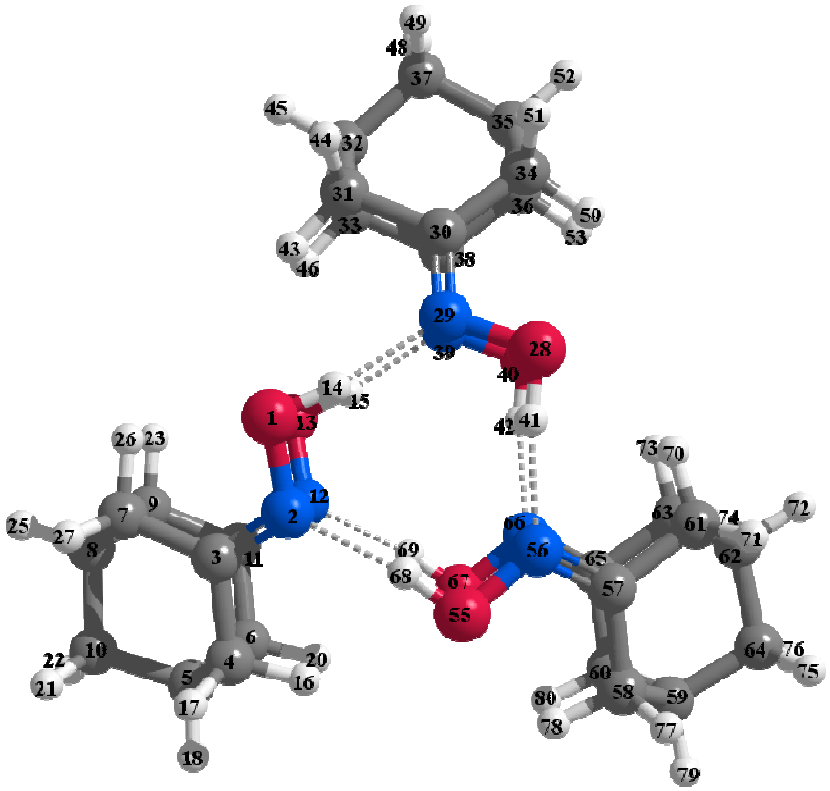
Cartesian coordinates:

81

Atom	X	Y	Z
C	3.81799	-4.24035	-0.08528
C	4.05298	-2.76300	-0.39566
C	2.35064	-4.45403	0.29136
C	2.01914	-3.64258	1.55203
C	1.43544	-4.08382	-0.88540
C	3.18785	-2.35079	-1.59568
C	3.77303	-1.90396	0.84665
C	1.73917	-2.71051	-1.40943
N	0.87173	-1.83734	-1.71176
O	-0.42763	-2.23719	-1.56154
H	-0.94996	-1.43014	-1.70783
H	4.07583	-4.84874	-0.95143
H	4.46490	-4.55989	0.73083
H	5.09373	-2.60884	-0.67347
H	2.18634	-5.50494	0.52043
H	3.55435	-2.88383	-2.47485
H	3.28647	-1.29051	-1.80153
H	3.83299	-0.84920	0.61109
H	4.53623	-2.11257	1.59816
H	2.57306	-4.07703	2.38671
H	0.96409	-3.71091	1.79980
H	1.59662	-4.79896	-1.69367
H	0.39191	-4.14311	-0.60246
C	-5.69573	-0.92517	0.04528
C	-4.64142	-1.98703	-0.26979
C	-5.00647	0.41510	0.30135
C	-4.07002	0.29141	1.51291
C	-4.26310	0.87788	-0.96073

C	-3.71023	-2.18691	0.93480
C	-3.86738	-1.58560	-1.53499
C	-3.32634	-0.18556	-1.45455
N	-2.12026	0.01157	-1.79365
O	-1.73480	1.32377	-1.74495
H	-0.77116	1.32869	-1.87763
H	-6.27620	-1.22130	0.91828
H	-6.39579	-0.83329	-0.78438
H	-5.75419	1.16912	0.53896
H	-5.13196	-2.93748	-0.46975
H	-2.90329	-2.86809	0.69563
H	-4.28182	-2.63523	1.74925
H	-4.68914	0.15268	2.40136
H	-3.50262	1.20473	1.66079
H	-3.71218	1.79115	-0.77739
H	-4.99496	1.08637	-1.74270
H	-3.06361	-2.28561	-1.74087
H	-4.55584	-1.62957	-2.38100
C	2.08651	5.27774	-0.02295
C	2.86392	3.99825	0.28431
C	0.62847	4.92807	-0.32344
C	2.86725	3.07281	-0.94057
C	2.26754	3.31776	1.52594
C	-0.02965	4.28209	0.90453
C	0.56043	4.01921	-1.55943
C	1.47826	2.83332	-1.45705
N	1.03120	1.70363	-1.81931
O	1.95250	0.69361	-1.76693
H	1.44188	-0.13212	-1.85205
H	2.14129	5.96197	0.82286
H	2.53179	5.79016	-0.87501
H	3.89868	4.24711	0.51121
H	0.07744	5.83796	-0.55223
H	0.86886	4.60541	-2.42719
H	-0.45492	3.68260	-1.74547
H	-1.03373	3.94626	0.67792
H	-0.10697	5.03062	1.69480
H	3.45426	3.54000	-1.73306
H	3.33316	2.12313	-0.71091
H	2.46521	3.95880	2.38718
H	2.74901	2.36470	1.71978
C	2.42503	-2.19989	1.43975
N	1.62006	-1.31598	1.86485
O	2.12784	-0.04459	1.81653
H	1.37428	0.55822	1.94247
C	-3.13737	-0.88687	1.42210
N	-1.93394	-0.72156	1.78768
O	-1.17619	-1.86237	1.75816
H	-0.25862	-1.57651	1.89508
C	0.77802	3.12950	1.42704
N	0.29473	2.01898	1.80171
O	-1.07054	1.94201	1.74569
H	-1.27321	0.99857	1.87141

Compound: trimer of **2**-*syn*



Cartesian coordinates:
81

Atom	X	Y	Z
O	-2.02896	0.76769	-2.11803
N	-1.91793	-0.57349	-1.86165
C	-2.99402	-1.13343	-1.49361
C	-4.30425	-0.42885	-1.28811
C	-5.02872	-0.91091	-0.02138
C	-4.33216	-0.42408	1.25931
C	-2.96416	-2.62015	-1.26856
C	-3.72371	-3.03839	-0.00232
C	-2.99761	-2.61705	1.28208
C	-5.12879	-2.43614	-0.02050
C	-3.02689	-1.12893	1.49447
N	-1.95357	-0.56786	1.86823
O	-2.06209	0.77707	2.10288
H	-1.11180	1.09868	-2.12110
H	-1.14335	1.10343	2.10833
H	-4.13926	0.64090	-1.26413
H	-4.93678	-0.63722	-2.15276
H	-6.02879	-0.48217	-0.03299
H	-4.98329	-0.62914	2.11079
H	-4.16648	0.64556	1.23416
H	-5.67115	-2.77593	-0.90203
H	-5.69254	-2.77417	0.84820
H	-3.50282	-3.08941	2.12669
H	-1.97032	-2.96782	1.28501
H	-3.79406	-4.12422	-0.00213
H	-3.44298	-3.10103	-2.12364
H	-1.93505	-2.96472	-1.24127

O	0.37373	-2.16294	-2.11700
N	1.47733	-1.39162	-1.86520
C	2.50249	-2.03859	-1.49467
C	3.77158	-1.26564	-1.26417
C	4.49269	-1.69650	0.02010
C	3.74242	-1.26297	1.28604
C	2.55280	-3.52381	-1.27996
C	3.30816	-3.89335	0.00651
C	2.51284	-3.52002	1.26754
C	4.67761	-3.21427	0.02530
C	2.46910	-2.03584	1.49435
N	1.44476	-1.38946	1.86862
O	0.33783	-2.16043	2.10657
H	-0.37328	-1.53652	-2.11770
H	-0.40665	-1.53114	2.11670
H	1.54691	-3.92388	-1.27454
H	3.07309	-3.96910	-2.12974
H	3.43935	-4.97348	0.01026
H	2.99514	-3.97770	2.13297
H	1.50276	-3.90762	1.22378
H	5.23602	-3.52044	0.90921
H	5.26095	-3.52426	-0.84095
H	3.55647	-0.20178	-1.25400
H	4.43995	-1.45274	-2.10668
H	5.46695	-1.21209	0.03064
H	3.52619	-0.19936	1.26905
H	4.39263	-1.44660	2.14340
O	1.71422	1.38552	-2.10235
N	0.49209	1.95718	-1.86694
C	0.53646	3.16818	-1.49522
C	1.79608	3.95272	-1.26459
C	1.71826	4.80994	0.00864
C	1.77592	3.95272	1.28285
C	-0.77067	3.88153	-1.28729
C	-0.77653	4.73357	-0.01125
C	-0.79116	3.88028	1.26398
C	0.44411	5.65468	-0.00107
C	0.51304	3.16787	1.49394
N	0.46358	1.95773	1.86788
O	1.68226	1.38793	2.12510
H	1.54083	0.42604	-2.11119
H	1.51145	0.42794	2.13260
H	-1.58388	3.16252	-1.28253
H	-0.93201	4.54617	-2.13812
H	-1.68425	5.33354	-0.01828
H	-0.96744	4.54416	2.11242
H	-1.60368	3.16077	1.24486
H	0.43184	6.30315	-0.87627
H	0.41799	6.30238	0.87442
H	1.94264	4.61268	-2.12131
H	2.64192	3.27746	-1.23341
H	2.58697	5.46506	0.01551
H	1.90834	4.61285	2.14175
H	2.62240	3.27780	1.26558

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