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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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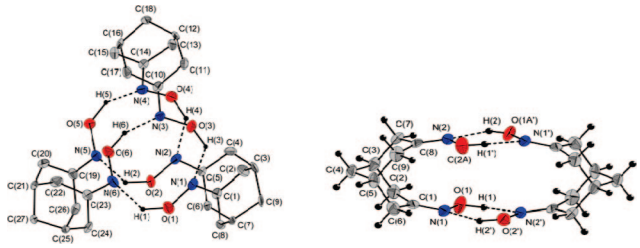
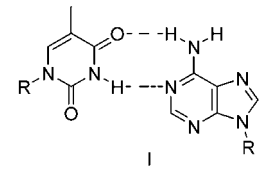


The formation and high stability of the H-bond-driven supramolecular architectures of the s*yn* and *anti* isomers of the dioxime of bicyclo[3.3.1]nonane-3,7-dione were investigated by single crystal X-ray diffraction, NMR, FTIR, and molecular modeling. Self-assembly of the achiral *syn* isomer into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

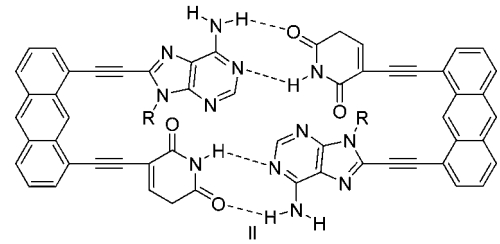
Self-assembly processes are based on noncovalent bonds, the driving forces of supramolecular chemistry.[1] The construction of supramolecular architectures with molecular species requires the formation of these intermolecular connections, usually by stacking interactions (CH$-\pi$, $\pi-\pi$ or p$-\pi$) 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



I

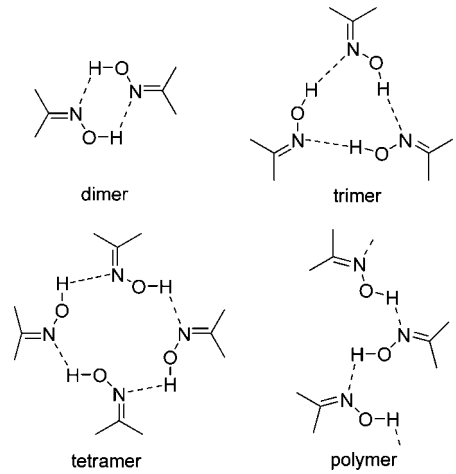
Watson-Crick (Adenine-Thymine, AT) interactions



II

Adenine-Uracyl (AU) interactions

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

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

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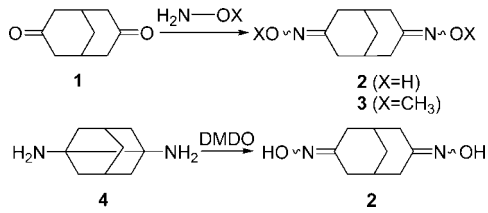
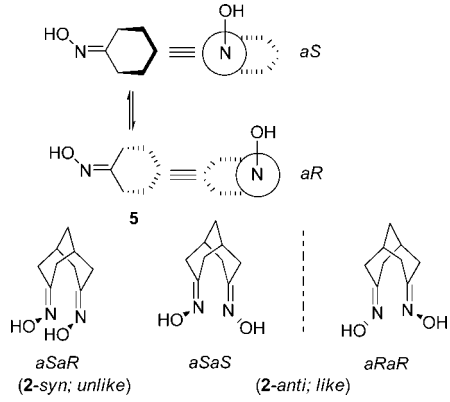
SCHEME 1



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]

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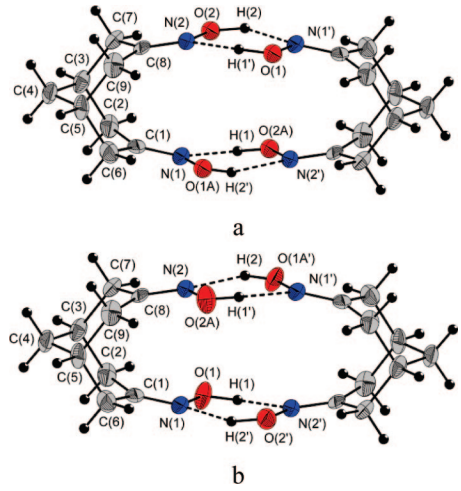

FIGURE 1. ORTEP diagrams for the cyclic dimers of **2**-*anti* (a: *aRaR*−*aRaR*; b: *aSaS*−*aSaS* associations).

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

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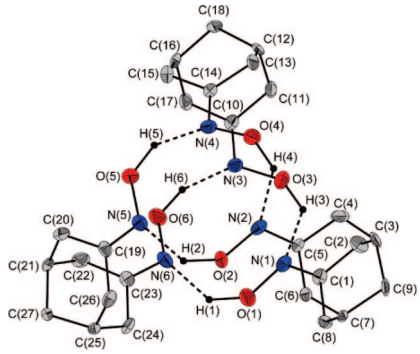

FIGURE 2. ORTEP diagram for the cyclic trimer of the achiral **2**-*syn* isomer.

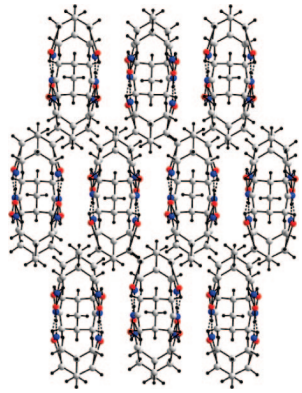

FIGURE 3. View of the lattice (along the *c* crystallographic axis) of **2**-*syn*.

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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