Anion Helicates: Double Strand Helical Self-Assembly of Chiral Bicyclic Guanidinium Dimers and Tetramers around Sulfate Templates

Jorge Sánchez-Quesada, Christian Seel, Pilar Prados, and Javier de Mendoza*

Departamento de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco, 28049-Madrid, Spain

Ionara Dalcol and Ernest Giralt

Departament de Química Orgànica
Universitat de Barcelona
Martí i Franqués 1-11, 08028-Barcelona, Spain

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Synthetic molecules possessing helicity derived from their primary or secondary structures could be related to polypeptides in the α-helix conformation.[1] On the other hand, compounds related to double-helical nucleic acids arise from the spontaneous self-assembly of molecular strands, usually promoted by metal templates (helicates). Double-stranded helicates have been reported with tetrahedral,[2] octahedral,[3] or nondirectional[4] transition metals, whereas triple-stranded helices result from octahedral coordination metals[5] or lanthanides.[6] Here, we describe the first example of a double-helical structure folding around anions.

Enantiomerically pure chiral bicyclic guanidinium salts[7] have been successfully employed for the molecular recognition of carboxylates (amino acids)[8] or phosphates (nucleotides).[9] Consequently, strands of tetraguanidinium salts **1** (chlorides and sulfates) as well as their diguanidinium precursors **2** and **3** were designed for the complexation and transport of oligonucleotides across biological membranes. In our design, the CH_2SCH_2 spacer unit was chosen to span the distance between two adjacent monoanions in the phosphodiester chain. In the case of a divalent sulfate counterion, the spacer is simply too short to wrap two guanidinium subunits in orthogonal planes around a single anion. Therefore, two strands of **1** are forced to fold in a double-helical structure of the predictable handedness imposed by the chiral nature of the receptor. In addition, and unlike with the cation helicates previously mentioned, neutral helices of guanidinium sulfate are obtained.

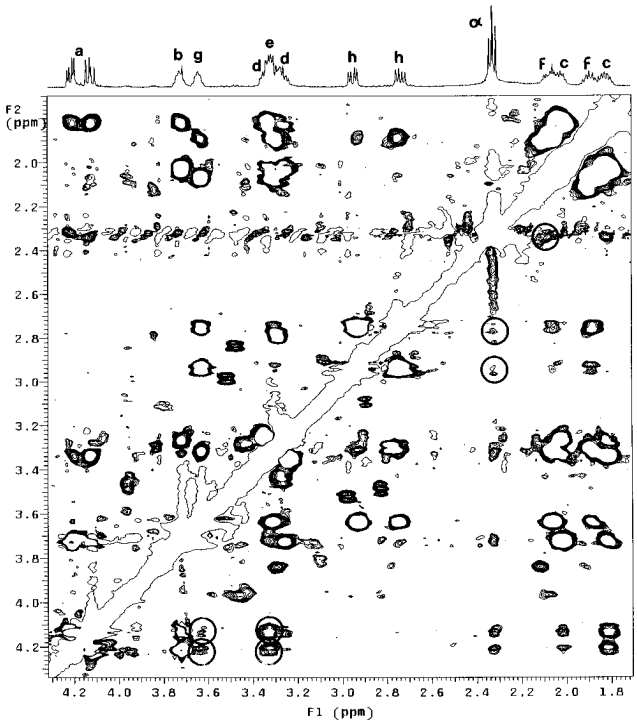
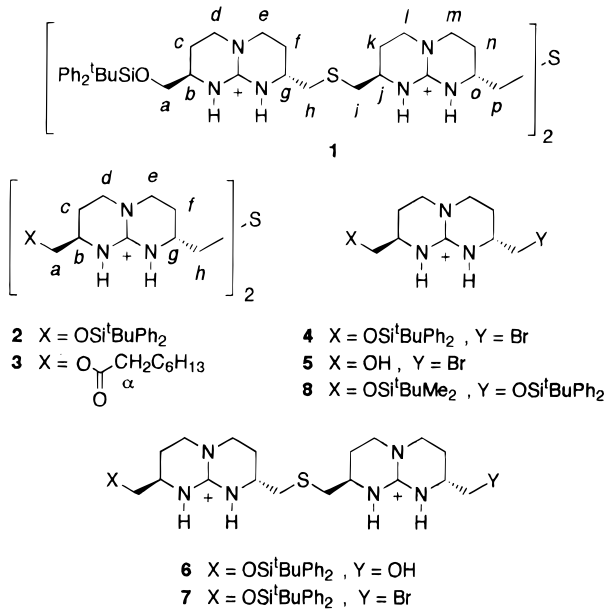


Figure 1. ROESY spectrum of **3** sulfate in $CDCl_3$ (mixing time, 400 ms). Circles show contacts depicted in text and Figure 2a.



1

2 X = OSi^tBuPh_2
3 X = O(C=O)$CH_2C_6H_{13}$

4 X = OSi^tBuPh_2 , Y = Br
5 X = OH , Y = Br
8 X = OSi^tBuMe_2 , Y = OSi^tBuPh_2

6 X = OSi^tBuPh_2 , Y = OH
7 X = OSi^tBuPh_2 , Y = Br

Sulfate salts of **1**−**3** were readily prepared from known compounds, in both enantiomeric forms. Thus, reaction of the chiral bicyclic guanidinium monobromo derivative **4**[10,11] with sodium sulfide (1 equiv) afforded diguanidinium **2**[10] in 87% yield. Silyl ethers were quantitatively removed by 12 N HCl/methanol (1:1), and the resulting diol was esterified with octanoic acid and carbonyldiimidazole as coupling agent to give

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(10) Peschke, W.; Schiessl, P.; Schmidtchen, F. P.; Bissinger, P.; Schier, A. *J. Org. Chem.* **1995**, *60*, 1039−1043. Improved procedures for the syntheses of **2** and **4** were employed. No disulfide formation was detected in the preparation of **2** with sodium sulfide. On the other hand, the yield of pure **4** as a colorless solid was enhanced from 59% to 84% by reaction of the corresponding guanidinium alcohol (Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3279−3284) with carbon tetrabromide and tetraphenylphosphine instead of thionyl bromide.

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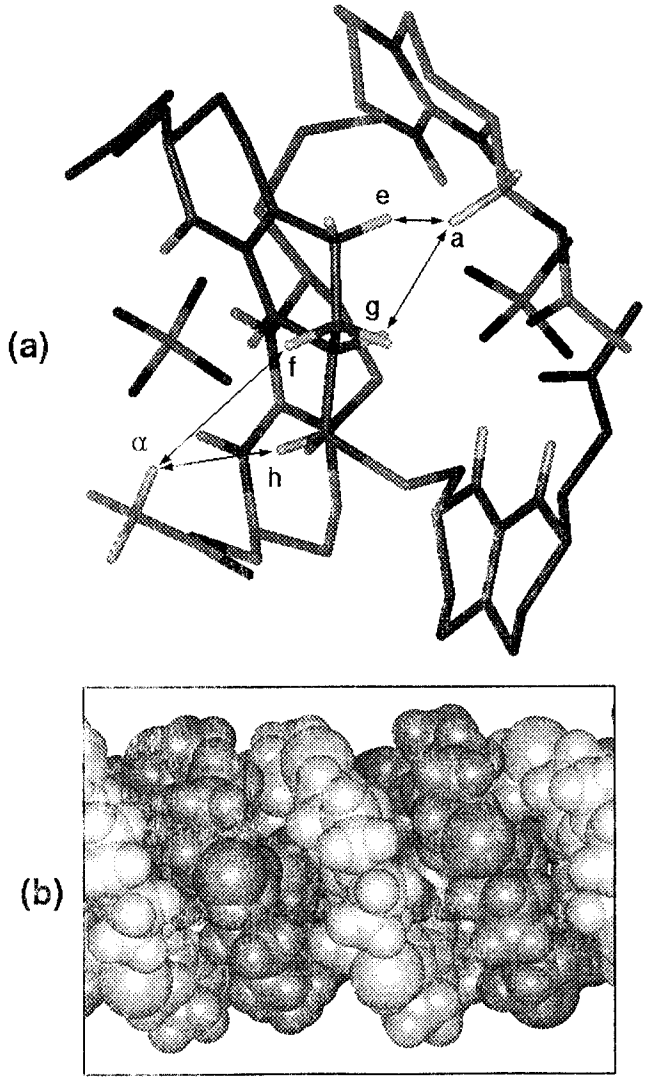

Figure 2. (a) Energy-minimized[13] molecular model of a diacetate analogue of **3** (arrows show ROE contacts observed in **3**). (b) CPK model of a polyguanidinium right-handed double helix made from two strands of subunits of *(R,R)* configuration.

3 in 72% yield. Similarly, tetramer **1** was prepared by reaction of bromoguanidinium **4** with thiourea, followed by treatment of the resulting thiouronium salt with cesium carbonate and bromo alcohol **5** (obtained quantitatively from **4** by acid hydrolysis), to afford the monoprotected diguanidinium alcohol **6** in 53% yield. Alcohol **6** was then transformed into bromide **7** with carbon tetrabromide and triphenylphosphine (80% yield). Treatment of **7** with 1 equiv of sodium sulfide gave **1** in 82% yield.

Counterions strongly influenced the ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of the salts. As in previously reported guanidinium oxoanion complexes,[8,9] strong downfield shifts of ~1 ppm were observed for the guanidinium NH protons when the anion changed from chloride to sulfate, accounting for the formation of two strong salt-bridged N—H···O hydrogen bond pairs. Additionally, in diester **3**, the A_2X pattern of the CH_2OCO group (labeled a) changed to an ABX system.[12] Particularly diagnostic for helix formation was the comparison between ROESY spectra of the chloride and sulfate salts of compound *(R,R)*-**3** (Figure 1). In the sulfate, contacts were observed between protons α and f, α and h, or between protons a and e, and a and g. Since distances between either α or a and each of the above-mentioned protons of the same chain are simply much too long for any cross peak to be observed, the signals must correspond to intermolecular contacts between *different* chains. This is precisely the situation when the two chains wrap around each other as shown in Figure 2. For tetramer *(R,R)*-**1**, a similar situation applies, although because of the increased complexity of the molecule, some assignments were only tentative.

(11) Unless specified, counterions refer to chloride. The synthetic scheme was performed either with guanidines of *(R,R)* or *(S,S)* configuration, although only compounds with *(R)* configuration are shown in the formulae. All new compounds were characterized by a full complement of high-resolution spectra and elemental microanalyses for C and H which are within 0.40% theory.

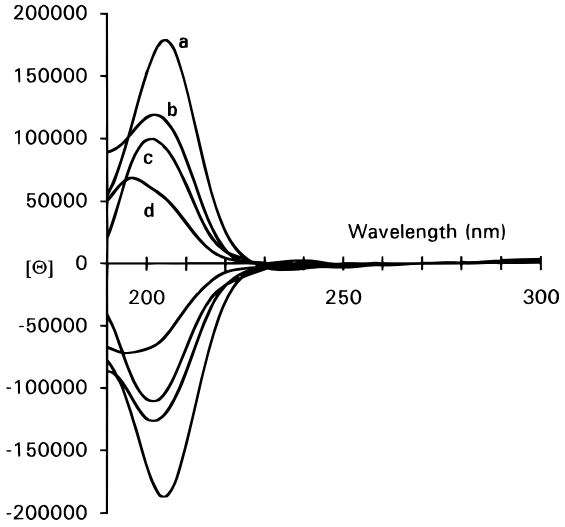

Figure 3. CD spectra in acetonitrile at 4 °C (molar ellipticities in deg cm^2 dmol^{-1} for 0.5 mM solutions): (a) *(S,S)*-**1** sulfate, (b) *(S,S)*-**1** chloride, (c) *(S,S)*-**2** sulfate, and (d) *(S,S)*-**2** chloride.

Finally, CD spectra of diguanidinium dichloride **2** and tetraguanidinium tetrachloride **1** were registered in acetonitrile, showing in each case almost complete mirror image spectra for both enantiomers (Figure 3, curves d and b, respectively). The higher ellipticities observed for the tetramer are due to the increased number of bicyclic guanidinium subunits. Similar shapes resulted from the corresponding sulfate salts (Figure 3, curves c and a), but in this case significant increases in ellipticity with respect to the chlorides were observed for the same number of bicyclic guanidinium subunits, accounting for the highly structured helical conformation. No such differences were observed for chlorides and sulfates of parent guanidinium **8**, whose CD spectra per cationic subunit were almost superimposable. Thus, changes in ellipticity are related not to the different anions employed but to the helical conformations of the corresponding polycations.

Presumably, tetraguanidinium chains like **1** could also wrap around the phosphate chains of double-stranded nucleic acids, giving rise to triple or quadruple helices with modified properties. This could find application in the delivery of the antisense nucleotides and ribozymes or eventually of therapeutic agents such as phosphorylated analogs of AZT and DDI across biological membranes.[9b]

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Supporting Information Available: Copies of spectral and physical data, 1D and 2D NMR as well as CD spectra for new guanidinium chlorides and sulfates (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) NMR spectral assignments were performed using 1D and 2D COSY and 2D ROESY experiments (mixing times, 150, 400, and 650 ms) at 25 °C in $CDCl_3$ (10 mg/mL). The additional cross peaks present in the ROESY spectra of (*R,R*)-3 sulfate, compared to the ROESY spectra of the dichloride, do not disappear on dilution of the sample, excluding the possibility of these being due to molecular contacts.

(13) Molecular mechanics calculations were made in vacuo, with a dielectric constant $\epsilon = 2r_{ij}$, with Insight-II 2.3.0/Discover packages (Biosym) using AMBER force field. CHARMM parameters and Spartan 3.0 electrostatic charges at the 6-31G* level were used for sulfate.