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Contribution of the anomeric effect to the solution and crystal structure of [1*S*,2*S*,6*S*,7*S*]-1,6-diaza-4,9-dioxa-2,7-dimethoxycarbonylbicyclo[4.4.1]undecane, a condensation product of L-serine methyl ester with formaldehyde☆

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Abstract

The reaction of L-serine methyl ester hydrochloride (**1**) with paraformaldehyde (**2**) in dichloromethane in the presence of triethylamine afforded a novel compound: [1*S*,2*S*,6*S*,7*S*]-1,6-diaza-4,9-dioxa-2,7-dimethoxycarbonylbicyclo[4.4.1]undecane (**4**) as a 2:3 adduct of **1** with **2**. ^{1}H and ^{13}C NMR spectroscopy were unable to discriminate between two possible symmetrical structures. The latter was unambiguously proved by X-ray crystallography. The crystal structure established: (i) the existence of two identical seven-membered rings each containing a N–C–O grouping; (ii) the existence of a long C–O–C–N–C–N–C–O–C sequence in which each nitrogen belongs simultaneously to a N–C–O (oxazolidine) and to a N–C–N (aminal) motifs; (iii) the existence of a chair-like conformation for both seven-membered rings; (iv) the antiperiplanar geometry of *p*N–C–O and consequently the manifestation of a strong anomeric effect in both N–C–O groupings, whereas anomeric effect was virtually absent in the N–C–N sequence, as corroborated by bond distances and bond angles. Chemical shifts, coupling constants and NOE effects confirm that the conformational features of **4** are preserved in solution.

Keywords: Anomeric effect; L-Serine; Formaldehyde; Condensation product

1. Introduction

The importance of the anomeric effect in determining the structure, conformational properties and reactivity of organic compounds is well recognized.[2–8] Although the bulk of information arises from carbohydrates, the anomeric effect is a more general

☆ Anomeric effects in non-carbohydrate compounds, Part II. For Part I, see Ref. 1.

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phenomenon.[2,6–9] It is observed not only in tetrahydropyran and tetrahydrofuran systems but also in various heterocycles as well as in acyclic structures provided a motif R–Y–C–X (where Y is an heteroatom with an appropriately oriented unshared pair of electrons and X an electronegative group) is present. Numerous crystal structures, especially those derived from carbohydrates, as well as quantum chemical calculations substantiate well-defined conformational preferences for R–Y–C–X fragments. Indeed, in pyranose (furanose) derivatives, anomeric effect favors conformations having the C-1–O-1 (C-1–X) acceptor bond in an axial orientation, i.e., antiperiplanar to the pseudoaxial sp^3 lone pair of the ring oxygen. In other words the preferred geometry of either cyclic or acyclic molecules containing such sequence is the one which maximizes the stabilizing interaction between the best donor lone-pair and the best acceptor bond, the so-called $n \rightarrow \sigma^*$ interaction.[10,11]

Such interaction induces changes in molecular geometry as observed in a variety of R–Y–C–X structures. Hence in pyranose derivatives, electron transfer results in the lengthening of the exocyclic anomeric C-1–O-1 (C-1–X) bond, in the contraction of the endocyclic O-5–C-1 bond by increasing its double-bond character and in the opening of the O-5–C-1–O-1 (O-5–C-1–X) angle as compared to its normal tetrahedral value.[12] We have shown recently that the anomeric effect governs the conformation of 1,3-oxazolidine ring (C–N–C–O–C grouping) in 2,8-diphenyl-5-hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]-octane.[1]

In principle, the anomeric effect should also apply to aminals (C–N–C–N–C grouping). In fact, there is little evidence in the literature for bond shortening and lengthening in aminals even when the conformation is ideally set up for electron delocalization.[13,14] Comparison of the reported aminal C–N bond lengths with respect to standard uncertainty values (s.u.) showed that most of them are within 3 s.u. values of one another. The effect is just above the noise level. However, in protonated aminals (R_2N–CHR–NR_3^+ grouping), the existence of a strong anomeric effect has been clearly established.[14]

For several reasons [including: (i) the symmetry of the molecule; (ii) the existence of two identical seven-membered rings, each containing a N–C–O motif; (iii) the existence of a long C–O–C–N–C–N–C–O–C sequence in which each nitrogen atom belong simultaneously to an oxazolidine and to an aminal functionality] we considered the title compound described below as an unique model to study intracyclic stereoelectronic effects and possibly the manifestation of a cooperative anomeric effect extending across the nine-atom sequence.

2. Results and discussion

L-Serine methyl ester hydrochloride (**1**) was reacted with paraformaldehyde (**2**) in dichloromethane in the presence of triethylamine, a procedure adapted from previous results by Freidinger et al.[14] In our case, the reaction was achieved at room temperature in the absence of acid catalyst. The condensation product which has never been reported before was suspected, on the basis of the reaction of formaldehyde with respectively (*R*)-phenylglycinol,[15] (*S*)-2-amino-1-phenylethanol[16] and 1-norephedrine[17] to be a 2:3-adduct, i.e., a compound with the empirical formula $C_{11}H_{18}O_6N_2$. This assumption was corroborated by the mass spectrum which displayed a molecular ion at m/z 274 and a parent peak at m/z 144 characteristic of the oxazolidinium ion derived from L-serine methyl ester. The ^{13}C NMR spectrum consisted of only six signals (see Table 1) reflecting the perfect symmetry of the molecule. This was confirmed by the ^1H NMR spectrum which displayed a six-proton singlet for the two methoxy groups. Comparison of the NMR spectrum of L-serine methyl ester with that of the above compound allowed to assign the three methylene groups arising from formaldehyde to: (i) a two-proton singlet at low field (4.56 ppm); (ii) a well-resolved four-proton AB pattern at 4.44 and 4.26 ppm for the low-field and high-field doublets respectively; (iii) a four proton AB pattern at respectively 4.24 and 3.92 ppm associated with a two-proton quartet at 4.0 ppm (see Table 1 for complete assignment).

Table 1
^1H and ^{13}C NMR data for **4** in $CDCl_3$ (solvent at 77.00 ppm/TMS)

Proton [a]	δ ppm [b]	J (Hz)	NOE [c]
H-11_A, H-11_B [d]	4.561		
H-5_{eq} (H-10_{eq})	4.431	5_{eq}, $11_B = 10_{eq}$, $11_A = 1.6$ 5_{eq}, $3_{eq} = 10_{eq}$, $8_{eq} = 0.6$	
H-5_{ax} (H-10_{ax})	4.258	5_{ax}, $5_{eq} = 10_{eq}$, $10_{ax} = -11.4$ 5_{ax}, $3_{eq} = 10_{ax}$, $8_{eq} = 0.6$	++
H-3_{eq} (H-8_{eq})	4.236	3_{eq}, $2 = 8_{eq}$, $7 = 3.0$ 3_{eq}, $3_{ax} = 8_{eq}$, $8_{ax} = -13.6$	
H-2 (H-7)	4.002	$2,3_{eq} = 7,8_{eq} = 3.0$ $2,3_{ax} = 7,8_{ax} = 9.8$	
H-3_{ax} (H-8_{ax})	3.917	3_{ax}, $3_{eq} = 8_{ax}$, $8_{eq} = -13.9$	+
–OCH_3	3.740		
Carbon	δ (ppm)	$^1J_{C-H}$ (Hz)	
C-5, C-10	87.44	157.3	
C-3, C-8	70.03	144.9	
C-2, C-7	65.58	139.6	
C-11	68.08	149.5	
OCH_3	52.28	147.4	
C=O	172.02		

[a] See Scheme 2 and Fig. 1 for atoms numbering.
[b] $CDCl_3$ solution (solvent at 7.280 ppm vs. TMS).
[c] NOE observed while irradiating signal at 4.561 ppm.
[d] H-11_A, H-11_B represent H-11 directed above ring A and ring B, respectively.

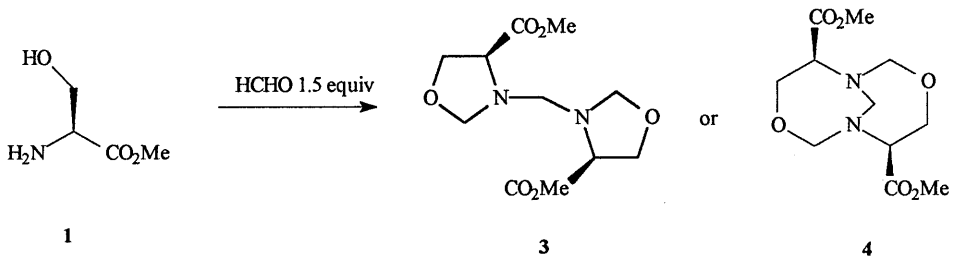
Table 2
Summary of crystal data, intensity measurements and refinement for **4**

Formula	$C_{11}H_{18}N_2O_6$
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	9.001(3)
b (Å)	14.274(4)
c (Å)	19.792(3)
V (Å^3)	2542.7(11)
Molecular weight	274.3
Z	8
D_{calc} at 170 K	1.433
Crystal size (mm^3)	$0.50 \times 0.30 \times 0.12$
Crystal color	colorless
Recrystallization solvent	diethyl ether
Mp (°C)	90–91
Method of data collected	$\omega - \theta$
Radiation (graphite monochromated)	Mo K_α
μ (cm^{-1})	1.17
Unique reflections	2791
Observed reflections	2491
Final no. of variables	362
R_1 (2491 observed)	0.0407
σ Cutoff	$F_o > 4\sigma(F_o)$
wR_2 (on F^2)	0.1057
Goodness-of-fit	1.043
Residual electron density	0.23 (−0.31)

However, the analytical and spectroscopic data reported above and in Table 1 proved inconclusive regarding the two possible structures of the 2:3-adduct, i.e., a *N*,*N*′-methylenebis(oxazolidine) type (**3**) and a bicyclo[4.4.1]undecane type (**4**) (Scheme 1).

In order to discriminate between both, we decided to have the X-ray crystal structure determined. The adduct was recrystallized from diethyl ether to afford crystals suitable for X-ray analysis.

Crystal structure of **4**.—Crystal data are presented in Table 2. The asymmetric unit contains two slightly different molecules identified as molecules 1 and 2. The positional and equivalent thermal isotropic parameters are listed in Table 3. Selected bond distances and bond angles for both molecules are given in Tables 4 and 5, respectively. As can be seen from Tables 3 to 5, structural parameters are very similar: equivalent interatomic distances and angles are generally equal within experimental error. The small differences observed



1 3 4

Scheme 1.

between molecule 1 and molecule 2 are very likely due to the conformational flexibility of the seven-membered rings and to differences in crystal packing.

For the sake of clarity, the following discussion is based on crystal data related to molecule 1 whose X-ray crystal structure and atom labeling are shown in the ORTEP view of Fig. 1. The geometry of the molecule is of the bicyclic type in agreement with that represented for compound **4** in Scheme 1. Methyl ester groups have a cis pseudo–equatorial relationship. The *S* configuration of α-carbon of both serine moieties is maintained at C-2 and C-7 of the bicycle whereas both bridgehead nitrogen atoms N-1 and N-6 displayed also the *S* configuration. Consequently, nitrogen lone-pairs adopt the out–out disposition depicted in Scheme 2(a) commonly observed in bicyclic structures when rings are small (three-

Table 3
Fractional atomic coordinates for the non-hydrogen atoms and the corresponding isotropic thermal parameters for **4** [a]

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq}
O-4	−0.1572(2)	0.5456(1)	1.0437(1)	0.0214(4)
O-9	−0.1420(2)	0.2446(1)	1.0134(1)	0.0237(4)
O-12	0.0944(3)	0.3463(2)	1.1717(1)	0.0607(9)
O-13	−0.1113(2)	0.3809(2)	1.2271(1)	0.0400(6)
O-14	−0.4137(2)	0.4256(2)	0.8633(1)	0.0344(5)
O-15	−0.1797(2)	0.3850(2)	0.8368(1)	0.0344(5)
N-1	−0.2475(2)	0.3417(2)	1.1013(1)	0.0172(5)
N-6	−0.3330(2)	0.4313(2)	1.0003(1)	0.0165(4)
C-2	−0.1158(3)	0.4016(2)	1.1087(1)	0.0188(5)
C-3	−0.1517(3)	0.5072(2)	1.1096(1)	0.0210(6)
C-5	−0.2954(3)	0.5278(2)	1.0095(1)	0.0184(5)
C-7	−0.2391(3)	0.3819(2)	0.9516(1)	0.0177(5)
C-8	−0.2371(3)	0.2744(2)	0.9603(1)	0.0222(6)
C-10	−0.2100(3)	0.2494(2)	1.0787(1)	0.0232(6)
C-11	−0.3709(3)	0.3830(2)	1.0627(1)	0.0173(5)
C-12	−0.0317(3)	0.3735(2)	1.1717(1)	0.0222(6)
C-13	−0.0411(4)	0.3532(3)	1.2899(1)	0.0383(8)
C-14	−0.2906(3)	0.4014(2)	0.8802(1)	0.0234(6)
C-15	−0.2156(4)	0.3966(3)	0.7661(2)	0.0461(9)
O-24	0.1507(2)	0.4542(1)	0.9769(1)	0.0202(4)
O-29	0.1399(2)	0.7548(1)	0.9970(1)	0.0197(4)
O-32	0.4228(2)	0.5700(2)	1.1469(1)	0.0340(5)
O-33	0.1815(2)	0.5839(2)	1.1719(1)	0.0334(5)
O-34	−0.1100(3)	0.6198(3)	0.8371(1)	0.0696(1)
O-35	0.1053(2)	0.6531(2)	0.7886(1)	0.0377(6)
N-21	0.3314(2)	0.6386(1)	1.0163(1)	0.0160(4)
N-26	0.2385(2)	0.5808(2)	0.9053(1)	0.0175(5)
C-22	0.2414(3)	0.5735(2)	1.0562(1)	0.0169(5)
C-23	0.2486(3)	0.4719(2)	1.0317(1)	0.0191(5)
C-25	0.2092(3)	0.4824(2)	0.9126(1)	0.0204(5)
C-27	0.1026(3)	0.6378(2)	0.9079(1)	0.0183(5)
C-28	0.1306(3)	0.7412(2)	0.9259(1)	0.0202(5)
C-30	0.2848(3)	0.7339(2)	1.0236(1)	0.0191(5)
C-31	0.3634(3)	0.6122(2)	0.9467(1)	0.0162(5)
C-32	0.2950(3)	0.5761(2)	1.1291(1)	0.0205(5)
C-33	0.2185(4)	0.5807(3)	1.2432(1)	0.0462(10)
C-34	0.0205(3)	0.6348(2)	0.8412(1)	0.0254(6)
C-35	0.0317(4)	0.6562(3)	0.7232(2)	0.0452(9)

[a] Atom numbering is as follows: O-4 to C-15 for molecule 1 and O-24 to C-35 for molecule 2.

Table 4
Selected bond distances (Å) in the two molecules of compound **4**

Molecule 1		Molecule 2	
O-4–C-3	1.416(3)	O-24–C-23	1.421(3)
O-4–C-5	1.439(3)	O-24–C-25	1.433(3)
O-9–C-8	1.421(3)	O-29–C-28	1.421(3)
O-9–C-10	1.431(3)	O-29–C-30	1.439(3)
N-1–C-10	1.431(3)	N-21–C-30	1.431(3)
N-1–C-2	1.469(3)	N-21–C-31	1.456(3)
N-1–C-11	1.471(3)	N-21–C-22	1.464(3)
N-6–C-5	1.430(3)	N-26–C-25	1.437(3)
N-6–C-11	1.456(3)	N-26–C-31	1.462(3)
N-6–C-7	1.463(3)	N-26–C-27	1.470(3)
C-2–C-12	1.513(4)	C-22–C-32	1.521(3)
C-2–C-3	1.542(4)	C-22–C-23	1.532(3)
C-7–C-14	1.513(4)	C-27–C-34	1.513(4)
C-7–C-8	1.543(4)	C-27–C-28	1.540(3)

Table 5
Selected bond angles (°) in the two molecules of compound **4**

Molecule 1		Molecule 2	
C-3–O-4–C-5	113.3(2)	C-23–O-24–C-25	113.6(2)
C-8–O-9–C-10	113.3(2)	C-28–O-29–C-30	112.9(2)
C-10–N-1–C-2	112.2(2)	C-30–N-21–C-22	112.7(2)
C-10–N-1–C-11	112.6(2)	C-30–N-21–C-31	113.6(2)
C-2–N-1–C-11	115.3(2)	C-22–N-21–C-31	117.1(2)
C-5–N-6–C-11	113.8(2)	C-25–N-26–C-31	112.6(2)
C-5–N-6–C-7	114.3(2)	C-25–N-26–C-27	112.6(2)
C-11–N-6–C-7	117.7(2)	C-31–N-26–C-27	116.7(2)
N-1–C-2–C-12	109.4(2)	N-21–C-22–C-32	108.7(2)
N-1–C-2–C-3	113.7(2)	N-21–C-22–C-23	114.0(2)
C-12–C-2–C-3	110.7(2)	C-32–C-22–C-23	108.1(2)
O-4–C-3–C-2	111.9(2)	O-24–C-23–C-22	112.6(2)
N-6–C-5–O-4	115.8(2)	N-26–C-25–O-24	115.6(2)
N-6–C-7–C-14	110.4(2)	N-26–C-27–C-34	111.1(2)
N-6–C-7–C-8	114.4(2)	N-26–C-27–C-28	113.7(2)
C-14–C-7–C-8	106.9(2)	C-34–C-27–C-28	108.0(2)
O-9–C-8–C-7	112.8(2)	O-29–C-28–C-27	111.7(2)
N-1–C-10–O-9	115.2(2)	N-21–C-30–O-29	115.1(2)
N-6–C-11–N-1	117.0(2)	N-26–C-31–N-21	117.3(2)

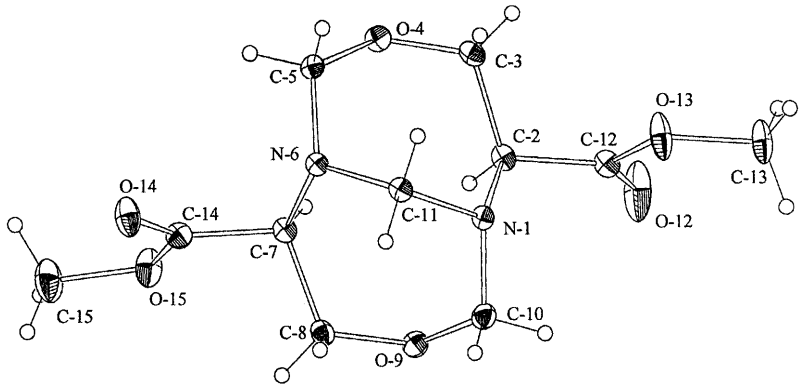
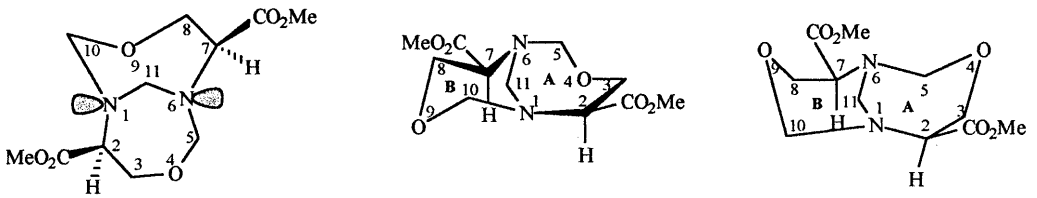


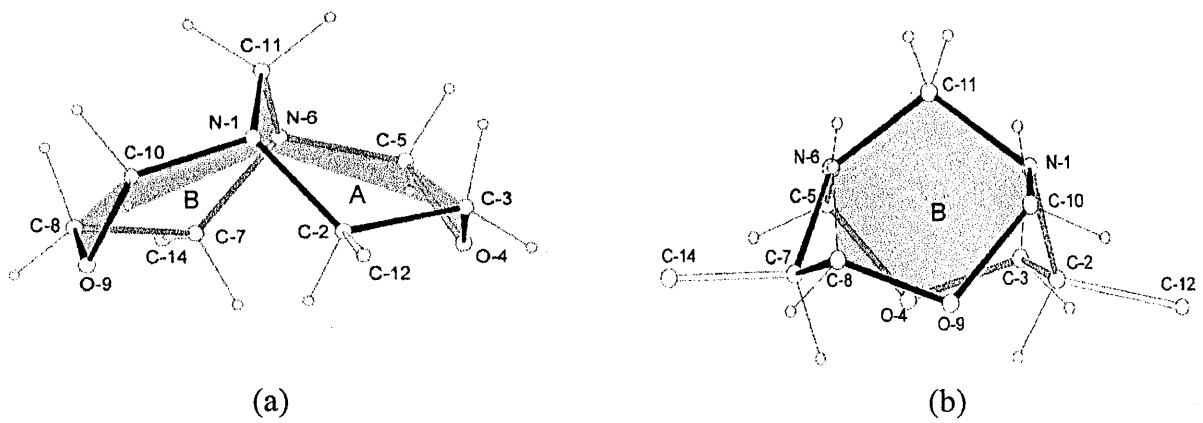
Fig. 1. ORTEP view of **4** (molecule 1) with atoms numbering. The thermal ellipsoïds are drawn at the 30% probability level.



a **b** **c**

out, out **chair, chair (O-4 endo, O-9 endo)** **boat, boat (O-4 exo, O-9 exo)**

Scheme 2.



Scheme 3.

and four-membered) or common-sized (five- and six-membered).[14]

In the solid state, **4** exhibits a C_2 molecular symmetry. The twofold axis lies in the plane N-1–C-11–N-6 passing through C-11 and bisecting the bond angle N-1–C-11–N-6 (see Scheme 3(a)) thereby confirming the symmetry of the bicyclic skeleton inferred from the ^{13}C and ^{1}H NMR spectra. Both seven-membered rings adopt the chair-like conformation depicted in Scheme 2(b).

The alternative boat–boat conformation (Scheme 2(c)) which, from molecular models seems to display more conformational flexibility is not observed. A similar situation was reported by Husson et al. for the condensation product of (*R*)-phenylglycinol with formaldehyde.[15]

The three-dimensional representations on Scheme 3 show clearly the chair-like conformation of both seven-membered ring A and B. On the basis of a reference six-membered ring chair materialized by the sequence N-1–C-3–O-4–C-5–N-6–C-11 for ring A and N-6–C-8–O-9–C-10–N-1–C-11 for ring B, C-2 and C-7 were shown to be noticeably out. C-2 is 0.663 Å down the plane N-1–C-3–C-5–N-6 (ring A) whereas C-7 was shown to be 0.580 Å down the plane N-1–C-10–C-8–N-6 (ring B). In addition, C-2 and C-7 are remote of respectively, 0.796 and 0.760 Å from planes O-4–C-3–N-1 and O-9–C-8–N-6.

Molecular modeling using GenMol program[18] showed that the chair–chair conformation (Scheme 2(b)) found in the crystal is disfavored [45.8 kcal mol^{-1} compared to 44.5 for the boat–boat counterpart (Scheme 2(c))]. However calculation does not take into account the stabilizing contribution of anomeric effects, which on the bis-1,3-oxazolidine derived from tris(hydroxymethyl)-aminomethane was evaluated to ≥ 1.5 kcal mol^{-1}.[1]

Stereoelectronic effects.—The more significant facts in relation with a possible contribution of anomeric effects to the structure and conformational features of compound **4** can be summarized as follows:

1. The difference between N-6–C-11 (1.456 Å) and N-1–C-11 (1.471 Å) bond distances which lies slightly above the noise level ($3\sigma = 0.009$ Å) appears to illustrate the negligible contribution of stereolectronic effects to the structure of the aminal N-6–C-11–N-1 grouping as already observed in other compounds.[13,14] This is even more evident in molecule 2 where equivalent bond lengths are 1.462 and 1.456 Å, respectively (see Table 4).
2. In contrast, anomeric effect does occur in both N–C–O sequences. N-6–C-5 (1.430 Å) and N-1–C-10 (1.431 Å) bonds are significantly shorter than either N-6–C-7 and N-1–C-2, respectively 1.463 and 1.469 Å (standard value for N-sp^3–C-sp^3 bond, 1.469 Å).
3. The C–O bonds in both oxazolidine functionalities are superior to standard value: 1.439 Å for O-4–C-5 and 1.431 Å for O-9–C-10 compared with respectively, 1.416 Å (O-4–C-3) and 1.421 (O-9—C-8).
4. The marked sp^2 character of nitrogen atoms, especially of N-6, is nicely illustrated by significant widening of nitrogen bond angles. Of special interest are the sum of bond angles: 345.8° for N-6 and 340.1° for N-1 compared with sp^3 standard value 328.5°. These values should be compared with those reported by Lemoine et al. for acyclic *N*,*N*′-methylenebis[(*S*)-5-phenyloxazolidine] (325.5 and 324.4°)[16] as well as by Engel et al. for *N*,*N*′-methylenebis[4 - methyl - 5 - phenyloxazolidine] (324 and 328.6°).[17] In compound **4,** flattening of both bridgehead nitrogen atoms N-1 and N-6 is accompanied by concomitant opening of the endo face of the bicycle which in turn minimizes transannular interaction between H-2 and H-7.
5. The significant contraction of N-6–C-5 and N-1–C-10 bonds and lengthening of O-4–C-5 and O-9–C-10 bonds reflect the delocalization of the unshared pair of electrons on nitrogen to the C–O σ* antibonding orbital in both N–C–O groupings. The antiperiplanar geometry of the *p*N–C–O motifs favors overlapping of *p*(N) and σ* orbitals as confirmed by torsion angles involving nitrogen atoms: O-4–C-5–N-6–C-11 (69.49°) and O-4–C-5–N-6–C-7 (69.75°). These show that C-5–O-4 bond bisects the C-11–N-6–C-7 bond angle and the same situation applies to O-9–C-10 with respect to C-11–N-1–C-2 angle (see Table 6).
6. None of the above data can reasonably support the hypothesis of a cooperative stereoelectronic effect between both N–C–O motifs through the N–C–N aminal grouping as it was observed previously for a O–C–N–C–O sequence.[1]
7. The results reported herein show that the O-9–C-10–N-1–C-11–N-6–C-5–O-4 system should be viewed as two independent N–C–O substructures. Each of them experiences a strong endo-anomeric effect, N-1 and N-6 working as electron donors and

O-9–C-10 and C-5–O-4 as acceptor bonds. The stereoelectronic effect appears to dictate the endo–endo configuration of oxygen O-4 and O-9 and subsequently the chair–chair conformation of the bicycle as depicted in Scheme 3.

The chair-like conformation of both seven-membered rings A and B was confirmed by the existence of a significant nuclear Overhauser effect (assessed from a NOESY experiment) between the two-proton singlet H-11 and the upfield doublet of the low-field AB pattern at 4.26 ppm assigned to axial proton H-5 and H-10 thereby confirming that the chair–chair conformation observed in the solid state is maintained in solution.

In the alternative boat–boat conformation (Scheme 2(c)), these protons would have been equatorial and neither them nor their axially oriented endo analogs would have experienced a nuclear Overhauser effect with protons H-11. An examination of molecular models showed that axial protons H-3 and H-8 are also in the vicinity of proton H-11. Indeed, a small NOE is observed on the upfield multiplet ascribed to protons H-3_{ax} and H-8_{ax} of the H-2, H-3_{ax}/H-8_{ax}, ABC pattern. Such interaction is precluded in the boat–boat conformation (Scheme 2(c)) where O-4 and O-9 adopt the exo–exo configuration. However it must be noted that the long-range coupling (1.6 Hz) observed between H-11_B and H-11_A and equatorial protons H-5 and H-10 would occur also in the alternative conformation (Scheme 2(c)). Careful analysis of the ^{1}H and ^{13}C NMR spectra using homo- and heteronuclear correlation sequences followed by spectrum simulations allowed us to unambiguously assign all signals and to determine chemical shifts and absolute value of coupling constants. The ^{1}H and ^{13}C NMR data are summarized in Table 1.

3. Conclusions

Elucidation of the structure of compound **4** both in the solid state and in solution has provided confirmation that $p(N) \rightarrow \sigma^*(C–N)$ delocalization is virtually absent in the N–C–N aminal motif whereas a strong anomeric effect is observed in both N–C–O groupings. Anomeric effect appears to dictate the endo–endo configuration of ring oxygens and consequently the chair-like conformation of both seven-membered rings.

4. Experimental

*Synthesis of [1*S*,2*S*,6*S*,7*S*]-1,6-diaza-4,9-dioxa-2,7-dimethoxycarbonylbicyclo [4.4.1]-undecane.*—To a suspension of L-serine methyl ester hydrochloride (**1**) (1.0 g, 6.4 mmol) in CH_2Cl_2 (50 mL) were added triethylamine (1.0 mL, 7.7 mmol) and paraformaldehyde (0.4 g). After being stirred at rt for 30 h, the reaction mixture was washed successively with HCl 1 N (10 mL) and satd Na_2CO_3 soln (10 mL). The organic layer was dried over anhyd $MgSO_4$ and evaporated to dryness to give a white solid. The latter was recrystallized from diethyl ether to afford nice crystals (0.8 g, 90%, mp 91–92°C; $[\alpha]_D^{20} = +54.5°$ (*c* 1.0, $CHCl_3$); FAB$^+$ MS (NBA): *m*/*z* 275 [M + H]$^+$, 144. ^{1}H and ^{13}C NMR data (Table 1).

Table 6
Torsion angles (°) between the direction of the O–C bonds and the directions of appropriate N–C bonds in the bicyclic core of **4** (molecule 1) [a]

Atoms defining the plane	O-4–C-5–N-6	C-5–N-6–C-11	O-4–C-5–N-6	C-5–N-6–C-7
Equation	a	b	a	c
Torsion angle (°)	69.5		69.8	
Atoms	O-9–C-10–N-1	C-10–N-1–C-11	O-9–C-10–N-1	C-10–N-1–C-2
Equation:	d	e	d	f
Torsion angle (°)	69.7		62.4	

[a] Equations of the planes: (a) $-4.304x+0.018y+17.383z=18.828$; (b) $-8.638x-3.601y+2.451z=1.978$; (c) $5.653x-3.595y+14.573z=11.144$; (d) $8.119x+1.250y+8.364z=7.628$; (e) $-5.875x+5.533y-12.833z=13.751$; (f) $0.874x-4.241y+18.800z=19.038$.

Anal. Calcd for $C_{11}H_{18}N_2O_6$ (274): C, 48.17; H, 6.56; N, 10.22. Found: C, 48.65; H, 6.46; N, 10.11.

Molecular modeling.—Molecular modeling was achieved on an Impact Silicon Graphics computer with the aid of the GENMOL program using the soft-proton option.[18]

NMR.—^{1}H and ^{13}C spectra have been recorded at 250.130 and 62.895 MHz respectively on a DRX-250 Bruker spectrometer. Digital resolution was 0.06 Hz/pt for ^{1}H and 0.09 Hz/pt for ^{13}C spectra. Iterative calculations were run with the GNMR 3.6 software from Cherwell Scientific Publishing Ltd. and simulations with Bruker NMRSIM 2.6.

X-ray structure determination.—Suitable crystals of **4** were grown from diethyl ether soln by slow evaporation. The crystal data and a summary of experimental data are given in Table 2.

A plate of size 0.3×0.4 mm was secured at the end of a glass pin with mineral oil, and immersed in a flow of nitrogen at 170 K on a CAD-4 automated diffractometer with graphite-monochromatized Mo K_α radiation ($\lambda = 0.71069$ Å). The crystals of compound **4** are orthorhombic, with space group $P2_12_12_1$.

X-ray data collection.—Lattice constants (Table 2) came from a least-squares refinement of 25 reflections obtained in the $13.2 < 2\theta < 28.8°$. The intensities were monitored after intervals of 60 min; no significant change in these intensities occurred. The structure amplitudes were obtained after the usual Lorentz and polarization reductions. No absorption corrections were made.

Structure determination and refinement.—Direct methods (SHELXS-86 program[19]) were used to solve the structure with 2791 independent data. The whole set of non-hydrogen atoms was obtained through a single calculation. After six cycles of least-squares refinement with isotropic thermal parameters to all atoms, the hydrogen atoms were positioned by calculation (SHELXL-93 program[20]), and included in the further stages of refinement (riding model). Anisotropic thermal parameters were given to all non-hydrogen atoms and the refinement converged to the final R_1 value of 0.0407 for 2491 $F_o > 4\sigma(F_o)$, and $wR_2 = 0.1057$ for all data. The final atomic coordinates with the associated thermal parameters are listed in Table 2. The labeling scheme is given in Fig. 1.

5. Supplementary material

Full crystallographic details have been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 146342). These data may be obtained on request from The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www/ccdc.cam.ac.uk).

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