Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5465-5468, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01166-5

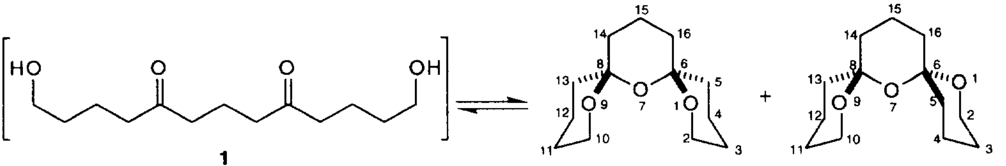
Cis- and *Trans*-1,7,9-Trioxadispiro[5.1.5.3]hexadecane: Stability Studies and Solution Structures

Glenn J. McGarvey,* Marshall W. Stepanian, Andrew R. Bressette, and Jeffrey F. Ellena

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Abstract: The stability of *cis*- and *trans*-1,7,9-trioxadispiro[5.1.5.3]hexadecanes was examined through equilibration studies with the result that the *trans*-isomer was more stable by 0.3-0.7 kcal/mol, depending upon the solvent. NMR studies indicate that the central ring of these compounds is in a twist-boat conformation in solution which allows these isomers to best accommodate conflicting steric and electronic effects on their stability.

In the previous Communication,[1] several synthetic approaches to the *cis*- and *trans*-isomers of 1,7,9-trioxadispiro[5.1.5.3]hexadecane were described. These studies are aimed at understanding the stereochemical course of thermodynamic spirocyclization from the acyclic diketodiol precursor (**1** → ***cis*-2** + ***trans*-2**, eq 1) and, consequently, the steric and electronic effects that influence the geometry of the ground state of these spiroketals. The results of previous studies allow one to anticipate the stereoelectronic influences on these cyclizations.[2,3] For the initial analysis, the all-chair conformations of species **2** may be considered. The *cis*-isomer (***cis*-2**), wherein both O1 and O9 are axially disposed about the central ring, incorporates four stabilizing anomeric effects.[4] However, previous synthetic studies have indicated the presence of a significant destabilizing effect which has been attributed to the dipole-dipole repulsion resulting from these 1,3-diaxial oxygens.[2,3] The *trans*-isomer (***trans*-2**), on the other hand, embodies a maximum of three anomeric effects, but is relieved of the dipole-dipole destabilization. Superimposed upon these stereoelectronic effects is the expected steric preference for an axial C-O bond over an axial C-C bond.



1

4 possible anomeric effects
dipole-dipole repulsion

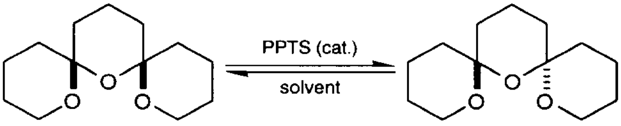
3 possible anomeric effects
no dipole-dipole repulsion

***cis*-2** ***trans*-2**

(1)

In an effort to assess the contributions of these effects, equilibration studies were carried out to determine the relative stabilities of these isomeric structures. Both ***cis*-2** and ***trans*-2** were subjected to acid-catalyzed isomerization (pyridinium *p*-toluenesulfonic acid) in a range of solvents to afford the results shown in the Table. In all cases, the isomerizations were carefully monitored[5] and allowed to proceed at least one half-life past the point at which changes in the isomer ratio ceased. Furthermore, it was demonstrated for each case that both isomers independently converged to the same isomer ratio with time.

TABLE



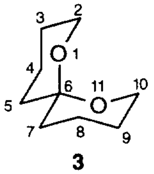
cis-2 **trans-2**

Entry	Solvent	Time (hours)	**cis-2 : trans-2**
1	Hexane*	24	1.00 : 3.35
2	THF	69.2	1.00 : 2.10
3	CH_2Cl_2	26.0	1.00 : 2.11
4	DMSO	53.3	1.00 : 1.85

* Due to the insolubility of pyridinium *p*-toluenesulfonic acid in hexanes, camphorsulfonic acid was used as the catalyst in this instance.

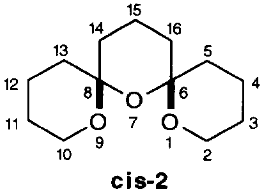
As indicated, the *trans*-isomer predominated in every instance with a modest solvent effect evident. It was anticipated that changes in the solvent dielectric constant would have the largest effect on the magnitude of the dipole-dipole repulsion contribution. This expectation was realized as the *trans*-isomer was more prominent in the low dielectric solvent hexane (ε=1.89)[6] relative to the significantly higher dielectric solvent DMSO (ε=24.3).[6] These data indicate that the cumulative stereoelectronic and steric effects in these isomers leads to an energy difference of approximately 0.3-0.7 kcal/mol favoring the *trans*-isomer, depending upon the solvent. Clearly, the overall stability of these isomers is the result of the interplay of all the steric and stereoelectronic effects and not dictated solely by available anomeric effect stabilization.

To properly understand the contributions of these steric/electronic effects, it is essential to understand the solution structures of the two species participating in the equilibrium. Toward this goal, a series of NMR experiments were carried out to unambiguously assign both the proton and carbon resonances and to extract the available coupling data. Both isomers showed 7 resonances in their ^{1}H-decoupled ^{13}C NMR spectra, clearly indicating that both solution structures are highly symmetrical. Through a comparison with the known ^{13}C assignments for 1,7-dioxaspiro[5.5]undecane **3**,[7,8] the resonances for ***cis*-2** and ***trans*-2** could be assigned as shown. With these assignments in hand, the ^{1}H resonances for each isomer were established using 2-D ^{1}H-^{13}C correlation methods (HETCOR,[9] HMQC[10]), which were augmented by COSY[9] and HOHAHA[11] experiments. As a result, the vicinal coupling constants could be obtained for C2,C10 and C5, C13 for both isomers. This data showed clearly the equatorial/equatorial, equatorial/axial, and axial/axial coupling constants consistent with well-defined chair conformations for these rings.[12] However, similar coupling data for C14, C16 and C15 was not forthcoming.



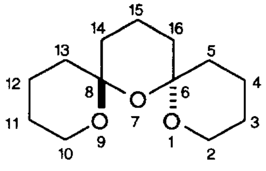
3

^{13}C Chemical	Shifts
C2, C10	60.3
C3, C9	25.4
C4, C8	18.6
C5, C7	35.8
C6	94.9



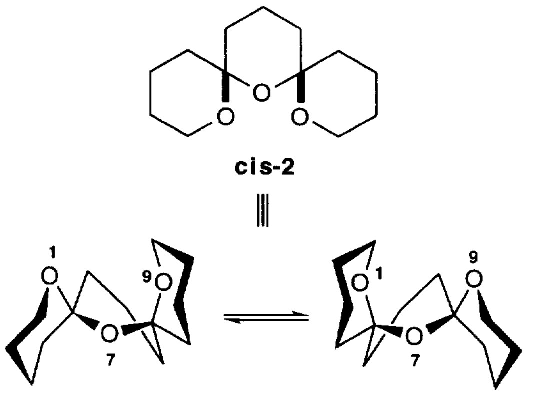
cis-2

	^{13}C Chemical Shifts	
cis-2		**trans-2**
61.97	C2,C10	62.26
25.53	C3,C11	25.45
19.10	C4,C12	19.06
37.64	C5,C13	36.29
96.22	C6,C8	96.52
34.77	C14,C16	33.45
14.09	C15	13.85

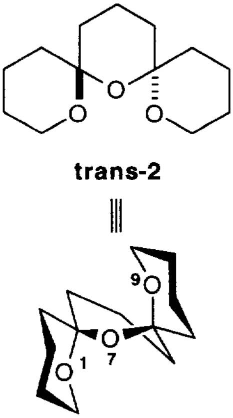


trans-2

An examination of the effect of temperature on the ^{13}C NMR proved very instructive in defining the solution conformation of these compounds. Upon cooling to -85° C, the spectrum for each isomer retains its 7 resonance simplicity, but the spectrum for the *cis*-isomer is accompanied by significant broadening of the resonance ascribed to C14/C16. This broadening we interpret to be the result of an exchange process of C14 and C16 which is consistent with a conformationally mobile, non-chair geometry for the central ring. Careful examination of molecular models and consideration of related x-ray crystallographic data[13] has led to an assignment of a twist-boat conformation for the solution structure of ***cis*-2**. The conformational flexibility of the central ring allows the rapid interconversion of all the carbon centers to accommodate the observed 7 resonance simplicity of its spectrum. Consistent with the lack of peak broadening at lower temperatures, the *trans*-isomer, ***trans*-2**, is defined by a single solution conformation which also incorporates the twist-boat geometry for the central ring. The 7 line simplicity of its ^{13}C NMR spectra is satisfied by the C2 symmetry of this structure.



rapid interconversion



C2 symmetry

These structures allow the central ring to accommodate a geometry which will maximize the available anomeric stabilization and minimize any destabilizing 1,3-steric and/or dipole repulsion effects. It appears that the *trans*-isomer benefits significantly from this deviation from the chair geometry as it allows an additional anomeric effect, though the relevant C-O bond angles are not ideal. The *cis*-isomer, while poised to accommodate four anomeric effects in the all-chair form, adopts the twist-boat geometry in the central ring, presumably to relieve the destabilization that would result from the dipole-dipole repulsion of the two axial C-O bonds. The overall result is that the *trans*-isomer is favored as a consequence of the stabilization offered by four imperfect anomeric effects, while the *cis*-isomer sacrifices some anomeric stabilization to relieve the destabilizing dipole repulsion. These geometrical compromises result in an overall thermodynamic preference for the *trans*-isomer.

The structural information made available from these studies demonstrate the significance of stereoelectronic effects in controlling the structures of these polycyclic arrays. While anomeric stabilization cannot be relied upon to thermodynamically select a *cis*-relationship between O1 and O9 because of competing dipole destabilization, the importance of the central ring conformation in defining the solution structure of these *bis*-spirocyclic compounds is clearly indicated. The realization of well-defined molecular geometries through the control of the central ring conformation will be the subject of future reports.

Acknowledgement. We would like to thank the National Institutes of Health for equipment grants that made available the high field NMR spectrometers used in this research.

References and Notes

1. See previous Communication.
2. For a recent review on spiroketal synthesis see: Vaillancourt, V.; Pratt, N.E.; Perron, F.; Albizati, K.F. *The Total Synthesis of Natural Products* **1992**, *8*, 533-691.
3. For an earlier study on these *bis*-spiroketals: Brimble, M.A.; Rush, C.J. *J. Chem. Soc. Perk. Trans. I* **1994**, 497-500, and references cited therein.
4. For extensive reviews on these stereoelectronic effects: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect*, CRC Press: Boca Raton, 1995.
5. The isomers ***cis*-2** and ***trans*-2** could be detected by TLC (SiO_2, 50% Et_2O/hexanes) and HPLC.
6. Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, John Wiley and Sons: New York, 1972.
7. Pothier, N.; Rowan, D.D.; Deslongchamps, P.; Saunders, J.K. *Can. J. Chem.* **1981**, *59*, 1132-1139.
8. This compound was prepared by the method previously reported: Amouroux, R. *Heterocycl.* **1984**, *22*, 1489-1492.
9. Hull, W.E. in Methods in *Stereochemical Analysis: Two-Dimensional NMR Spectroscopy, Applications for Chemists and Biochemists*; Carlson, R.M.; Croasmun, W.R., eds.; VCH Publishers, Inc.: New York, 1987; Vol. 9, Chap. 2.
10. Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565-569.
11. Bax, A.; Davis, D.G. *J. Magn. Reson.* **1985**, *65*, 355-360. This technique proved especially useful for the establishment of connectivities of the independent spin systems found in this class of compounds.
12. For ***cis*-2**: C2/C10$_{equatorial}$, $J_{vic,\ eq}$=3.6 Hz, $J_{vic,\ ax}$=3.9 Hz, J_{gem}=10.5 Hz; C5/C13$_{equatorial}$, $J_{vic,\ eq}$=3.6 Hz, $J_{vic,\ ax}$=3.6 Hz, J_{gem}=13.0 Hz; C5/C13$_{axial}$, $J_{vic,\ eq}$=4.1 Hz, $J_{vic,\ ax}$=12.9 Hz, J_{gem}=13.0 Hz.

    For ***trans*-2**: C2/C10$_{equatorial}$, $J_{vic,\ eq}$=2.1 Hz, $J_{vic,\ ax}$=4.0 Hz, J_{gem}=10.8 Hz; C2/C10$_{axial}$, $J_{vic,\ eq}$=3.5 Hz, $J_{vic,\ ax}$=11.0 Hz, J_{gem}=10.8 Hz; C5/C13$_{equatorial}$, $J_{vic,\ eq}$=3.4 Hz, $J_{vic,\ eq}$=3.4 Hz, J_{gem}=12.6 Hz; C5/C13$_{axial}$, $J_{vic,\ eq}$=4.3 Hz, $J_{vic,\ ax}$=13.1 Hz, J_{gem}=12.6 Hz.
13. While the parent *bis*-spiroketals ***cis*-2** and ***trans*-2** have not yielded to x-ray crystallographic characterization, several substituted *bis*-spiroketals have been analyzed by this method, including the 14-phenylsulfonyl,[3] 15-keto,[14] 15-methylene,[14] 2-phenyl-15-keto[14] derivatives.
14. Stepanian, M.W.; McGarvey, G.J., unpublished data.

(*Received in USA* 15 *May* 1996; *revised* 7 *June* 1996; *accepted* 9 *June* 1996)