Acknowledgment. The authors express their sincere gratitude to Dr. B. Paul and B. F. Mayer of the Grace Cancer Drug Center's Chemistry Resource Laboratory for their scaleup preparation of FdC (institutional core grant CA 16056). The authors would also like to thank Dr. B. Dolnick for the use of the ABI 381A DNA Synthesizer and Waters HPLC. This work was supported in part by NIH Grant CA13038.

Registry No. 1A, 10356-76-0; 1B, 143774-48-5; 1B Z=H, 143774-47-4; 4,4′-dimethoxytrityl chloride, 40615-36-9; 2-cyanoethyl *N,N,N′,N′*-tetraisopropylphosphorodiamidite, 102691-36-1.

Simultaneous Determination of Conformation and Configuration Using Distance Geometry

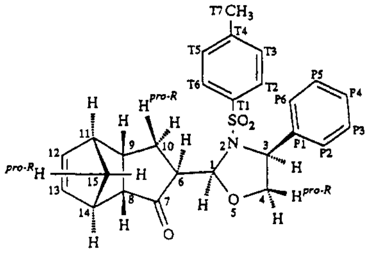
Dale F. Mierke* and Michael Reggelin†

Organisch Chemisches Institut, Technische Universität München, Lichtenbergstraße 4, W-8046 Garching, Germany, and Institut für Organische Chemie, Universität Frankfurt, Niederurseler Hang, W-6000 Frankfurt/Main 50, Germany

Received April 16, 1992

Introduction

We have recently shown that for a small, complex oxazolidine the conformation and relative configuration of the stereogenic centers could be solved simultaneously with the use of distance restraints from NOESY data in molecular dynamics (MD) simulations.[1] With the use of an extremely large force constant for the NOE constraints, the energy of the NOE term is many times larger than the energetic component of the force field set to maintain the configuration, and therefore, the stereogenic centers can switch producing the stereochemistry consistant with the experimental data. This procedure was illustrated with the title compound 1,[1] which has been synthesized in the course of examining asymmetric Diels–Alder reactions with chiral oxazolidines.[2]



The induced stereo configuration at the bridgehead positions C8 and C9 as well as the stereo configuration at C6 was determined from NOEs and restrained MD (rMD) simulations as described above. Starting with the (1*S*,3*S*,6*S*,8*R*,9*R*,11*R*,14*S*) (exo) structure, the chirality at the bridgehead positions quickly reversed, forming the endo structure.[1] In contrast, beginning with the endo structure the NOEs were completely fulfilled.

During this study we ran into the problem that there were no parameters for some of the bonds, bond angles, and dihedrals in the potential energy force field used. This is a commonly occurring situation; the parameters to describe specific moieties or groups in naturally occurring or synthetic molecules are not defined. Most of the programs widely available today have been designed specifically for peptides and proteins[3-6] or DNA.[7] Although, there is a large body of work concentrating on a variety of functional groups (e.g., the MM2 program[8] and later versions[9]), transferring parameters from one program to the one in use is often problematic; the question arises of maintaining a self-consistent force field.

However, it is often the case that the geometry of the moiety or functionality, for which no parameters exist, is either known or can be approximated (without introduction of too great of error) from X-ray structures of related molecules. The problem therefore is not the equilibrium values of the bond lengths, bond angles, or torsions, but the force constants that should be utilized as a penalty for moving away from the equilibrium value (not to mention the partial atomic charges or Lennard–Jones parameters for the nonbonded terms of the force field).

Small synthetic or natural molecules have several properties that are quite favorable for conformational analysis that should allow one to overcome the aforementioned drawbacks. In solution, these small molecules are rapidly tumbling (i.e., small correlation time) which at the field strengths used in modern NMRs lead to sizeable, positive NOEs. In addition, it is commonly the case that the spectral resolution of the proton resonances is good, easing the assignment and accurate integration of NOEs. Of course, as previously discussed by us[1] and others,[10] great care must be used in the interpretation of the NOEs to ensure that external relaxation (leakage) is negligible and that the molecule is conformationally homogeneous (absence of a rapid conformational equilibrium). We know of no sound procedure for addressing the latter problem. It is common to work under the assumption of one conformation (or family of closely related conformations) and examine the reproduction (back-calculation) of the experimental observations. If there is a rapid equilibration between conformations (which differ significantly) then inconsistencies between the experimental and back-calculated data will appear.[11] Agreement between the experimental and theoretical data can then only be obtained with the assumption of two or more conformations.

Considering the large number of NOEs (large relative to molecular weight) and the well-defined geometry (bond lengths and angles) it seemed reasonable that conformations of such molecules could be generated using distance geometry (DG) techniques. Here, we describe the use of DG in the conformational examination of oxazolidine 1. In addition, DG calculations were carried out to examine the possibility of determining the relative configuration,

---

† Universität Frankfurt.

(1) Reggelin, M.; Hoffmann, H.; Köck, M.; Mierke, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3272.

(2) Hoffmann, H.; Dyrbusch, M.; Hoppe, D. Manuscript in preparation.

(3) Momany, F. A.; McGuire, R. F.; Burgess, A. W.; Scheraga, H. A. *J. Phys. Chem.* **1975**, *79*, 2361.

(4) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.

(5) Dauber-Osguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. T. *Proteins: Structure, Function and Genetics* **1988**, *4*, 31.

(6) van Gunsteren, W. F.; Berendsen, H. J. C. *Groningen Molecular Simulation Library Manual*; Biomos B.V., Nijenborgh 16, NL 9747 AG Groningen, 1987.

(7) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

(8) Allinger, N. L. *J. Am. Chem. Soc.* **1974**, *96*, 8127.

(9) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

(10) (a) Won, H.; Olsen, K. D.; Wolfe, R. S.; Summers, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 2178. (b) Olsen, K. D.; Won, H.; Wolfe, R. S.; Hare, D. R.; Summers, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 5884.

(11) Kessler, H.; Griesinger, C.; Müller, A.; Lautz, J.; van Gunsteren, W. F.; Berendsen, H. J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3393.

0022-3263/92/1957-6365$03.00/0

Table I. Averages and Standard Deviations of Dihedral Angles of Compound 1 from Distance Geometry Calculations with (DG1) and without (DG2) Chiral Constraints and Previous Restrained MD Simulation

torsion				DG 1		DG 2		rMD
				avg	SD	avg	SD	Avg[a]
T2	T1	S	N2	12	92	9	99	−56
T1	S	N2	C3	28	103	7	108	−66
S	N2	C3	C4	−134	24	−129	25	−138
S	N2	C3	P1	8	106	22	102	−87
S	N2	C1	C6	−93	15	−96	16	−88
N2	C1	O5	C4	−19	5.3	−18	5.8	−16
N2	C3	C4	O4	−21	13	−24	14	−18
N2	C1	C6	C7	−150	31	−104	57	−164
C1	O5	C4	C3	26	6.4	27	6.2	23
C1	C6	C7	C8	123	6.6	121	4.4	124
C1	C6	C10	C9	−123	4.8	−121	5.1	−123
C6	C7	C8	C9	5	6.2	8	3.4	5
C7	C8	C9	C10	−16	4.8	−17	2.1	−7
C7	C8	C14	C13	−49	6.6	−44	14	−52
C8	C9	C10	C6	20	1.4	20	1.2	7
C8	C14	C13	C12	−52	11	−55	10	−66
C8	C14	C15	C11	60	6.2	60	9.1	64
C9	C11	C12	C13	77	11	74	30	66
C9	C11	C15	C14	−63	5.6	−64	5.7	−65
C10	C9	C11	C12	55	5.7	56	2.7	57
C11	C12	C13	C14	−3	1.0	−4	4.3	1

[a] Results taken from ref 1.

solely from the distance restraints.

Experimental Methods

The DG calculations were carried out using a modified version of the DISGEO program[12,13] kindly provided by Prof. Ruud Scheek (University of Groningen). The list of distance bounds for the DG calculation was constructed from the covalent primary structure using bond lengths, bond angles, chirality, and planarity. The upper and lower bounds were taken as ±2%, respectively, of these calculated distances. For atoms that have a rotatable torsion between them, the lower and upper bounds are calculated from the minimum and maximum possible distance, respectively, with a complete rotation of the dihedral. For molecule 1, there are only four dihedrals that can make a complete rotation (the torsions about T1–S, S–N2, C3–P1, and C1–C6). However, in this calculation, to allow for more flexibility, all of the torsions, except those in the two aromatic rings, have been considered as fully rotatable. Recently, to introduce a smaller amount of flexibility to the system, a modification has been described which adjusts the distances for partial rotations about dihedrals.[14]

In addition to the geometric distance bounds described above, the experimentally determined distances, derived from 53 NOEs, were utilized. The upper and lower bound constraints were calculated with ±5% of the distance obtained from a series of NOESY spectra.[1]

To reduce the size of the problem the hydrogen atoms not involved in NOEs were not included in the calculation. In addition, the protons that cannot be distinguished (i.e., H-T3 and H-T5) were described by a pseudoatom. This was necessary for the following proton pairs: T2–T6, T3–T5, P2–P6, and P3–P5. A pseudoatom was also used for the three methyl protons of T7. It is important to state that the three pairs of methylene protons (C4, C10, and C15) have been diastereotopically assigned through homo- and heteronuclear coupling constants and therefore are explicitly included in the calculation, resulting in a total of 52 atoms (26 carbon, 4 oxygen, 1 nitrogen, 1 sulfur, 15 hydrogen, and 5 pseudo atoms).

Distances between these constraints which also satisfy the triangular inequalities were then chosen randomly and embedded with the metric matrix method. The structures successfully embedded were partially minimized with a conjugate gradient minimizer (EM) followed by MD with application of SHAKE[15] beginning at 500 K for 2 ps and then with a gradual reduction in temperature over the next 5 ps. Both the EM and MD utilized only the holonomic constraints (i.e., geometric and experimental distance constraints) as the potential and for generation of forces. The structures were then grouped together and restrained MD run with the restraints applied to the ensemble (the experimental distances are averaged over all of the structures with an inverse power of 3) and not to each individual structure. The calculation and optimization of 100 structures required less than 1 h of CPU using a single processor on a Silicon Graphics 4D/240SX.

Results and Discussion

The average and standard deviation of the dihedral angles of the 100 embedded structures are given in Table I (DG1). The root mean square (rms) difference of all of the atoms of the average structure with that determined from rMD is 1.2 Å. This large variation comes from the three torsions, T1–S, S–N2, and C3–P1. It is important to realize that there is no experimental data to suggest a preferred orientation about these torsions in solution as indicated by the large deviation about these torsions, ~100 °C (Table I). Excluding the atoms of the two aromatic rings, the rms difference is 0.15 Å; the average conformation is almost identical with that derived from the NOE-restrained MD simulations.

The question of determination of the stereo configuration at the bridgehead of 1 was addressed by an additional DG calculation. In the DG method used here, the absolute configuration of a chiral center is maintained by calculating the volume extended by the atoms bound to the central atom.[12] These are then used as restraints in the optimization of structures following the embedding procedure (EM and MD). For the C8 and C9 bridgehead atoms, no chiral constraints were utilized in this second calculation (DG2). In addition, all of the upper-bound distance restraints calculated from the known geometry involving the bridgehead protons were increased to allow for the possibility of both stereo configurations. Therefore, the experimental restraints were the only driving force in the determination of the stereo configuration.

---

(12) Havel, T. F. *DISGEO*, Quantum Chemistry Exchange Program Exchange No. 507, Indiana University, 1986.

(13) Crippen, G. M.; Havel, T. F. *Distance Geometry and Molecular Conformation*; Research Studies Press LTD.: Somerset, England; John Wiley: New York, 1988.

(14) Wertz, D. A.; Shi, C.-X.; Venanz, C. A. *J. Comput. Chem.* **1992**, *13*, 41.

(15) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* 1977, *23*, 327.

The average values of the dihedral angles from the second calculation (DG 2, Table I) are almost identical to those found from the calculation employing all of the chiral restraints. The rms differences are larger, to be expected with the looser distance restraints, but the correct relative configuration was obtained. This indicates that DG is indeed useful in the calculation of not only conformation but also the relative configuration of a questionable center. However, it must be stressed that the bridgehead protons of 1 have many favorable properties in this respect; they are in the middle of a rigid moiety with known geometry and involved in a large number of NOEs.

Conclusions

It has been demonstrated that DG is a useful and efficient method for the determination of the conformation of small synthetic or naturally occurring molecules. Most members of this class of molecules have properties favorable for the examination by DG: NOEs are large and easily measured and the geometry (a minimum of bond lengths and angles) is usually well-defined. The determination of unknown relative configurations from DG has also been investigated. Although the correct stereo configurations were developed, compound 1 may be a special case. It is clear that more example compounds will have to be calculated before DG can be proposed as a general method for the calculation of relative configurations from NOE derived distances.

Acknowledgment. The authors wish to thank Dr. Holger Hoffmann (Schering, Berlin) and Matthias Köck (Technical University München) for their help with this project and Dr. Ruud Scheek (University of Groningen) for the DG and associated programs and help in the use of them. D.E.M. acknowledges the support and useful comments of Prof. Horst Kessler (Technical University München). The Deutsche Forschungsgemeinschaft is gratefully acknowledged for financial support.

Origin of the Unusual Infrared Absorption Band at ~1600 cm^{-1} in 1,4-Dioxaspiro[2.2]pentanes

B. Andes Hess, Jr.,*,† Jin K. Cha,*,‡ L. J. Schaad,*,† and Prasad L. Polavarapu*,†

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, and Department of Chemistry, University of Alabama, Tuscaloosa, Alabama 35487

Received August 11, 1992

Crandall and co-workers have recently reported the synthesis of a large number of derivatives of 1,4-dioxaspiro[2.2]pentane (1, see Figure 1).[1] All of these spiro dioxides exhibited a band of medium intensity between 1600 and 1650 cm^{-1} in their infrared absorption spectra. Crandall has noted, "Although the vibrational origin of this band remains a mystery, it appears to be a dependable characteristic of this spiro-fused heterocyclic system." This prompted us to carry out an ab initio study of the vibrational spectrum of 1 to determine the vibrational mode responsible for this unusual band as well as to provide a theoretical spectrum to aid in the eventual identification of parent 1.

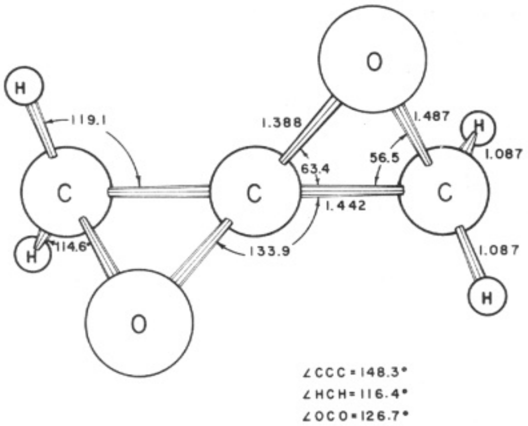


Figure 1. The calculated MP2/6-31G* structure of 1,4-dioxaspiro[2.2]pentane (1). Lengths are in angstroms and angles in degrees. The structure has C_2 symmetry with the C_2 axis through the central carbon atom and perpendicular to the page.

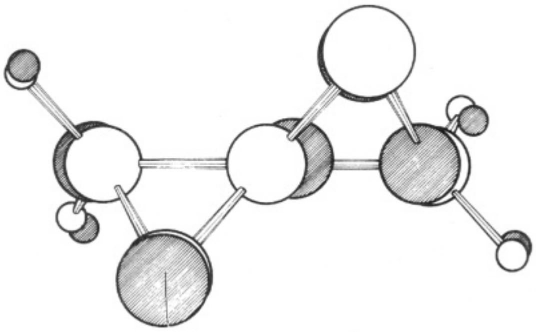


Figure 2. The B vibration at 1721 cm^{-1} calculated to give rise to the "mystery band" in 1,4-dioxaspiro[2.2]pentanes. Unshaded circles represent the equilibrium atomic positions of Figure 1. Shaded circles show displacements in this B normal mode. Bonds are drawn between equilibrium atoms (ref 5).

Table I. MP2/6-31G* Vibrational Frequencies and Absorption Intensities of 1[a]

symmetry	frequency (cm^{-1})	intensity (km/mol)	description[a]
A	320	4.69	mixture of external angle bends at C*
B	399	10.21	mixture of external angle bends at C*
A	461	2.25	mixture of external angle bends at C*
A	632	4.10	C–O stretch and C*–O stretch
B	832	72.53	C–O stretch and C*–O stretch
B	869	44.68	H–C bend and C*–O stretch
A	905	18.72	C*–O stretch and H–C bend
A	1039	5.49	C–O stretch and C–C* stretch
B	1099	22.87	H–C bend
A	1110	21.94	H–C bend
B	1114	27.49	H–C bend
A	1136	14.95	H–C bend
B	1196	12.12	H–C bend and C*–O stretch
A	1232	2.91	C–C* stretch and H–C bend
B	1514	12.20	H–C bend
A	1150	0.51	H–C bend
B	1721	97.01	C–C* stretch
A	3185	7.06	C–H stretch
B	3186	9.38	C–H stretch
B	3288	6.91	C–H stretch
A	3289	9.79	C–H stretch

[a] C* is the central carbon atom.

MP2/6-31G* calculations were carried out using the program CADPAC 4.0.[2] The geometry was first fully optimized with a C_2 symmetry constraint (see Figure 1). Of note are the relatively short (1.388 Å) bonds between the spiro carbon and oxygen. The total MP2/6-31G* en-

---

† Vanderbilt University.

‡ University of Alabama.

(1) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153 and references cited therein.

(2) Amos, R. D.; Rice, J. E. *CADPAC: The Cambridge Analytic Derivatives Package*; issue 4.0, Cambridge, 1987.

0022-3263/92/1957-6367$03.00/0