Conformational Preference in 2,4-Dimethoxybicyclo[3.3.1]nonan-9-one and Related Molecules. Analysis of Vicinal NMR Coupling Constants in Multiple Rotor System by Combined Molecular Mechanics and Generalized Karplus Equation[1]

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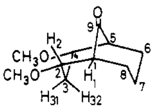
Received May 5, 1983

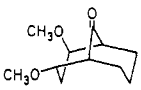
The vicinal proton–proton coupling constants of the stereoisomers of 2,4-dimethoxybicyclo[3.3.1]nonan-9-one (**1**) were calculated with the empirically generalized Karplus equation; 18 combinations of CH_3O rotamers for each stereoisomer were used to obtain the conformer distribution. For the 1*R*,2*S*,4*R*,5*S* isomer (**1c**), the observed $J_{H_2H_{31}}$ vicinal coupling constant (3.90 Hz) was well reproduced (3.85 Hz) by the MM2′-calculated composition of 82% chair–chair and 18% boat–chair conformers.

The empirically generalized Karplus equation,[3] which reproduces vicinal $^3J_{HH}$ coupling constants with standard deviation of ca. 0.4 Hz, adds a new prospect to the application of molecular mechanics calculations. Because molecular mechanics can rapidly minimize a large number of structures,[4-6] one should be able to calculate the average H–C–C–H coupling constants of a complex conformational mixture with high precision. The previous limitation on ^{1}H NMR analysis to rigid molecules now appears to have been removed.[7] We report here the application of the combined techniques to a stereochemical problem involving a number of rotamers.

The three possible configurational isomers of 2,4-dimethoxybicyclo[3.3.1]nonan-9-one (**1a–c**) have been isolated.[8,9] All of them were assigned chair six-membered rings based on the lanthanide-induced shift analysis of ^{1}H NMR spectra.[8] However, some ambiguity remained for the syn-diaxial isomer **1c**, since the possibility of its being in boat-chair (BC) conformation with two methoxy groups in equatorial positions could not be excluded. The europium atom appeared to coordinate with all three oxygen atoms of these substrates, and the coordination might have shifted the conformational equilibrium from the BC toward the chair–chair (CC) conformer. There are reasons for believing that the BC conformation of **1c** should be more stable than the CC conformer. Thus, in addition to the obvious relief of repulsive interaction between the syn-diaxial methoxy groups in going from CC to BC, the boat cyclohexanone ring in the latter lacks the flagpole interaction of a boat cyclohexane. Raber[10] has estimated that bicyclo[3.3.1]nonan-9-one (**2**) contains 22% of the BC conformer in solution at room temperature, based on lanthanide-induced shift studies. This BC content is considerably higher than that of bicyclo[3.3.1]nonane (**3**) (5 ± 4% at 65 °C).[11]



1a



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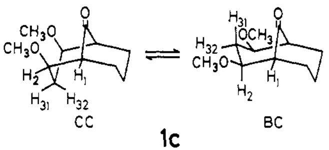
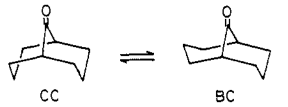


1c



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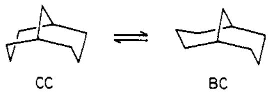

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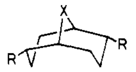

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Molecules with the ring system of **3** usually exist in the CC conformation, but because of their flattened, extended structure arising from the nonbonded C_3–C_7 interaction, the conversion of the CC into the BC form is more rapid than in cyclohexane.[11-14] While the introduction of an

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Table I. ^{1}H NMR Coupling Constants (Hz) of 2,4-Dimethoxybicyclo[3.3.1]nonan-9-ones 1

		1a	1c	1b
$^3J_{H_1H_2}$ obsd		ca. 5.0	ca. 2.0	ca. 5 (ca. 2)^b
calcd^a	CC	4.55	1.91	4.65 (2.09)^b
	BC	9.21	2.77	9.14 (3.31)^b
	av	4.55	2.08	4.66 (2.10)^b
$^3J_{H_2H_{31}}$ obsd		6.35	3.90	
calcd	CC	6.22	2.15	6.15 (2.24)^c
	BC	3.78	11.17	3.94 (11.19)^c
	av	6.22	3.85	6.15 (2.27)^c
$^3J_{H_2H_{32}}$ obsd		11.72	4.88	
calcd	CC	10.29	4.10	10.27 (3.80)^d
	BC	2.35	4.95	2.27 (4.88)^d
	av	10.29	4.27	10.25 (3.80)^d
$^2J_{H_{31}H_{32}}$ obsd		13.67	15.62	

^{a} Calculated using the empirically generalized Karplus equation.[3] Dihedral angles are based on the MM2′-calculated structure. Hydrogen positions are corrected.[3] Distribution of CH_3O–C rotamers is taken into account. See text. ^{b} $J_{H_4H_5}$. ^{c} $J_{H_4H_{31}}$. ^{d} $J_{H_4H_{32}}$.

endo substituent at C_3 shifts the equilibrium entirely to BC,[15–17] the effects of C_2 (C_4) substituents are less well understood. A 2-hydroxy group, either *R* or *S*, does not alter the preference for the CC conformation in **2**.[18,19] In 9-thiabicyclo[3.3.1]nonane-2,6-dione (**4**, X = S, R = O)[20a] and 2(*R*),6(*S*)-dichloro- (**4**, X = SO_2, R = Cl)[20b] and 2-(*R*),6(*S*)-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxides (**4**, X = SO_2, R = ONO_2)[20c] the bicyclic skeletons are skewed but still have the CC conformation.[21] Compound **2** has the CC conformation in the crystal even when an axial chloro group is present.[22,23]

We have determined the 400-MHz ^{1}H NMR and the ^{13}C NMR spectra of **1a–c**, and our analysis of them provides evidence for the existence of the BC conformer of **1c** in solution.

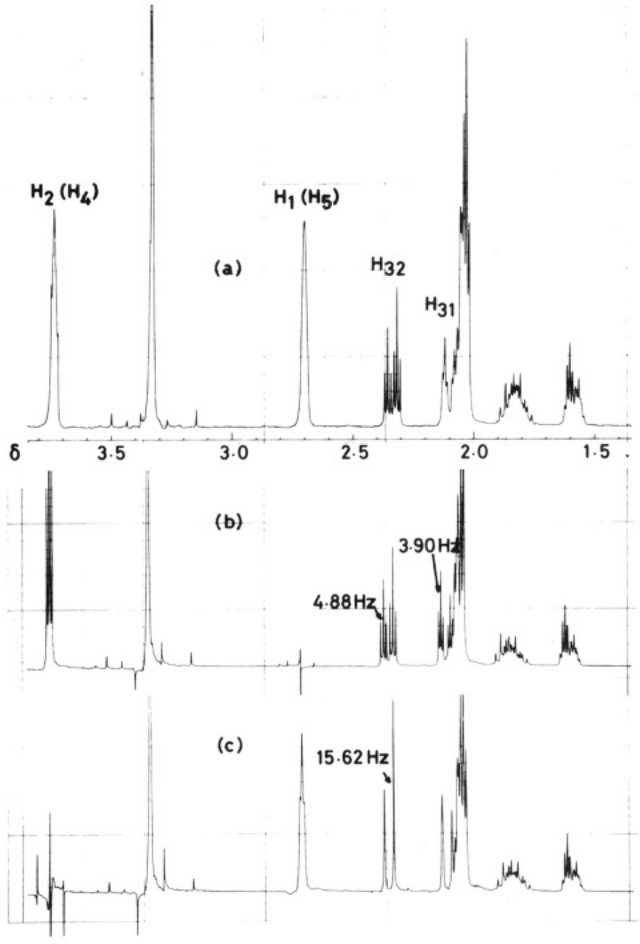

Figure 1. ^{1}H NMR spectra of **1c** in $CDCl_3$ at 400 MHz. (a) Original spectrum. (b) Irradiation at 2.7 ppm (H_1 and H_5). (c) Irradiation at 3.7 ppm (H_2 and H_4).

Table II. ^{13}C NMR Chemical Shifts^a of 1

carbon	1c	1a	1b
C_1 (C_5)	51.30	49.57	49.46 (49.95)
C_2 (C_4)	83.57	76.55	78.39 (80.94)
C_3	31.85	34.73	32.72
C_6 (C_8)	32.29	27.20	30.23 (27.79)
C_7	18.74	20.37	19.61
C_9	215.45	214.09	215.24
CH_3O	56.34	56.18	56.07^b

^{a} At ambient temperature in $CDCl_3$, in ppm from internal Me_4Si. ^{b} Only one signal was observed.

Results

^{1}H NMR Spectra of 1. At 400 MHz, sufficient resolution was obtained for the interesting peaks. For **1a**, where the CC conformation with two equatorial substituents should be dominating, the assignment of H_3 protons is straightforward (Table I); higher field triplets at 1.98 ppm have a large coupling constant (11.72 Hz) with the axial H_2, hence they are assigned to H_{32}. Thus the lower field counterpart at 2.45 ppm is due to H_{31}.

For **1c**, two broad peaks at 3.74 and 2.70 ppm are assigned to H_2 (H_4) and H_1 (H_5), respectively (Figure 1a). The two double triplets centered at 2.34 and 2.10 ppm should be assignable to the two H_3 protons. Small vicinal coupling constants in these two peaks (3.90 and 4.88 Hz, Table I) give the strongest evidence for the predominant CC conformation for **1c**, since the BC conformer should

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have a coupling as large as that of H_2H_{32} of **1a** for one of H_3 protons trans to H_2. The observation of practically identical coupling constants in these triplets prompted decoupling experiments. Irradiation at H_1 (2.70 ppm) simplified the 2.10 ppm peak but did not affect the 2.34 ppm peak (Figure 1b), indicating that H_1 and the proton at 2.10 ppm are coupled by a W mechanism. The W coupling is further supported by irradiation at H_2 (3.73 ppm): the two H_3 peaks became an AB quartet, with the higher half at 2.34 ppm of significantly lower intensity than the lower half due to broadening by small coupling (Figure 1c). These observations suggest that the six-membered ring carrying these protons is predominantly in the chair form (hence CC) wherein H_1 and $H_{3\mathrm{equatorial}}$ (H_{31}) are capable of W coupling. In the boat form (BC) this coupling would be lost for either of the H_3 protons. Hence the 2.34 ppm peak is assigned to $H_{3\mathrm{axial}}$ (H_{32}).

The order of chemical shifts for the H_3 protons, equatorial higher than axial, is the reverse of the usual order in a chair cyclohexane ring. This anomaly can be explained by the effect of the electronegative substituent. An axial electronegative substituent like methoxy shifts the adjacent axial proton to lower fields and the equatorial to higher fields.[26] In contrast, equatorial electronegative substituents usually shift adjacent protons in the same direction (higher field), and hence no anomaly for the H_3 protons of **1a** was observed.

The proton NMR spectrum of the asymmetric **1b** was too complex to analyze, hence the proposed CC conformation is based on its ^{13}C NMR spectrum.

^{13}C NMR Spectra of 1. Room-Temperature Spectra. We wished to see whether ^{13}C NMR data (Table II) were consistent with the indication from ^{1}H NMR that **1c** is predominantly in the CC conformation in solution. The assignment was straightforward for **1a** and **1c**, based on the combination of the splitting pattern at the off-resonance decoupling condition, the relative intensities, and the substituent effect of the methoxy group.

The situation is slightly more complicated for **1b** where the C_1/C_5, C_2/C_4, and C_6/C_8 pairs are not equivalent. The C_2/C_4 and C_6/C_8 pairs can be differentiated by chemical shift considerations. Thus, the chemical shifts of C_2 and C_8 of **1b** are expected to be close to those of **1a**, while the shifts for C_4 and C_6 of **1b** are close to those of **1c**. Of the two signals due to C_2 (C_4) of **1b**, the high-field one is attributed to C_2, which has the equatorial methoxy group. This criterion cannot be applied to the C_1/C_5 pair since the chemical shift difference in **1b** is very small (ca. 0.5 ppm). A relaxation study[27] provides some clue to differentiating the two resonances on which this tentative assignment is based.

The C_2 (C_4) resonance of **1c** appears at a lower field than that of **1a**, which may seem anomalous for the predominant CC conformation of **1c**.[28,29] However, this anomaly can be explained by considering the effects of the α- and γ-methoxy groups. If the substituent effect of a methoxy group on ^{13}C resonances of a cyclohexane ring approximates that of a hydroxy group,[30] a similar anomaly can be found in hydroxy steroids[31] and hydroxydecalins.[32] In these compounds, the α-effect of a hydroxy group does not depend primarily on whether the substituent is axial or equatorial but rather on the number of γ-gauche carbon atoms bearing hydrogen that can interact with the hydroxy group. One such interaction will cause an upfield shift of about 3.5 ppm.[30] The axial methoxy groups on C_2 (C_4) of **1c** do not have such γ-gauche carbon atoms while the equatorial methoxy groups on C_2 (C_4) of **1a** do have such a γ-gauche carbon for each (C_6 and C_8). Hence the α-effect should shift the C_2 (C_4) resonance of **1c** downfield from that of **1a**. However, the C_2 resonance depends not only on the C_2 methoxy group (α-effect) but also on the C_4 methoxy (γ-effect). In hydroxy steroids, the γ-effect caused by an axial hydroxy group (−3.5 ppm) is much smaller than that caused by an axial methyl group in cyclohexane (−8.6 ppm).[33] The γ-effect is further reduced to almost null when the γ-carbon atom does not bear hydrogen that can interact with the hydroxy group.[31] Since C_2 of **1c** does not bear a hydrogen atom capable of interacting with the C_4 methoxy group, the effect of the C_4 methoxy group on the C_2 resonance should be very small, if any. Thus, the combined α- and γ-effects lead to the prediction that the C_2 (C_4) resonance of **1c** should be at a lower field than that of **1a**. The relative locations of the C_1 (C_5) and C_6 (C_8) resonances of **1a** and **1c** can be explained on a similar basis. In hydroxy steroids, the β-effect of a hydroxy group (+9.3 ppm) varies with the number of γ-gauche interactions between the hydroxy group and the γ-carbon atom connected to the β-carbon atom in question (−2 ppm for each interaction).[31] Thus, the resonance of C_1 (C_5) of **1a**, with one such proton on C_6 (C_8) should be upfield from that of **1c**, which does not have such a proton.

The upfield shift (ca. 5 ppm) of C_6 (C_8) of **1a** compared with that of **1c** also supports the proposed structure. Thus, C_6 and C_8 of **1a** are γ-gauche to the methoxy group on C_2 (C_4) whereas those of **1c** are antiperiplanar, so that the resonance of the former is upfield from the latter. If **1c** were in the BC form, its C_6 (C_8) resonance should be at about the same field as that of **1a** since C_6 (C_8) of the former are also in a γ-gauche relationship to a methoxy group.

The observed chemical shifts for **1c** do not fit the BC form. The C_2 (C_4), C_3, and C_7 resonances of a hypothetical BC form (BC-**3**) of bicyclo[3.3.1]nonane are expected to shift upfield by 7 ppm as compared with those of CC-**3**; a smaller but a similar upfield shift is predicted for the C_6 (C_8) resonances. Since there should be no effect of the methoxy groups of **1c** in a BC form to shift these carbon resonances lower than those of **1a**, this difference between the BC and CC forms should be reflected in the chemical shifts of substituted species. Thus, if **1c** were largely in a BC conformation, its ^{13}C resonances, particularly C_6 (C_8), would have been upfield from the corresponding resonances of **1a**. Thus the data indicate that the BC conformer of **1c** is not predominant in solution.

Low-Temperature Spectra. Previous investigations of ^{13}C NMR spectra of **3**,[28] **2**,[28] and hydroxybicyclo[3.3.1]nonanes[30] at various temperatures indicated that the interconversion of conformers was too fast to be observed by dynamic NMR. With the expectation that substitution of the cyclohexanone moiety of **2** with two methoxy groups should affect the interconversion barrier, low temperature ^{13}C NMR spectra of **1c** were recorded in CS_2–tetrahydrofuran-d_8 (1:1). As the temperature was lowered, peaks other than the one due to the methoxy carbon gradually

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Table III. Conformational Energies and Interconversion Barriers of Bicyclo[3.3.1]nonane (3) and Derivatives as Calculated by MM2′ (kcal/mol, 25 °C, $D = 1.5$ (gas))

	BC–CC	barrier CC⟶BC
3	4.67	7.6
2	2.61	7.1
1c	0.52[a] (0.88)[a,b]	7.0[c]
6	0.09	7.3

[a] Partitioned among nine CH_3O–C rotamers (Table IV). [b] Dielectric constant 10.0. [c] Refers to the rotamer B (Table IV).

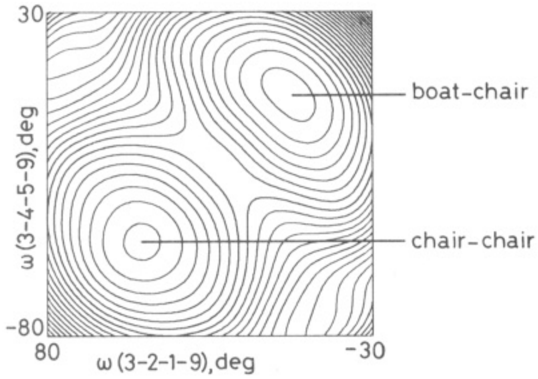


Figure 2. Torsional energy surface of **1c** (rotamer B) obtained by driving C_3–C_2–C_1–C_9 and C_3–C_4–C_5–C_9 dihedral angles from 80° to −30° and from −80° to 30°, respectively.

broadened, and the half-width was ca. 6 Hz at −120 °C.[34] Because of instrument limitations we could not reach the coalescence temperature. From the half-width, however, the maximum $\Delta G^{\ddagger}$ value can be estimated to be below ca. 8 kcal/mol under the assumption that this process is an exchange between two sites of equal population. This estimate is in accordance with the values reported for the ring inversion of cyclohexanone and substituted cyclohexanones.[35]

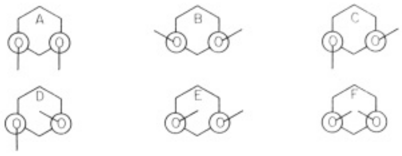
Combined Molecular Mechanics and Generalized Karplus Equation Calculation of 1c. While both ^1H and ^{13}C NMR spectra of **1c** can be qualitatively explained in terms of the CC conformer, the possibility of rapid equilibrium with a small proportion of BC conformer still cannot be excluded. In order to assess this possibility, we utilized the combined molecular mechanics–generalized Karplus equation technique.[36] As the empirical force field, we used MM2′.[37] This force field originates from Allinger's MM2[38] but has been slightly modified for a harder torsional potential.

Test calculations of **2** and **3** with MM2′ using MM2 heteroatom parameters gave acceptable results (Table III).[39,40] Noteworthy is the good agreement of the calculated (−30.71 kcal/mol) with the observed (−30.5 ± 0.6 kcal/mol)[41] heat of formation of CC-**3**. For **1**, nine combinations of rotamers around the two CH_3O–C bonds are taken into account (Table IV). Six of them (A–F) are unique. The conformational energy of **1c** given in Table III is based on the energy partitioning over these rotamers.[42] Conformational energies of **3**, **2**, and **1c** are small and decrease rapidly in this order as expected, and the population of the BC conformer can be significant for **1c**. The height of the barrier for the interconversion of CC into BC (7.0 kcal/mol), obtained from the calculated torsional energy surface (Figure 2), agrees with the estimate from ^{13}C NMR ($\Delta G^{\ddagger} < 8$ kcal/mol).

Table IV. Relative Steric Energies (kcal/mol) of CH_3O–C Bond Rotamers[a] in 1c at Dielectric Constant (D) 1.5 and 10.0 As Calculated by MM2′

	boat–chair		chair–chair	
	$D =$ 1.5	$D =$ 10.0	$D =$ 1.5	$D =$ 10.0
A	0.97	1.50	0.11	0.00
B	0.29	0.66	0.10	0.20
C	0.55	1.07	0.00	0.13
D	2.65	3.42	3.36	4.15
E	2.33	3.01	3.25	4.10
F	4.70	5.46	*d*	*d*
final relative steric energies[b]	0.52	0.88	0.00	0.00
population[c]	30.99	18.49	69.01	81.51

[a] Methoxy-ring carbon rotamer conformations as seen from the top of a chair six-membered ring:



[b] Population weighted. [c] Symmetry numbers were taken into account in the population calculation. [d] Attempted minimization led spontaneously to the corresponding boat–chair conformer.

The calculated interconversion energy (BC–CC) of **1c** was 0.52 kcal/mol for vapor phase, but the energy of such a polar molecule should be considerably different in $CDCl_3$. Following Allinger,[4,43] we treated the dielectric constant in the electrostatic potential term as an adjustable parameter. The best agreement between the observed and calculated $^3J_{HH}$ values was obtained when this parameter was increased from 1.5 (vapor phase value) to 10.0. At this point, the interconversion energy was 0.88 kcal/mol, which corresponds to an 18% population of the BC conformer (Table IV).[44]

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[34] In a typical example, the half-width of the C_1 (C_5) signal was 1.3 Hz at 0 °C and 6.4 Hz at −120 °C with a digital resolution of 0.5 Hz.

[35] Jackman, L. M.; Cotton, F. A., Eds. "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1975; Chapter 14.

[36] MNDO performed unsatisfactorily for the conformational behavior of 1.

[37] Jaime, C.; Ōsawa, E. *Tetrahedron* **1983**, *39*, 2769–2778.

[38] (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134. (b) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.

[39] Carbonyl and ether parameters were transferred from MM2.

[40] The BC–CC differences for **2** and **3** appear too large compared to experimental observation.[10,11] However, large uncertainties in the experimental values preclude further assessment.

[41] Parker, W.; Steele, W. V.; Watt, I. *J. Chem. Thermodn.* **1977**, *9*, 307–310.

[42] About 20 subroutines were added to the QCPE version of MM2 program,[38b] so that all possible rotamers arising from the rotation of up to 10 specified bonds are minimized and vicinal coupling constants across up to 5 specified bonds computed, all automatically in one job.

[43] Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51–56.

[44] This value is about twice as large as the bulk dielectric constant of $CHCl_3$ (5.0). For comparison, Allinger recommends 7.5 for an effective D of benzene ($D = 2.3$).[38b] It should be noted here that the adjustment of the dielectric constant is not a general solution of the problem. For example, MM2 never gave correct stability order for **1c** even if the dielectric constant was changed over a range of 20. Nor did the adjustment of D work when the atomic charges as obtained by MNDO calculations were used in place of the bond moment scheme in MM2 and MM2′. On the other hand, our success in reproducing the experimental coupling constant does not necessarily mean that the effective dielectric constant of $CDCl_3$ should always be taken as 10. The inadequacy of the fixed bond moment approach used in MM2 (and in MM2′) to calculate electrostatic potential has been criticized,[4,44a] and no serious physical significance should be attached to the conventional treatment of dielectric constant as a variable. (a) Philip, T.; Cook, R. L.; Malloy, T. B. Jr.; Allinger, N. L.; Chang, S.; Yuh, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2151–2156. (b) Dosen-Mikovic, L.; Jeremic, D.; Allinger, N. L. *Tetrahedron* **1981**, *37*, 3455–3461. (c) Meyer, A. Y. *J. Comput. Chem.* **1981**, *2*, 384–391. (d) Dosen-Micovic, L.; Jeremic, D.; Allinger, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 1716–1722, 1722–1733.

Table V. Key Dihedral and Valence Angles and Nonbonded Distances in Bicyclo[3.3.1]nonane (3) and Derivatives As Calculated by MM2′[a]

	3,[b] CC	2, CC	1c[c] CC	1c[c] BC	6 CC	6 BC
C_3-C_2-C_1-C_9, deg	54.4 (53.1)[d]	52.5	52.0	1.8	49.8	2.4
C_1-C_2-C_3-C_4, deg	−43.8 (−44.0)[d]	−44.1	−44.9	−53.7	−39.9	−52.3
$C_2C_3C_4$, deg	112.4 (113.2)[d]	112.9	114.5	112.0	116.4	112.1
$C_3\cdots C_7$, Å	3.16 (3.06)[c]	3.16	3.15	3.72	3.17	3.73
$C_2\cdots C_4$, Å	2.55	2.56	2.60	2.56	2.63	2.56
$H_{3a}\cdots H_{7a}$, Å	1.95	1.95	1.93		1.96	
O···O, Me···Me, Å			3.00		3.49	

[a] In the gas phase. [b] MM2′ values (unparenthesized) essentially agree with those of MM2, ref 14a. [c] Refers to the rotamer B. [d] Electron diffraction at 65 °C, ref 14a.

Vicinal coupling constants for the protons on the methoxy-substituted cyclohexane ring of **1** (Table I) were computed based on MM2′-calculated H-C-C-H dihedral angles and the generalized Karplus equation (CAGPLUS).[3,45] For each CC or BC conformer, the calculated coupling constant is the sum of partitioned contribution from the nine CH_3O-C rotamers (Table II, A-F).

$$J^{cc} = \sum_i^m n_i J_i^{cc}$$

$$\sum_i n_i = 1$$

where $m = 9$ and n_i is the fraction of the ith rotamer with the calculated coupling constant J_i. For the "average" coupling constant, the summation extends over all rotamers of CC and BC conformers ($m = 18$).[42]

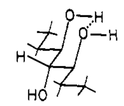
Compound **1a** can be used as the internal standard to check the ability of the generalized Karplus equation to reproduce experimental coupling constants for these systems, since we can completely ignore the BC conformer for **1a** (MM2′ predicts that the CC conformers of **1a** should be at least 6 kcal/mol more stable than the BC). The experimental constants should be identical with those calculated for CC, and this expectation was realized for $J_{H_1H_2}$ and $J_{H_2H_{31}}$, while the calculated $J_{H_2H_{32}}$ was marginally underestimated.

With **1c**, the agreement between the observed and the calculated constants are better. Especially noteworthy is $J_{H_2H_{31}}$, since the calculated J values are quite different for CC and for BC and should best reflect the conformer composition. Taking the standard deviation of the Karplus equation into account, we consider the computed composition (18%) of BC conformer in **1c** as the upper limit of the estimate.

Discussion

The predominance of the CC form in the conformational mixture of **1c** may appear surprising, since the OH and CH_3 groups have similar van der Waals' radii,[46] and two syn-diaxial methyl groups on chair cyclohexanone usually lead to significant deformation of the ring.[47] Actually, syn-diaxial O-O repulsions in *cis*-1,3-cyclohexanediol and its acetate are about half those of the corresponding CH_3-CH_3 interactions in *cis*-1,3-dimethylcyclohexane,[48] owing to the smaller steric size of the oxygen lone pair compared with that of the C-H bond.[49]

The calculated skeletal structural features of CC-**1c** are almost identical with those of the parent molecule **2** (Table V). Inspection of the calculated structure reveals that the extra strain caused by introducing two methoxy groups onto **2** to produce **1c** was absorbed into the substituents as indicated by elongated C-O bonds (1.429 Å for C_2-O, 1.422 Å for OCH_3), a large CH_3-O-C angle (113.8°), and several close H-H contacts involving methyl groups. The O-O nonbonded distance is 3.00 Å, longer than the C_2-C_4 distance (2.60 Å). The C_2-O and C_4-O bonds are not parallel but make an angle of 16° to each other. Probably this nonparallel arrangement of two strong C-O bond dipoles is highly effective in relieving the strain. It may be pertinent to cite here the complete absence of a 1,3-syn-planar arrangement of two OH groups such as **5** in sugar alcohols in crystals.[50] In **5**, the formation of an intramolecular six-membered hydrogen-bonded ring would



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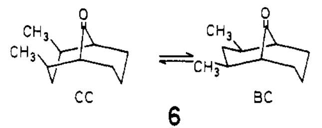

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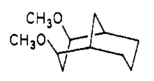
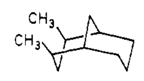


CC-**7**



CC-**8**

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(45) The empirically generalized Karplus equation is parameterized based on MM1[3]-calculated geometries. Since MM2′ gives geometries as good as MM1,[33] the Karplus parameters should be transferable to MM2′. Calculated hydrogen coordinates were further corrected[3] before computing H-C-C-H dihedral angles. According to Haasnoot (personal communication), "hydrogen positions obtained by MM1 displayed systematic errors when comparison is made of the calculated proton-proton torsion angles and the valency angles involving protons with corresponding neutron diffraction studies. These errors were attributed to the "hard" proton nonbonded potentials in combination with the rather "soft" valency bond angle potentials prescribed for MM1. Perusal of all neutron diffractions studied (about 60) yielded a very consistent pattern for the hydrogen positioins which was translated into the guidelines: (a) methylene groups have a (local) C_{2v} symmetry with a H-C-H bond angle of 107.6°; (b) methine protons have equal bond angles to the heavy atoms." Whereas MM2 uses "softer" hydrogen (and MM2′ even softer), these corrections were nevertheless carried out in our calculations. The effect of the correction is, however, small. Haasnoot states that a random error of 1° in the torsion angle leads to an increase of the rms deviation between calculated and experimental coupling constants in the data set containing 315 couplings of 0.1 Hz.

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(50) References 49c, p 107.

have placed the two C-O dipoles into a highly repulsive "close-and-parallel" situation. Note that the g^+g^- arrangement of the O–C–C–C–O unit in **5** appears similar to that in CC-**1c**, but that in the latter some freedom of deformation allowed the conformation to remain as the predominant component.

Returning to the effect of 2,4-substituents on the CC–BC equilibrium in **2** or **3**, we might expect that replacement of methoxy in **1c** by methyl groups (to give **6**) would shift the equilibrium toward the BC conformation. According to MM2′ calculations (Table III), BC-**6** should be as stable as CC-**6**, whose bicyclic skeleton is enormously deformed (Table V). Calculatioins predict that for *cis*-2(a),4(a)-dimethoxy- and *cis*-2(a),4(a)-dimethylbicyclo[3.3.1]nonane (**7** and **8**), CC is more stable than BC by 2.4 and 2.3 kcal/mol, respectively.

Conclusions

Agreement between the observed and calculated $J_{H_2H_{31}}$ coupling constants of **1c** indicates that its solution in $CDCl_3$ contains up to 18% of the BC conformer. Both dynamic ^{13}C NMR and molecular mechanics calculatioins indicate a very low interconversion energy barrier for CC → BC for **1c** (7–8 kcal/mol). The combined use of molecular mechanics and the empirically generalized Karplus equation appears to be a useful technique for studying the conformation of flexible molecules.

Experimental Section

Materials. The configurational isomers of **1** were prepared as reported.[8]

NMR Measurements. ^1H NMR spectra were taken on a JEOL FX-400 spectrometer at 400 MHz, using Me_4Si as internal standard and $CDCl_3$ as solvent.

Ambient-temperature ^{13}C NMR spectra of **1** were recorded on a JEOL FX-90Q spectrometer at about 35 °C in $CDCl_3$ at 22.5 MHz at a concentration of about 10% (v/v). The spectral width was typically 5000 Hz with 8K data points for acquisition. A pulse width of 15 ms (45°) and a delay of 3 s were used.

Low-temperature ^{13}C NMR spectra of **1c** were obtained in a 1:1 mixture of CS_2 and tetrahydrofuran-d_8 by using a concentration of 10% (v/v). Measurement conditions were similar to those at ambient temperature except that the spectral width was 2000 Hz.

(1*R*,2*R*,4*S*,5*S*)-2,4-Dimethoxybicyclo[3.3.1]nonan-9-one (1a): NMR δ 3.43 (false quintuplet, H_2, H_4, 2 H, J = 5.86 Hz), 3.33 (s, OCH_3, 6 H), 2.79 (br, H_1, H_5, 2 H), 2.45 (d tr, H_{31}, 1 H, $J_{H_2H_{31}}$ = 6.35 Hz, $J_{H_{31}H_{32}}$ = 13.67 Hz), 2.34–2.29 (complex, H_{7e}, 1 H), 1.98 (d tr, H_{32}, 1 H, $J_{H_2H_{32}}$ = 11.72 Hz, $J_{H_{31}H_{32}}$ = 13.67 Hz), 1.92–1.79 (complex, H_6 and H_8, 4 H), 1.55–1.49 (complex, H_{7a}, 1 H).

(1*RS*,2*RS*,4*RS*,5*SR*)-2,4-Dimethoxybicyclo[3.3.1]nonan-9-one (1b): NMR δ 3.78 (false quintuplet, H_4, 1 H, J = 5.86 Hz), 3.67 (br, H_2 1 H), 3.33 (s, OCH_3, 3 H), 3.30 (s, OCH_3, 3 H), 2.84 (br, H_1, 1 H), 2.71 (br, H_5, 1 H), 2.40–2.32 (complex, H_{31}, H_{32}, 2 H), 2.18–2.05 (complex, H_6, 2 H), 1.99–1.74 (complex, H_8, H_{7e}, 3 H), 1.57–1.50 (complex, H_{7a}, 1 H).

(1*R*,2*S*,4*R*,5*S*)-2,4-Dimethoxybicyclo[3.3.1]nonan-9-one (1c): NMR δ 3.74 (br, H_2, H_4, 2 H), 3.32 (s, OCH_3, 6 H), 2.70 (br s, H_1, H_5, 2 H), 2.34 (d tr, H_{32}, 1 H, $J_{H_2H_{32}}$ = 4.88 Hz, $J_{H_{31}H_{32}}$ = 15.62 Hz), 2.10 (d tr, H_{31}, 1 H, $J_{H_2H_{31}}$ = 3.90 Hz, $J_{H_{31}H_{32}}$ = 15.62 Hz), 2.07–2.01 (complex, H_6, H_8, 4 H), 1.89–1.78 (complex, H_{7e}, 1 H), 1.62–1.56 (complex, H_{7a}, 1 H).

Acknowledgment. We thank Dr. C. A. G. Haasnoot and Prof. C. Altona for comments and preprints, and Drs. P. M. Ivanov and A. Buda for critical comments. Partial financial support was provided by the Ministry of Education through a Grant-in-Aid for Scientific Research and by Kureha Chemical Industries Co. Calculations were carried out at the Computing Centers of Hokkaido University and the Institute of Molecular Science.

Registry No. **1a**, 78038-14-9; **1b**, 77976-01-3; **1c**, 78038-15-0; **2**, 17931-55-4; **3**, 280-65-9; **6**, 87372-90-5.

Dibromocarbonyl Ylides. Deoxygenation of Aldehydes and Ketones by Dibromocarbene

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Received April 11, 1983

The reaction of phenyl(tribromomethyl)mercury (**4**) with benzaldehyde-α-^{13}C results in benzal-α-^{13}C bromide and CO. The generality of this deoxygenation was shown by treatment of other aldehydes and ketones with mercurial **4** (1.8:1, benzene, 80 °C, 4 h): [RCHO (% CO)], Ph (46), Et (35), *i*-Pr (39), *t*-Bu (19); [RCOR′(% CO)] Ph, Ph (6), Ph, Me (15), Me, Me (16), Et, *n*-Bu (19), Me, c-C_3H_5 (20), c-C_3H_5, c-C_3H_5 (20), cyclohexanone (38), cyclopentanone (19), norcamphor (46). Additional products in selected cases include (for acetophenone) α-bromostyrene, (for cyclohexanone) 1-bromocyclohexene and 1,1-dibromocyclohexane, (for norcamphor) 2,2-dibromonorbornane, 1,2-dibromonorbornane, 2-bromo-2-norbornene and 1-bromonorbornene, and (for pivaldehyde) 1,1-dibromo-2,2-dimethylpropane. The yields of CO from the treatment of a series of benzaldehydes with mercurial **4** (1.8:1 benzene, 80 °C, 20 h) are given in parentheses: ArCHO (% CO), 4-MeO (81), 4-Me (61), 3-Me (55), H (50), 4-F (46), 3-MeO (58), 4-Cl (46), 4-Br (47), 3-Cl (34), 3,4-Cl_2 (27). A Hammett-type correlation of log (yield)/(yield)$_0$ vs. σ gave $\rho = -0.50$ (r = 0.94).

The production of carbon monoxide has been noted in the alcoholysis of haloforms under strongly basic conditions.[1,2] A variety of evidence from these studies suggests the formation of an intermediate alkoxyhalocarbene which can break down to the corresponding carbocation and CO in a one- or two-step process.

$$:CX_2 + RO^- \xrightarrow{-X^-} RO\ddot{C}X \rightarrow R^+ + CO + X^-$$

By analogy, a similar alkoxyhalocarbene (**2**) has been

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[2] Closely related is the hydrolysis of chloroform in aqueous base: Robinson, E. A. *J. Chem. Soc.* **1961**, 1663.

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