Carbon-13 Nuclear Magnetic Resonance Spectroscopy in Conformational Analysis of 9-Azabicyclo[3.3.1]nonane Derivatives

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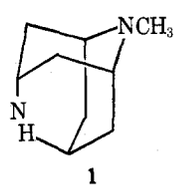
Carbon-13 NMR spectroscopy is demonstrated to be a powerful tool in conformational analysis and stereochemical assignment of 9-azabicyclo[3.3.1]nonanes. Endo alcohol **2** is shown to have the chair–boat conformation **2a** while exo alcohol **3** exists in the double chair conformation. Similarly quaternary ammonium chloride **13** is shown to exist in a chair–boat conformation in spite of a severe steric interaction. 9-Alkyl-9-azabicyclo[3.3.1]nonan-3-ones **6–9** are shown to prefer conformations with the *N*-alkyl group over the piperidone side of the molecule rather than over the piperidine side.

Carbon-13 nuclear magnetic spectroscopy[1,2] is a powerful tool for structure determination of organic compounds and is an exceedingly sensitive probe for conformational analysis because of the dependence of carbon chemical shifts upon steric effects within molecules.[3–5] Most of the effort has been directed toward cyclohexanes and their fused polycyclic counterparts (i.e., decalins[6] and perhydroanthracenes[7]). Spirocyclic compounds have also been studied.[8] The bridged polycyclic substrates which have been examined in detail are those of rather rigid molecular structures, such as the norbornyl,[9] bicyclooctyl,[10c] and adamantyl[10a,b] skeletons. Very little attention has been accorded to conformationally flexible bridged bicyclic structures. We have undertaken an investigation of the conformational manifestations of steric effects in the 9-azabicyclo[3.3.1]nonane (granatanine) system by carbon-13 NMR spectroscopy. This ring system was selected on account of its being composed of two six-membered rings, the symmetry of which facilitates chemical shift assignments, and in particular because of the delicate balance between chair–chair and chair–boat conformations as a function of substituent stereochemistry. The 9-azabicyclo[3.3.1]nonane ring system is known[11] to adopt a double chair conformation which is slightly flattened to relieve the transannular steric interactions of the endo hydrogens on carbons 3 and 7 (see formula 1). A 3-endo substituent larger than hydrogen forces



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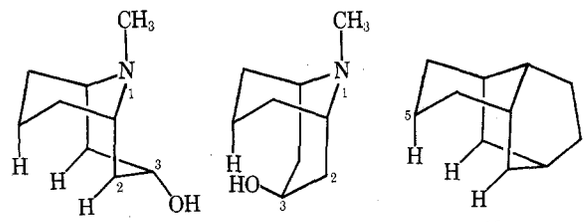
the substituted bridge to flip so that the substituted piperidine ring has a boat conformation as shown in **2a**.[11]

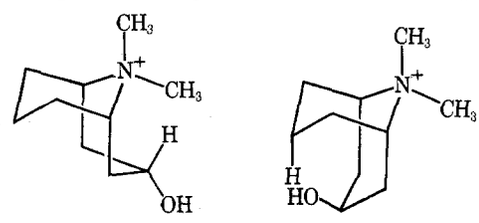
Results and Discussion

Table I collects the carbon-13 chemical shifts for the granatanine substrates we have studied in this investigation. Assignments were made on the basis of relative signal intensities and with the aid of coupled spectra. We focus first on the granatanols **2** and **3**, which differ structurally only in the configuration of the hydroxyl group at carbon 3. The major difference in the ^{13}C NMR chemical shifts is at carbon 7, the atom most remote from the site of the stereochemical difference. We attribute this difference to the fact that the endo isomer **2** exists predominantly in the chair–boat conformation **2a** in order to relieve the transannular steric interactions in the chair–chair conformation **2b**.[12,13] However, in conformation **2a**, the endo-7-hydrogen atom is in a gauche relationship with the endo hydrogens at carbons 2 and 4, and thus, according to the findings of Grant and coworkers, carbon 7 should be sterically shielded by approximately 5 ppm compared to a suitable model. Employing the parent amine **1** as the model, we find that indeed α-granatanol (**2**) has its 7-carbon signal shifted upfield by 5.9 ppm relative to the 3(7) carbon of **1**. β-Granatanol (**3**), which exists predominantly in the double-chair conformation,[12,13] displays its 7 carbon at 19.8 ppm, only 0.6 ppm upfield of the corresponding carbon signal of granatanine (**1**). In support of our interpretation is the carbon-13 NMR spectrum of homotwistane (**10**), which contains an unusually high field signal (15.2 ppm) for carbon 5, attributed to the gauche interactions that carbon experiences as a consequence of the rigid chair–boat conformation.[14] Lawton and Haslanger have observed similar differences in ^{13}C spectra of 3-exo and 3-endo substituted bicyclo[3.3.1]nonanes.[15] Somewhat surprising is the fact that carbons 2 and 4 of endo alcohol **2** show essentially the same chemical shift difference with respect to **1** as shown by carbons 2 and 4 of exo alcohol **3**. The observed shift (approximately 9.5 ppm) is that which would be expected for the introduction of a β hydroxyl group.[16] Grant has also observed the lack of reciprocity for the chemical shifts of sterically interacting moieties.[4]



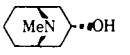
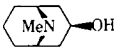
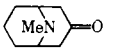
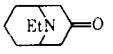
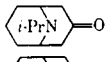
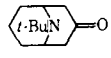
2a 2b 10

We have also measured the carbon-13 NMR spectra of the quaternary ammonium chlorides **11–13**; Table II presents the ^{13}C chemical shifts. Again the most striking difference in chemical shifts is that found for carbon 7: in endo isomer **12**, carbon 7 resonates 5.4 ppm upfield of the corresponding carbons of the parent salt **11** while the 7 carbon of the exo epimer **13** is within 0.2 ppm of carbon 3(7) of **11**. Thus, we conclude that endo alcohol **12** also exists preferentially in the chair–boat conformation **12a**. This finding is interesting since it implies that the transannular 3,7 in-



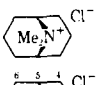
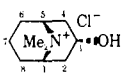
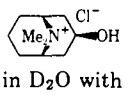
12a 12b

Table I
Chemical Shifts of 9-Azabicyclo[3.3.1]nonane Derivatives[a,b]

	Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	N-C-C
1		52.3	26.4	20.4	(26.4)	(52.3)	(26.4)	(20.4)	(26.4)	40.9
2		51.9	34.9	62.0	(34.9)	(51.9)	25.1	14.5	(25.1)	40.4
3		53.9	35.3	64.4	(35.3)	(53.9)	27.4	19.8	(27.4)	40.5
4		79.4	37.9	21.7	29.5	50.9	(29.5)	(21.7)	(37.9)	
5		82.5	33.8	22.0	25.6	57.6	(25.6)	(22.0)	(33.8)	34.2
6		55.8	41.8	210.0	(41.8)	(55.8)	29.7	16.1	(29.7)	41.1
7		53.6	42.4	210.1	(42.4)	(53.6)	30.0	16.8	(30.0)	46.4[c]
8		50.6	42.7	211.3	(42.7)	(50.6)	30.3	16.6	(30.3)	47.5[c]
9		48.4	47.0	212.7	(47.0)	(48.4)	32.3	17.2	(32.3)	54.1[c]

[a] Downfield from internal tetramethylsilane. [b] Chemical shifts of symmetry-related atoms are enclosed in parentheses. [c] Chemical shifts for N-C-C: 7, 13.7; 8, 21.9; 9, 32.3.

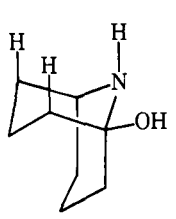
Table II
Chemical Shifts of 9-Azoniabicyclo[3.3.1]nonane Compounds[a,b]

	Compd	C-1	C-2	C-3	C-6	C-7	N-C	N-C'
11		65.0	27.2	18.4			53.0	
12		63.9	35.3	59.4	26.9	13.0	52.8	53.4
13		66.3	36.6	63.2	26.8	18.2	52.6	53.5

[a] Measured in D_2O with external $NaO_3SCH_2CH_2CH_2Si(CH_3)_3$. [b] Chemical shifts for symmetry-related atoms are omitted.

teraction associated with conformation **12b** is more severe than the steric crowding between the methyl group and the hydrogen at the flagpole positions of the boat portion of the molecule.

We next address the question of the steric effect of the substituent attached to nitrogen on the chemical shifts of various carbon atoms. The bridgehead alcohols **4** and **5** are



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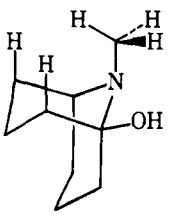

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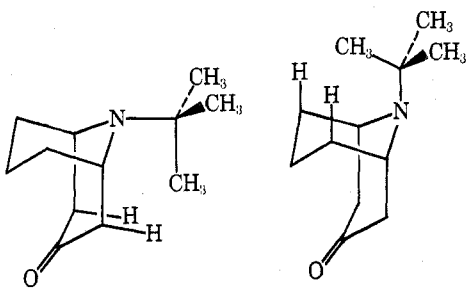
useful for this purpose. Upon substitution of methyl for hydrogen, carbons 2(8) and 4(6) undergo upshield shifts of 4.1 and 3.9 ppm, respectively. A substituent at the 9 position of the bicyclo[3.3.1]nonane system must be axial to one of the six-membered rings, and because of pyramidal inversion at nitrogen, the *N*-methyl group has axial character alternately in each ring. The axial nature of the methyl group introduces gauche steric interactions with the carbons 2, 4, 6, and 8 and thus the observed upfield shifts for these carbons are expected based on the findings of Grant.[4] A similar methyl-induced shift (approximately 3 ppm) has been reported for nortropane and tropane.[17]

Finally, we note the small difference in chemical shift for carbons 6 (and 8) in the isomeric alcohols **2** and **3**. Exo alcohol **3**, with the double-chair conformation, should have its *N*-methyl axial in each piperidine ring approximately 50% of the time. Carbons 6 and 8 of **3** experience γ-gauche interactions with the *N*-methyl group 50% of the time and resonate at δ 27.4. Endo alcohol **2**, with the chair–boat conformation, has its *N*-methyl group axial to the chair ring and in a γ-gauche relationship to carbons 6 and 8 nearly all the time. In alcohol **2**, carbons 6 and 8 resonate at δ 25.1, 2.3 ppm upfield from the corresponding resonance for **3**. Significantly, the chemical shifts of carbons 6 (and 8) of quaternary salts **12** and **13** are virtually identical.

The pseudopelletierine derivatives **6–9** also provide valuable information relating carbon-13 chemical shifts to conformational ramifications of steric interactions induced by substituents on nitrogen. Of particular interest are carbons 2, 4, 6, and 8, which show only small downfield shifts (about 0.3 ppm) as two of the methyl hydrogens of pseudopelletierine (**6**) are sequentially exchanged for methyl groups to provide the ethyl and isopropyl substrates **7** and **8**. When the final hydrogen is replaced by a methyl group, a substantial downfield shift is observed. The direction and magnitude of the observed shifts are in accord with Stothers' results for δ-steric effects.[18] In the case of *tert*-butyl derivative **9**, a methyl group must be situated in the midst of the axial hydrogens on carbons 2, 4, 6, and 8, thus introducing severe δ-steric interactions. The most significant feature of these sterically induced shifts is that the shift in-

crements per methyl group are greater, especially with *tert*-butyl derivative **9**, at carbon 2(4) than at carbon 6(8). From



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this we infer that, as the nitrogen atom undergoes pyramidal inversion, the *tert*-butyl group spends more time on the piperidone side of the molecule than on the piperidine side. This is probably due to flattening of the piperidone bridge in accommodating the sp^2-hybridized carbonyl carbon which diminishes somewhat the severity of the steric interactions. We have observed similar steric effects with the syn and anti epimers of 9-phenyl-9-phosphabicyclo-[3.3.1]nonan-3-one 9-oxide.[19]

Conclusion

With the results reported here, we have demonstrated the power of carbon-13 NMR spectroscopy in determining conformational preferences in bridged bicyclic substrates. Specifically, ^{13}C NMR spectroscopy can be utilized to ascertain simply the conformations and the configuration of 3-substituted and 9-substituted bicyclo[3.3.1]nonanes.

Experimental Section

The carbon-13 NMR spectra were measured at 25.15 MHz with a Jeol JNM PS-100 spectrometer interfaced with a Nova 1200 computer. The amines **1–9** were run in deuteriochloroform with tetramethylsilane as internal standard. The quaternary ammonium chlorides **11–13** were run in D_2O with the sodium salt of 3-trimethylsilylpropanesulfonic acid in D_2O as external reference. In all cases 10-mm tubes were employed and the sample concentrations were on the order of 0.5 *M*.

All of the amines utilized in this study were prepared according to literature procedures: **1**,[20] **2**,[21] **3**,[22] **4**,[23] **5**,[20] and **6–9**.[24] The quaternary ammonium chlorides **10–13** were prepared by the addition of excess methyl iodide to a solution of the corresponding amine in methylene chloride. The resulting precipitate was collected by filtration and then dissolved in hot water and passed through a 25 × 1 cm column packed with Amberlite IRA-401 ion exchange resin in the chloride form. Concentration of the eluent afforded the desired methochloride salts.

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Registry No.—**1**, 491-25-8; **2**, 2038-40-6; **3**, 6376-00-7; **4**, 56258-83-4; **5**, 56258-84-5; **6**, 552-70-5; **7**, 27092-59-7; **8**, 56258-85-6; **9**, 56258-86-7; **11**, 56258-87-8; **12**, 56258-88-9; **13**, 56258-89-0; methyl iodide, 74-88-4.

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Reaction of Azulene with Tetracyanoethylene Oxide

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Azulene reacts with tetracyanoethylene oxide (TCNEO) to give 1-dicyanomethylazulene (**2**), 1-azuloyl cyanide (**4**), and 1-azulyltricyanoethylene (**6**) as the principal stable products. The major product was **4** (49%). The formation of **4** appears to involve carbon–carbon cleavage of the epoxide ring in TCNEO. A number of minor, unstable products were not characterized.

Tetracyanoethylene oxide (TCNEO) has been found to react readily with nucleophiles,[2,3,6] alkenes and alkynes,[2,4,5,7] aromatic rings,[2,4,5] Schiff bases,[6] and reducing agents.[5] The nucleophiles gave products derived from degradative scission of the epoxide ring, the alkenes gave stereospecific 1,3-dipolar-like addition, and the reducing agents abstracted oxygen and generated TCNE. With the aromatic compounds studied, which were all benzenoid and included benzene, naphthalene, anthracene, phenanthrene, furan, and thiophene, two distinct modes of reaction were