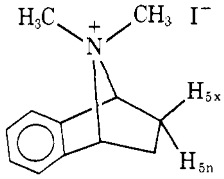
Nuclear Magnetic Resonance Studies of Rigid Bicyclic Systems. 6.[1] Angular Dependence of Vicinal $^{14}N-^{1}H$ Spin Couplings in Bicyclic Ammonium Salts

Marc J. O. Anteunis,*[2,3a] Frans A. M. Borremans,[3a] Jan Gelan,[3a]
Alan P. Marchand,*[2,3b] and Robert W. Allen[3b]

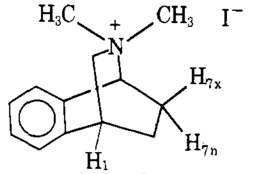
Contribution from the Laboratorium voor Organische Chemie, Rijksuniversiteit Gent, Krijgslaan 271-S4, B-9000 Gent, Belgium, and the Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019. *Received October 31, 1977*

Abstract: Normal (undecoupled) and ^{14}N-decoupled ^{1}H NMR spectra were obtained at 300 and 100 MHz for the methiodides of *N*-methyl-7-aza-2,3-benzonorbornene (I), *N*-methyl-5-aza-2,3-benzobicyclo[2.2.2]oct-2-ene (II), 5-*N,N*-dimethylamino-1,3-dioxane [IIIa (axial NMe_3^+), IV (equatorial NMe_3^+)], *cis*-2-methyl-5-*N,N*-dimethylamino-1,3-dioxane (IIIb), 5-methyl-5-*N,N*-dimethylamino-1,3-dioxane (IIIc), *trans*-2,5-dimethyl-5-*N,N*-dimethylamino-1,3-dioxane (IIId), and *exo*-5-*N,N*-dimethylamino-2,3-benzonorbornene (V). *J* values for vicinal $^{14}NCCH$ couplings were obtained by comparison of bandwidths of signals before and after heteronuclear decoupling. A plot of the *J* values thus obtained vs. the NCCH torsion angle, ϕ, was fit to the Karplus relation; the best (least-squares) fit was obtained for $J = 1.41 \pm 0.08 - (0.56 \pm 0.13) \cos \phi + (1.51 \pm 0.12) \cos 2\phi$. From this plot, the value of *J* at $\phi = 180°$ could be estimated at ca. 3.5 Hz, a value significantly lower than that ($J = 5$-6 Hz) suggested earlier by Tori and co-workers.

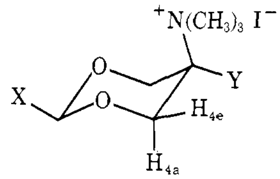
Vicinal $^{14}N-^{1}H$ spin couplings, $J_{^{14}NCCH}$, have been observed in a number of quaternary ammonium salts, both in alkylammonium[4] and enammonium[5-9] systems. Dependence of this vicinal coupling constant upon the dihedral angle between coupling nuclei, ϕ, has been noted.[4] In the present work, we report $J_{^{14}NCCH}$ values for systems I-V, and we show that the dependence of this coupling constant upon ϕ in saturated systems follows a Karplus-type relationship.[10,11]



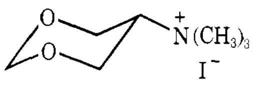
I



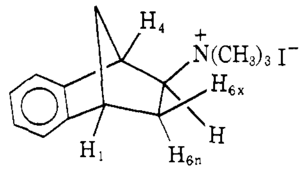
II



IIIa, X = Y = H
b, X = CH_3; Y = H
c, X = H; Y = CH_3
d, X = Y = CH_3



IV



V

Syntheses. The syntheses of compounds IIIa, IIIb, and IV have been described previously.[12] Compound I was prepared via addition of benzyne[13] to *N*-carbethoxypyrrole,[14] followed by lithium aluminum hydride reduction of the resulting Diels-Alder adduct and amine quaternization. Compound II was synthesized via the reaction sequence indicated in Chart I. The method by which IIIc was synthesized is shown in Chart II. A scheme similar to that shown in Chart II was utilized for the synthesis of IIId, with the exception that acetaldehyde was

Chart I

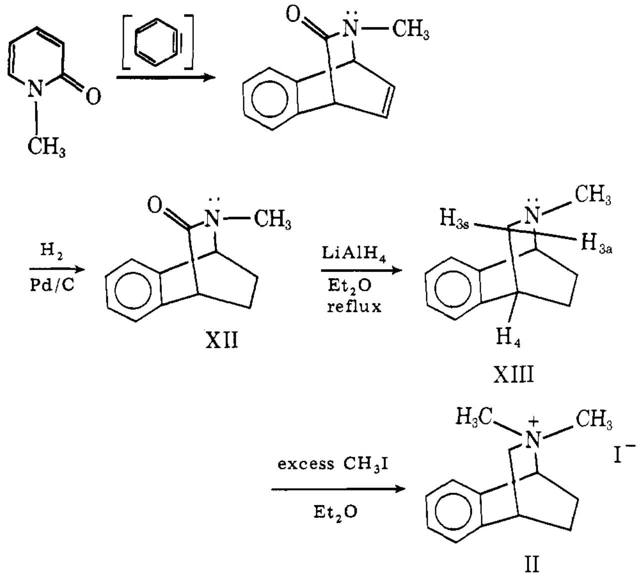


Chart II

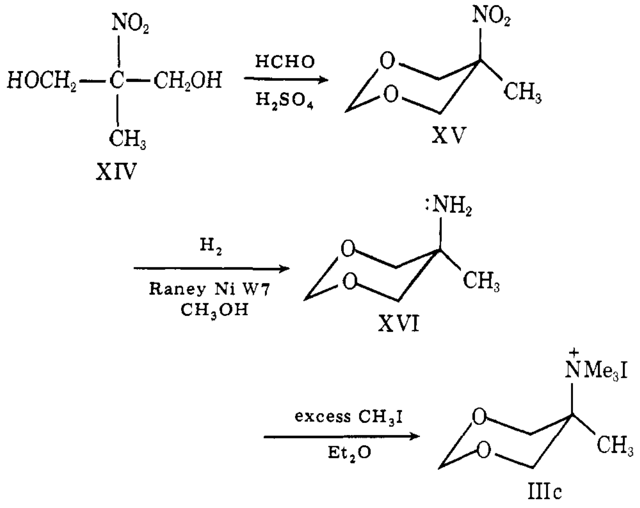
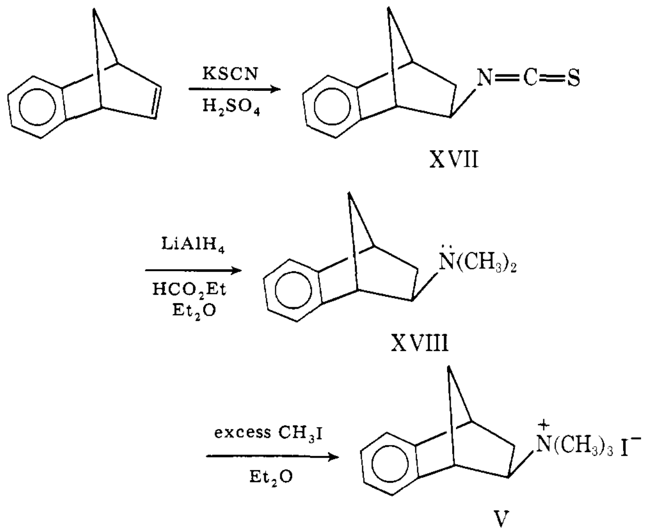


Chart III



used in the first step of the reaction sequence in place of formaldehyde.

Compound V was prepared by the method indicated in Chart III. The addition of isothiocyanic acid to norbornene has been studied by Dively et al.[15] The assignment of exo stereochemistry to the HSCN adduct with 2,3-benzonorbornadiene in the present work is made by analogy to the results of Dively's study[15] and by analogy to the known stereochemistry of electrophilic addition of other acids, HX, to norbornenes and to 2,3-benzonorbornadiene.[16] Reduction of isothiocyanate XVII with excess lithium aluminum hydride followed by addition of excess ethyl formate afforded the corresponding dimethylamine (XVIII) in 47% yield. This procedure for the synthesis of XVIII was suggested by Wright's earlier observation[17] that amines, in the presence of excess lithium aluminum hydride, can be readily alkylated by esters. This procedure offers a convenient "one-pot" synthesis of V from XVII.

Discussion

Quadrupolar relaxation of the ^{14}N nucleus is rapid in the presence of a large electric field gradient (e.g., in nonsymmetrically substituted amines and ammonium salts, where the electron charge distribution is nonspherically symmetric).[18,19] In such systems, ^{14}N-^{1}H coupling will generally be unobservable. However, in systems in which the electric field is homogeneous in the vicinity of the ^{14}N nucleus, that nucleus will experience an increase in its spin-lattice relaxation time (T_1). Under these conditions, a relatively sharp line ^{1}H spectrum results wherein ^{14}N-^{1}H coupling becomes observable.[8,20-22] In the present study, these effects were noted in the ^{1}H NMR spectra of *N*-methyl-7-aza-2,3-benzonorbornene, *N*-methyl-5-aza-2,3-benzobicyclo[2.2.2]octane, and in their corresponding methiodide salts (I and II, respectively) and trifluoroacetates. Comparison of the ^{14}N-decoupled ^{1}H NMR spectra of the parent amines and their corresponding trifluoroacetate salts with the corresponding normal (non-^{14}N-decoupled) ^{1}H NMR spectra reveals no evidence of ^{14}N-^{1}H coupling in the normal (undecoupled) spectra. However, ^{14}N couplings with β protons ($J_{^{14}NCCH}$ vicinal couplings) are clearly demonstrated via comparison of the normal (undecoupled) and ^{14}N-decoupled ^{1}H NMR spectra of methiodides I and II (Figure 1).

One can also take advantage of the temperature dependence of ^{14}N nuclear quadrupolar relaxation when extracting the ^{14}N-^{1}H couplings from the ^{1}H NMR spectra of quaternary ammonium salts.[22-26] Temperature effects on the normal (non-^{14}N-decoupled) ^{1}H NMR spectrum of I are shown in Figure 2. Coupling between ^{14}N and endo-5,6-β-^{1}H which is washed out by rapid ^{14}N quadrupolar relaxation at room temperature (30 °C) becomes observable at higher temperature (85 °C; compare trace a with trace b in Figure 2).

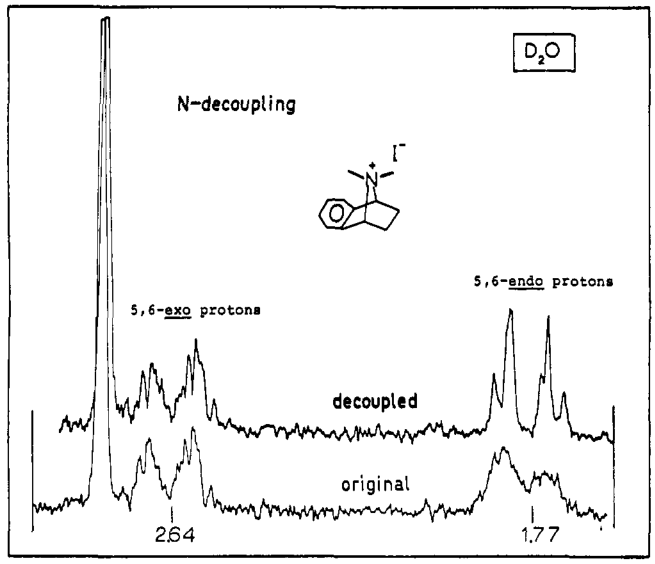
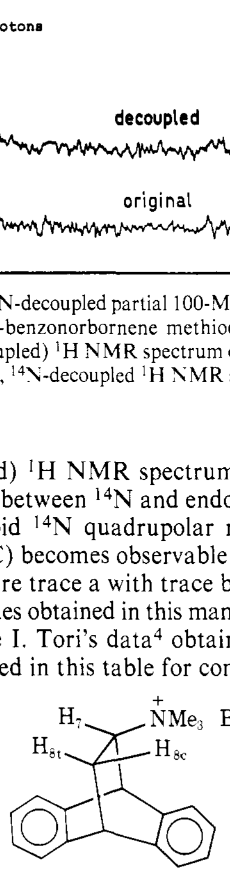
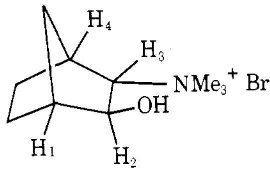


Figure 1. Normal and ^{14}N-decoupled partial 100-MHz ^{1}H NMR spectrum of *N*-methyl-7-aza-2,3-benzonorbornene methiodide (I). Lower trace, original (non-^{14}N-decoupled) ^{1}H NMR spectrum of the 5,6-exo and endo protons in I; upper trace, ^{14}N-decoupled ^{1}H NMR spectrum of the 5,6-exo and endo protons in I.

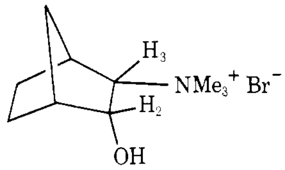
The $J_{^{14}NCCH}$ values obtained in this manner for systems I-V are shown in Table I. Tori's data[4] obtained for compounds VI-VIII are included in this table for comparison. Tori[4] observed a dependence of $J_{^{14}NCCH}$ upon torsion angle; however, his observations were restricted to compounds having *NCCH* torsion angles of 0, 60, 79, and 120°. Furthermore, the complications introduced via electronegativity effects of the C-2 hydroxyl groups in VII and VIII were recognized, but they could not be accounted for quantitatively.[27] Accordingly, no relationship between $J_{^{14}NCCH}$ and ϕ could be derived from Tori's study.



VI



VII



VIII

Of the systems studied by Tori,[4] only VI contains no highly electronegative heteroatomic substituents (other than the nitrogen atom whose couplings with β protons were being investigated) which might influence the magnitude of $J_{^{14}NCCH}$. Systems I, II, and V utilized in the present study possess this same virtue. Our results, taken together with Tori's data[4] for systems VI-VIII, now permit evaluation of the relationship between $J_{^{14}NCCH}$ and ϕ; a plot of $J_{^{14}NCCH}$ vs. ϕ is shown in Figure 3. The solid line in Figure 3 represents the best fit to the Karplus[11,28] relation: $J = A + B\cos\phi + C\cos 2\phi$ (see Ex-

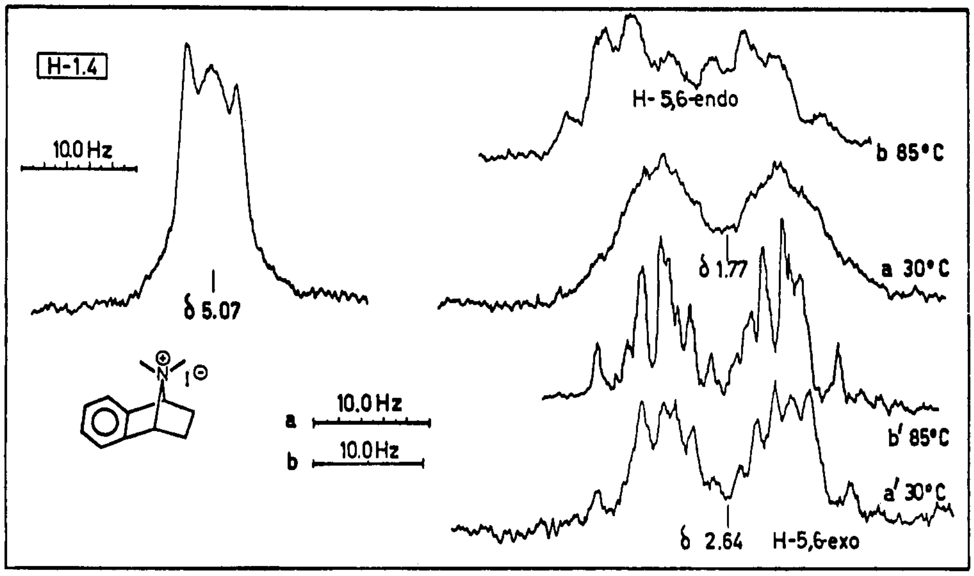


Figure 2. Temperature effects on ^{14}N nuclear quadrupolar relaxation in I. Traces a and b, 100-MHz ^1H NMR spectra of the 5,6-endo protons in I at 30 and 85 °C, respectively; traces a′ and b′, 100-MHz ^1H NMR spectra of the 5,6-exo protons in I at 30 and 85 °C, respectively.

Table I. Vicinal Couplings, $J_{^{14}NCCH}$ (Hz), in Systems I–VIII

Compd	Proton	Torsion angle ϕ, deg[d]	$J_{^{14}NCCH}$, Hz (obsd)[a]
I	H_{5x}	90	0
	H_{5n}	150	3.0
II	H_1	180	3.5
	H_{7x}	90	0
	H_{7n}	150	2.5
IIIa	H_{4e}	54[b]	0.7
	H_{4a}	174[b]	3.4
IIIb	H_{4c}	54[b]	0.7
	H_{4a}	174[b]	3.6
IIIc	H_{4e}	54[b]	0.5
	H_{4a}	174[b]	3.55
IIId	H_{4e}	54[b]	0.5
	H_{4a}	174[b]	3.4
IV	H_{4e}	66[b]	0.7
	H_{4a}	54[b]	0.9
V	H_4	30	0.3
	H_{6x}	0	2.8
	H_{6n}	120	0.8
VI[c]	H_4	60	0.3
	H_{8c}	0	2.7
VII[c]	H_4	79	0
VIII[c]	H_2	120	0.3
	H_4	79	0

[a] In most cases, J values were obtained by comparison of bandwidths of (often still poorly resolved) signals at elevated temperatures before and after heteronuclear decoupling (see Experimental Section). Error magnitude is expected to be greatest for small $^{14}NCCH$ couplings as these are most adversely affected by the uncertainties introduced by the effects of ^{14}N T_1 on ^1H NMR line shapes. [b] From x-ray crystallographic data on 2-(*p*-chlorophenyl)-1,3-dioxane; see A. J. DeKok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, **89**, 313 (1970). [c] Tori's data (ref 4). [d] Estimated via inspection of Dreiding models, unless otherwise noted.

perimental Section). Inspection of this plot reveals the existence of a clear minimum at $\phi = 90°$; a maximum in the plot occurs at $\phi = 180°$.

The values obtained in the present study for $\phi = 180°$ (i.e., ca. 3.5 Hz for the appropriate ^{14}N–^1H couplings in systems II and III) probably represent minimal $J_{^{14}NCCH}$ values. Since $J_{^{14}NCCH}$ is positive,[29] the effect of the oxygen atoms in the 1 and 3 positions of III should be to reduce the magnitude of $J_{^{14}NCCH}$ relative to the corresponding values in the corresponding carbocyclic system.[20,30] In system II, ring strain effects should operate to alter the electronegativity of C-1 relative to C-7 and C-8, thereby decreasing the magnitude of $J^{180}_{^{14}NCCH}$ relative to other $J_{^{14}NCCH}$ values in the same system.[31,32] A similar effect operates in system V to decrease $J_{^{14}NCCH}$. Although the foregoing arguments serve to establish that $J^{180}_{^{14}NCCH}$ should be somewhat greater than the ca. 3.5 Hz which we observe, our results nevertheless should serve to temper Tori's prediction[4] that $J^{180}_{^{14}NCCH}$ should fall in the range of 5–6 Hz.

Experimental Section

Melting points are uncorrected. NMR spectra were obtained utilizing Varian HR-300 and Varian HA-100 spectrometers ($CDCl_3$ solvent, Me_4Si internal standard, vide infra). Mass spectra were obtained at 70 eV utilizing a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. Elemental microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Amine methiodides were prepared from the corresponding amines in all cases by refluxing the amine with excess ethereal methyl iodide solution.

N-Carbethoxy-7-aza-2,3-benzonorbornadiene (IX). *N*-Carbethoxypyrrole[33] (7.9 g, 0.057 mol) was dissolved in dry tetrahydrofuran (THF, 100 mL) and brought to reflux. Isoamyl nitrite (6.67 g, 0.057 mol) and a THF solution of anthranilic acid (7.81 g, 0.057 mol) were added simultaneously to the refluxing *N*-carbethoxypyrrole–THF solution via separate dropping funnels. After the additions were complete (2.5 h), the resulting mixture was refluxed for an additional 1.5 h. The mixture was concentrated, and a volume of chloroform equal to the volume of THF removed by distillation was then added to the residue. The resulting solution was washed first with water, then with saturated aqueous sodium bicarbonate solution, and finally with water. The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was then concentrated. The resulting residue, a black oil, was chromatographed on neutral alumina (1:9 ethyl acetate–hexane eluent). Compound IX was thereby isolated (6.2 g, 51%). Recrystallization from ether–hexane afforded colorless needles: mp 59.5–60.0 °C; NMR ($CDCl_3$) δ 1.07 (t, $J = 7$ Hz, 3 H, $-OCH_2CH_3$), 3.95 (q, $J = 7$ Hz, 2 H, $-OCH_2CH_3$), 5.45 (unsymmetrical t, 2 H, bridgehead protons), 6.73–7.23 (complex m, 6 H, aryl and vinyl protons); mass spectrum *m/e* (rel intensity) 216 (44), 215 (parent ion, 100), 189 (63), 170 (28), 142 (11), 117 (8), 116 (9), 89 (5), and 63 (4).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.73; H, 6.01; N, 6.59.

N-Carbethoxy-7-aza-2,3-benzonorbornene (X). Compound IX (1.00 g, 4.65 mmol) was dissolved in diethyl ether (50 mL). Palladized charcoal (ca. 50 mg) was added, and the mixture was hydrogenated on a Parr apparatus until 1 equiv of hydrogen had been taken up.

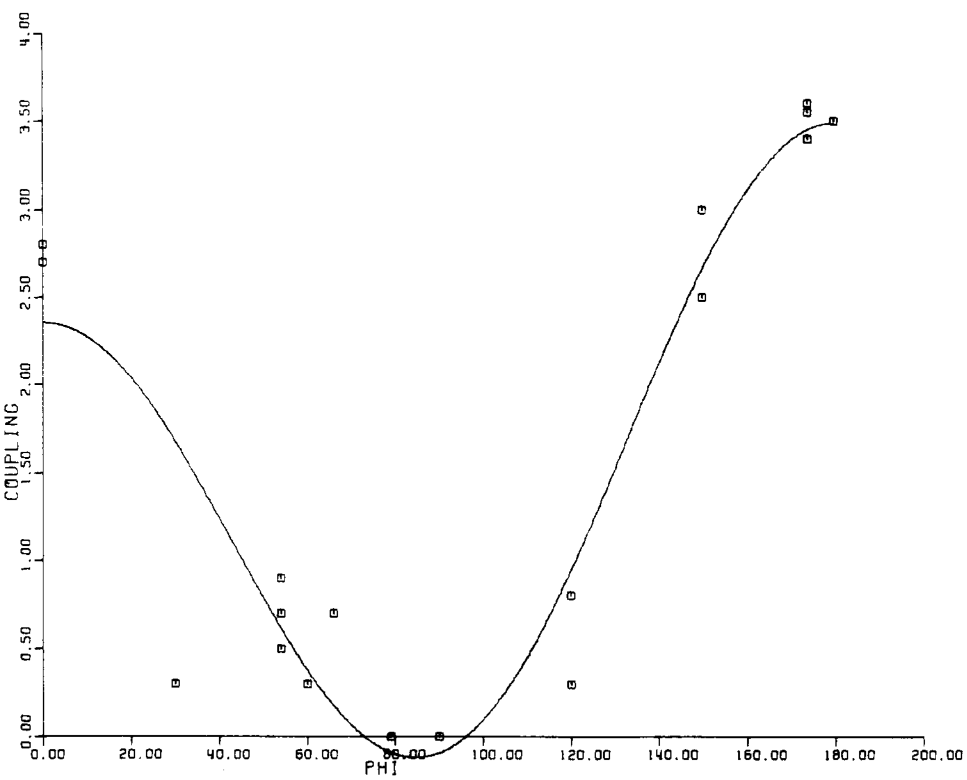


Figure 3. Plot of $J_{^{14}NCCH}$ vs. ϕ for systems I-VIII.

Removal of the catalyst and solvent followed by microdistillation (60 °C, 0.1 mm) afforded a colorless liquid (0.93 g, 92%). An analytical sample was obtained via preparative VPC techniques utilizing a 0.64 cm × 3 m 25% FFAP on Chromosorb W column (column temperature 170 °C): NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 1.18 (m, 2 H, 2,3-endo protons), 2.08 (m, 2 H, 2,3-exo protons), 3.98 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.12 (m, 2 H, 1,4-(bridgehead) protons), 7.05 (m, 4 H, aromatic ring protons); mass spectrum m/e (rel intensity) 218 (5), 217 (29, parent ion), 189 (5), 151 (6), 150 (6), 118 (12), 89 (25), 77 (15), 63 (22), and 51 (26).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 72.17; H, 6.98.

N-Methyl-7-aza-2,3-benzonorbornene (XI). A solution of X (5.0 g, 23 mmol) in dry THF (20 mL) was added dropwise to a stirred solution of lithium aluminum hydride (0.91 g, 24 mmol) in dry THF (30 mL). The resulting mixture was refluxed (8 h) and then quenched with water (1 mL), 10% aqueous sodium hydroxide solution (1 mL), and again with water (3 mL). The reaction mixture was then filtered, and the organic layer was separated from the filtrate. The organic layer was dried (Na_2SO_4), filtered, and then concentrated, affording crude XI. Sublimation (50 °C, 1 mm) afforded pure XI as a waxy solid (3.04 g, 83%): NMR ($CDCl_3$) δ 1.13 (dd, 2 H, J_{5n5x} = ca. 11, J_{5n6x} = ca. 3 Hz, 5,6-endo protons), 2.04 (s, 3 H, NCH_3), 2.12 (m, 2 H, 5,6-exo protons), 4.02 (m, 2 H, 1,4-(bridgehead) protons), 7.12 (s, 4 H, aromatic ring protons); IR (film) 3060 (m), 2980 (m), 1260 (m, sh), and 760 cm^{-1} (s); mass spectrum m/e (rel intensity), 159 (3, parent ion), 132 (24), 131 (100), 130 (24), 116 (18), 115 (12), 90 (14), 89 (15), 77 (10), 65 (5), 63 (9), and 51 (7).

Compound XI was further characterized via its picrate derivative, mp 179-180 °C.

Anal. Calcd for $C_{17}H_{16}N_4O_7$: C, 52.54; H, 4.15. Found: C, 52.68; H, 4.12.

N-Methyl-1:4-ethano-1,2,3,4-tetrahydroisoquinoline (XIII). A solution of N-methyl-1:4-ethano-1,2,3,4-tetrahydro-3-isoquinolone[34] (XII, 700 mg, 3.74 mmol) in ether (10 mL) was added dropwise with stirring to a solution of excess lithium aluminum hydride (200 mg) in ether (50 mL). The resulting solution was refluxed (8 h) and then quenched with water (15 drops). The reaction mixture was then filtered, and the organic layer was separated from the filtrate. The organic layer was then dried (Na_2SO_4), filtered, and concentrated. Microdistillation of the residue (55 °C, 0.1 mm) afforded XIII as a colorless oil (505 mg, 78%): NMR ($CDCl_3$) δ 1.37 (m, 2 H, ethano bridge protons), 1.79 (m, 1 H, ethano bridge proton), 2.21 (m, 1 H, ethano bridge proton), 1.89 (dt, 1 H, J = 13 and ca. 1-2 Hz, $H_{3\text{-syn}}$), 1.98 (s, 3 H, NCH_3), 2.88 (m, 1 H, H_4), 3.28 (dd, J = 13 and ca. 1-2 Hz, 1 H, $H_{3\text{-anti}}$), 3.49 (m, 1 H, H_1), 7.14 (m, 4 H, aromatic ring protons); IR (film) 2930 (m), 2850 (m), 1250 (br), and 750 cm^{-1} (sh); mass spectrum m/e (rel intensity) 173 (7, parent ion), 144 (100), 130 (21), 129 (15), 115 (14), 103 (5), 102 (4), 85 (5), 83 (6), 77 (8), 72 (5), 63 (5), and 51 (5).

Compound XIII was further characterized via its picrate derivative, mp 163.5-165.0 °C.

Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51. Found: C, 53.47; H, 4.38.

5-Methyl-5-N,N-dimethylamino-1,3-dioxane Methiodide (IIIc).[35] 2-Methyl-2-nitro-1,3-propanediol (XIV) was synthesized by a procedure described in the literature.[36] Reaction of XIV with formaldehyde according to a published procedure[12] afforded the corresponding acetal, XV. Reduction of acetal XV with hydrogen over Raney nickel W7[12] afforded the crude amine (XVI). Crude XVI (2.0 g) was refluxed (8 h) with methyl iodide (16 g) in water (20 mL) containing potassium carbonate (6 g). The reaction mixture was then evaporated to dryness, and the residue was continuously extracted with chloroform on a Soxhlet apparatus (8 h). The chloroform extract was concentrated, and the residue was placed on a strongly basic ion exchange column which had been previously charged with 10% aqueous potassium iodide solution. The eluent from the ion exchange column was then concentrated, and the residue was dissolved in ethanol. The resulting ethanol solution was filtered and then concentrated, affording 1.0 g (21%) of IIIc, mp 270 °C. A satisfactory Volhard titration was obtained for IIIc thus prepared.

***trans*-2,5-Dimethyl-5-N,N-dimethylamino-1,3-dioxane Methiodide (IIId).**[35] The reaction of 2-methyl-2-nitro-1,3-propanediol (XIV)[36] with acetaldehyde (benzene-ethanol solvent, p-toluenesulfonic acid catalyst) was performed using the procedure described by Anteunis and Becu.[37] The resulting acetal was reduced using hydrogen over Raney nickel W7,[12] affording a mixture of *cis*- and *trans*-2,5-dimethyl-5-amino-1,3-dioxane. The pure cis and trans isomers were isolated via preparative VPC techniques (Carbowax column; the cis:trans isomer ratio was found to be 70:30). Quaternization of the trans amine using the procedure described above for the preparation of IIIc afforded pure IIId (47%), mp ca. 270 °C. Quaternization of the cis amine afforded the corresponding cis methiodide (74%), mp 258 °C. Satisfactory Volhard titrations were obtained for both methiodides thus prepared.

2,3-Benzonorbornene *exo*-5-Isothiocyanate (XVII). To a solution of benzonorbornadiene[38] (1.0 g, 7 mmol) in benzene were added 50% aqueous sulfuric acid solution (2 mL) and potassium isothiocyanate (1.0 g, 10 mmol). This mixture was stirred at room temperature (2 h), after which time additional potassium isothiocyanate (1 g) and 50% aqueous sulfuric acid solution (2 mL) were added. The resulting mixture was refluxed (1 h). After cooling to ambient temperature, the mixture was diluted with water (50 mL) and extracted with chloroform (2 × 50 mL portions). The combined chloroform extracts were washed first with saturated aqueous sodium bicarbonate solution (50 mL) and then with water (50 mL). The organic layer was dried (Na_2SO_4), filtered, and then concentrated. The residue was microdistilled (50-60 °C, 1 mm), affording XVII as a colorless oil (1.18 g, 84%). Upon standing at room temperature for several days, this oil gradually solidified. Recrystallization of the solid material thereby obtained from ether-pentane afforded pure XVII as colorless plates: mp 35.5-36.0 °C; NMR ($CDCl_3$) δ 1.85-2.2 (m, 4 H, 7, 6-exo, and 6-endo protons), 3.4-3.8 (m, 3 H, 1-, 4-, and 5-endo protons), 7.14 (s, 4 H, aromatic ring protons); IR (KBr pellet) 2980 (m), 2100 (s), 1460 (m), 1320 (m), and 750 cm^{-1} (sh); mass spectrum *m/e* (rel intensity) 201 (89, parent ion), 142 (10), 128 (10), 116 (100), 115 (92), 102 (7), 91 (7), 89 (11), 77 (7), 65 (8), 63 (16), 51 (10), 50 (7), and 39 (16).

Anal. Calcd for $C_{12}H_{11}NS$: C, 71.60; H, 5.51. Found: C, 71.65; H, 5.69.

***exo*-5-*N,N*-Dimethylamino-2,3-benzonorbornene (XVIII).** An ethereal solution of isothiocyanate XVII (1.50 g, 7.46 mmol) was added dropwise to a stirred solution of lithium aluminum hydride (354 mg, 9.33 mmol) in ether (50 mL). The resulting solution was refluxed gently (3 h). Additional lithium aluminum hydride (150 mg, 4.15 mmol) was then added, followed by addition of ethyl formate (750 mg, 10 mmol), and the reaction mixture was refluxed for an additional 8 h. After cooling to ambient temperature, the reaction mixture was quenched with water (0.5 mL); 10% aqueous sodium hydroxide solution was then added (0.5 mL), and an additional quantity of water (1.5 mL) was also added to quench the reaction. The resulting mixture was filtered to remove aluminum salts. The filtrate was then dried (Na_2SO_4), filtered, and concentrated. The residue was microdistilled (60-70 °C, 1 mm), affording XVIII as a colorless oil (650 mg, 47%): NMR ($CDCl_3$) δ 1.3-1.75 (m, 2 H, 6-exo and 6-endo protons), 1.96 and 2.06 (m, 2 H, 7-protons), 2.3 (s, 6 H, $N(CH_3)_2$), 3.28 (m, 1 H, 4-proton), 4.02 (m, 1 H, 1-proton), 7.1 (m, 4 H, aromatic ring protons); IR (film) 2980 (w), 1430 (w), and 750 cm^{-1} (sh); mass spectrum *m/e* (rel intensity) 188 (10), 187 (45, parent ion), 149 (25), 128 (26), 116 (100), 115 (80), 72 (77), 71 (100), 58 (100), 57 (57), and 42 (37).

Compound XVIII was further characterized via its picrate derivative, mp 137-138 °C.

Anal. Calcd for $C_{19}H_{20}N_4O_7$: C, 54.81; H, 4.80. Found: C, 55.12; H, 4.98.

NMR Spectral Measurements. Normal (non-^{14}N-decoupled) ^{1}H NMR spectra (300 MHz) were first obtained at elevated temperature (i.e., at 50 °C for spectra obtained using $CDCl_3$ solvent and at 90 °C for spectra obtained using D_2O solvent) utilizing a Varian HR-300 NMR spectrometer. Estimates of proton chemical shifts and proton-proton coupling constants obtained from these spectra were refined in the following manner. Trial sets of chemical shift and proton-proton couplings obtained from these 300-MHz spectra were used to computer simulate spectra at 100 MHz.[39] The computer-generated spectra were then compared with the corresponding ^{14}N-decoupled NMR spectra which were obtained at 100 MHz using a Varian HA-100 NMR spectrometer equipped with an HD-60 ^{14}N decoupler (manufactured by NMR Specialties Co., New Kensington, Pa.). This procedure was necessitated by the fact that heteronuclear decoupling was available to us only at 100 MHz and not at 300 MHz. In all cases, the final chemical shifts and proton-proton coupling values were considered to be those which afforded a computer-simulated 100-MHz NMR spectrum which was identically superimposable upon the corresponding experimentally obtained ^{14}N-decoupled 100-MHz NMR spectrum. This procedure was then repeated in each case adding an estimated value for $J_{^{14}NCCH}$ until congruence was reached between each computer-simulated spectrum and the corresponding normal (non-^{14}N-decoupled) NMR spectrum. Using this procedure in cases where signals were poorly resolved or where quadrupolar broadening could not be eliminated entirely by raising the temperature, we found that a variation of approximately ±20% in the value of $J_{^{14}NCCH}$ afforded computer-simulated NMR spectra which agreed closely with the corresponding experimentally obtained spectra. We therefore offer this figure as a reasonable estimate of the error in our reported $J_{^{14}NCCH}$ values.

Plot of J vs. φ for Systems I-VIII (Figure 3). The data given in Table I were processed through a computer program[40,41] to fit a curve of the form[11,28] $J = A + B \cos \phi + C \cos 2\phi$. The best equation (mean deviation = 0.24 Hz) was obtained for the following parameters (± standard deviation): $A = 1.41 \pm 0.08$; $B = -0.56 \pm 0.13$; $C = 1.51 \pm 0.12$. The shape of the curve shown in Figure 3 for $0° \leqslant \phi < 60°$ (for which experimental data are sparse) was obtained by assuming the applicability of the Karplus equation.[11,28,42,43] It is further assumed that all vicinal couplings in systems I-VIII have the same relative sign.[11,28,44]

Acknowledgments. One of us (A.P.M.) gratefully acknowledges sabbatical leave support from the U.S. Educational Foundation in Belgium in the form of a Senior Fulbright/Hays Research Fellowship and from the Institut de Chimie, Université de Liège (Belgium), where a portion of the work reported herein was performed. We also thank the University of Oklahoma Research Council for partial support of this study. We are grateful to the referees and to the editors for providing detailed comments which materially aided us in revising the manuscript.

References and Notes

(1) Part 5: A. P. Marchand, D. R. Cornell, R. E. Hopla, B. N. Fowler, D. D. Washburn, and C. C. Zinsser, *Tetrahedron Lett.*, 3277 (1972).
(2) Inquiries should be addressed to either author.
(3) (a) Rijksuniversiteit Gent; (b) University of Oklahoma.
(4) Y. Terui, K. Aono, and K. Tori, *J. Am. Chem. Soc.*, **90**, 1069 (1968).
(5) M. Ohtsuru and K. Tori, *Chem. Commun.*, 750 (1966).
(6) J. M. Lehn and R. Seher, *Chem. Commun.*, 847 (1966).
(7) M. Ueyama and K. Tori, *Org. Magn. Reson.*, **4**, 913 (1972).
(8) K. Tori, T. Iwata, K. Aono, M. Ohtsuru, and T. Nakagawa, *Chem. Pharm. Bull.*, **15**, 329 (1967).
(9) M. Ohtsuru, K. Tori, J. M. Lehn, and R. Seher, *J. Am. Chem. Soc.*, **91**, 1187 (1969).
(10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(11) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(12) R. Van Cauwenberghe, M. Anteunis, and L. Valckx, *Bull. Soc. Chim. Belg.*, **83**, 285 (1974).
(13) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **48**, 12 (1968).
(14) P. A. Cantor and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 970 (1958).
(15) W. R. Dively, G. A. Bunton, and A. D. Lohr, *J. Org. Chem.*, **34**, 616 (1969).
(16) (a) See G. H. Schmid and D. G. Garratt in "The Chemistry of Functional Groups", Supplement A, S. Patai, Ed., Wiley-Interscience, New York, N.Y., 1977, pp 732-744. (b) Addition of hydrogen halides to 2,3-benzonorbornadiene has been studied; see S. J. Cristol and J. M. Sullivan, *J. Am. Chem. Soc.*, **93**, 1967 (1971).
(17) W. R. Wright, Jr., *J. Org. Chem.*, **27**, 1042 (1962).
(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959, pp 102, 216.
(19) M. Witanowski and G. A. Webb, *Annu. Rep. NMR Spectrosc.*, **5a**, 395-404 (1972).
(20) P. G. Gassman and D. C. Heckert, *J. Org. Chem.*, **30**, 2859 (1965).
(21) R. A. Ogg and J. D. Ray, *J. Chem. Phys.*, **26**, 1339, 1340 (1957).
(22) Y. Kawazoe, M. Tsuda, and M. Ohnishi, *Chem. Pharm. Bull.*, **15**, 214 (1967).
(23) J.-F. Bielmann and H. Callot, *Bull. Soc. Chim. Fr.*, 397 (1967).
(24) J. A. Pople, *Mol. Phys.*, **1**, 168 (1958).
(25) J. M. Anderson, J. D. Baldeschwieler, D. C. Dittmer, and W. D. Phillips, *J. Chem. Phys.*, **38**, 1260 (1963).
(26) J. M. Lehn and P. Kintzinger in "Nitrogen NMR", M. Witanowski and G. A. Webb, Ed., Plenum Press, New York, N.Y., 1973, pp 80-161.
(27) See also H. Booth, *Tetrahedron Lett.*, 411 (1965).
(28) (a) S. Karplus and M. Karplus, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 3204 (1972); (b) M. Barfield and H. L. Gearhart, *Mol. Phys.*, **27**, 899 (1974).
(29) W. McFarlane, *J. Chem. Soc. A*, 1660 (1967).
(30) E. W. Randall and D. G. Gilles, *Prog. Nucl. Magn. Reson. Spectrosc.*, **6**, 119-174 (1970).
(31) K. Tori, R. Muneyuki, and H. Tanida, *Can. J. Chem.*, **41**, 3142 (1963).
(32) J. I. Musher, *Mol. Phys.*, **6**, 94 (1963).
(33) P. A. Cantor and C. A. VenderWerf, *J. Am. Chem. Soc.*, **80**, 970 (1958).
(34) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 491 (1971).
(35) With F. Anteunis-De Ketelaere.
(36) B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 34 (1940).
(37) M. Anteunis and C. Becu, *Synthesis*, 23 (1974).
(38) T. F. Mich, E. J. Nienhouse, T. E. Farina, and J. J. Tufariello, *J. Chem. Educ.*, **45**, 272 (1968).
(39) The SIMEQ-16/II computer program, obtained from Dr. M. J. A. de Bie, University of Utrecht, The Netherlands, was used for generating all computer-simulated NMR spectra.

(40) A locally written computer program, NLLSQ, based on the Marquardt algorithm,[41] was used. We thank Dr. Eric Enwall for kindly obtaining for us the computer-drawn plot shown in Figure 3.

(41) D. W. Marquardt, *J. Soc. Ind. Appl. Math.*, **11,** 431 (1963).

(42) The observed values of $J_{^{14}NCCH}$ measured in ^{15}N-enriched amino acids measured approximately at their isoelectric points agree remarkably well with the values predicted on the basis of the curve shown in Figure 3, e.g., $J^{trans}_{^{14}NCCH}$ = 3.6 and $J^{gauche}_{^{14}NCCH}$ = 1.3 Hz.[43]

(43) R. L. Lichter and J. D. Roberts, *J. Org. Chem.*, **35,** 2806 (1970).

(44) $J_{^{14}NCCH}$ values for torsion angles, ϕ, of 60 and 180° are predicted to have *opposite* signs "due to a substituent effect involving the lone pair electrons on the nitrogen and the π-electrons of the carbonyl groups".[28b]

Proton and Carbon-13 Nuclear Magnetic Resonance Studies of the Conformational Dynamic Properties of Seven-Membered Rings. 2,4-Benzodioxepin and Its Derivatives

A. Blanchette, F. Sauriol-Lord, and M. St-Jacques*

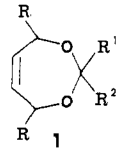
Contribution from the Département de Chimie, Université de Montréal, Montréal, Canada. *Received November 23, 1977*

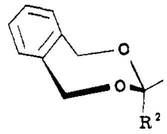
Abstract: The conformational and dynamic properties of 1,3-dioxa-5,6-benzocycloheptene (**5**, 2,4-benzodioxepin) and three of its 2,2-disubstituted and two of its 2-monosubstituted derivatives have been investigated by ^{1}H and ^{13}C DNMR methods. Analysis of the spectra of low temperatures (below coalescence) indicates that the most stable seven-membered ring conformations detected for solutions in CHF_2Cl are C (79%) and TB (21%) for **5**, TB for **6**, **7**, and **8** (the disubstituted derivatives), C for the 2-methyl-derivative (**9**), and TB for the 2-methoxy derivative (**10**). Thus the polar nature of the single methoxy substituent causes a change in the ring conformation as a consequence of the anomeric effect. Free-energy barriers were determined for the chair inversion of **5** (8.0 kcal/mol) and for the twist-boat pseudorotation of **6**, **7**, **8**, and **10** (10.0, 9.0, 9.9, and 6.7 kcal/mol, respectively). The substituent effects on both the conformational and dynamic properties of the seven-membered rings are discussed and explained.

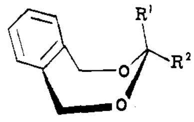
Recent theoretical and expermental investigations[1-5] of the conformational dynamic properties of seven-membered carbocycles have provided much valuable information concerning this fundamental cyclic system. The need for extending such knowledge to rings with heteroatoms has given rise to several studies concerned with the conformation of six-,[6-8] seven-,[9-12] and eight-membered[13] heterocycles containing the OCH_2O unit. However, the results for seven-membered rings have revealed that quantitative experimental characterization is apparently more elusive than for the other two ring systems.

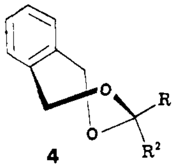
The family of molecules derived from 1,3-dioxacycloheptene (1,3-dioxepin) and 1,3-dioxa-5,6-benzocycloheptene (1,5-dihydro-3*H*-2,4-benzodioxepin[14]) constitutes a fundamental system whose conformational properties compared to those of the cycloheptene–benzocycloheptene system[1,5] should permit characterization of the effects of the OCH_2O, OCHRO, and OCR_2O fragments in the seven-membered ring.

It appears that previous works on this class of molecules have not provided the quantitative results required to fully characterize the important conformational and dynamic effects associated with the OCH_2O unit. On one hand, Gianni and co-workers[11] have studied the carbon-13 magnetic resonance spectra of several methyl and alkyl derivatives of 1,3-dioxacycloheptene (**1**) at ambient temperature. The unknown conformation of the unsubstituted compound used as reference for calculating γ shifts and the impossibility to detect mixtures of conformations significantly limit the scope of their conclusions. On the other hand, preliminary ^{1}H DNMR results[15] at 60 MHz and moderately low temperatures suggested that, among the three possible conformations (chair (**2**), boat (**3**), or twist-boat (**4**)), 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene exists as a twist-boat (TB) whereas the stable conformation of the parent compound was not identified.

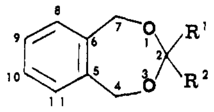

1


2


3


4

In order to gain a more quantitative understanding of the conformational dynamic properties of the seven-membered ring involved we undertook a DNMR investigation of compounds **5–10.** Our specific objectives were first to characterize the conformation(s) of the parent compound (**5**), the 2,2-disubstituted derivatives (**6, 7,** and **8**), and the 2-monosubstituted derivatives (**9** and **10**) and secondly to determine the effect of the various substituents on the ring dynamics. The well-known axial preference of 2-methoxy-1,3-dioxane,[6] because of the anomeric effect, adds special interest to the investigation of **10** whose conformational properties could be determined by this particular effect.



5; $R^1 = R^2 = H$

6: $R^1 = R^2 = CH_3$

7; R^1, R^2 = tetramethylene

8; R^1, R^2 = pentamethylene

9; $R^1 = H$, $R^2 = CH_3$

10; $R^1 = H$, $R^2 = OCH_3$

Consequently we report results from ^{1}H (100 MHz) and ^{13}C

0002-7863/78/1500-4055$01.00/0