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Properties of Bridgehead-Substituted Polycycloalkanes. Synthesis and NMR Analysis of ^{15}N-Labeled 1-Aminobicycloalkanes and Their Hydrochlorides

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Abstract: NMR analysis of adamantane and four bicycloalkanes substituted at the bridgehead with ^{15}N-labeled amino and ammonio groups is described. It is found that where most of the one-bond carbon-nitrogen coupling constants are relatively large, those in 1-aminobicyclo[1.1.1]pentane and its hydrochloride are significantly reduced; in fact, in the latter compound one-bond ^{13}C-^{15}N coupling could not even be detected. Values of experimentally determined vicinal couplings were in accord with those expected on the basis of the number of three-bond pathways available for transmission of spin-spin information; INDO calculations, however, suggest that in the more highly strained systems there is a substantial contribution to ^3J(CN) arising from through-space interactions and that these oppose through-bond effects. Large four-bond ^{15}N-^{1}H couplings were found to occur in 1-aminobicyclo[1.1.1]pentane and its hydrochloride; MO calculations indicate that through-space interactions constitute the predominant mechanism contributing to $^4J(^{15}\text{N}-^1\text{H})$, although in this case through-bond and through-space effects reinforce each other. The nitrogen-15 chemical shifts of the amine hydrochlorides were determined, and they appear to occur in random fashion.

In view of their importance in organic chemistry both ^{1}H and ^{13}C NMR spectroscopy have been the subject of intensive investigation for some time. Examination of less common nuclei has become more prominent over recent years and, of these, nitrogen occupies a unique position because of its importance in biological systems. In earlier work the abundant nuclide, nitrogen-14, was the main focus of attention but, because of its associated quadrupole moment, the ^{14}N nucleus produces signals which are very broad due to the operation of highly efficient relaxation mechanisms. The development of higher sensitivity FT spectrometers, however, has led to major changes in nitrogen NMR spectroscopy so that now the study of the ^{15}N nucleus is much more widespread despite its low natural abundance (0.36%) and low sensitivity (^{15}N vs. ^{1}H = 1:515). Considerable progress in the field has coincided with this change of emphasis.[1-3]

For some years now we have been investigating the NMR properties of bridgehead-substituted polycyclic compounds of the kind displayed in Figure 1. These substrates attracted our attention for the following reasons. On the one hand they represent a sequence of compounds ranging from the essentially strain-free adamantyl system **1** to the highly constrained molecule **5**; this is reflected in the order of increased s character of the exocyclic orbital of the bridgehead carbon along the series. Second, these systems possess rigid carbon frameworks with a well-defined geometry. Finally, structural measurements show that in the more highly strained members the internuclear distance between the bridgehead carbons becomes progressively smaller and the potential for through-space interactions is, therefore, greatly enhanced. Our studies have so far included compounds in which the substituent, X, is magnetically active, generally with nuclear spin $^1/_2$. Our principal objective has been the measurement of the spin-spin coupling constants between the substituent, X, and the various ring carbons with particular emphasis on the magnitude of the one-bond and vicinal couplings, ^1J(CX) and ^3J(CX).

At this stage we have reported our observations on the derivatives X = ^{19}F,[4-6] ^{117,119}SnMe$_3$,[7] ^{13}CH$_3$,[8-10] and COOH.[11] We now discuss the results of our recent study of the ^{15}N-labeled amines **1d-5d** and ammonium salts **1e-5e**.

Results and Discussion

Synthesis of the ^{15}N-Labeled Substrates. In view of their accessibility and versatility, the bridgehead acids **1-5**, X = COOH, were selected as precursors to the required amines. A number of classical rearrangement processes are available for effecting the carboxylic acid → amine transformation. In practice, however, the Hofmann rearrangement was considered to be the only viable procedure for inserting the ^{15}N label because ^{15}NH$_4$Cl, although expensive, is by far the most economical of the reagents required for the possible alternative sequences. Operational difficulties are frequently encountered in performing the traditional Hofmann reaction,[12] but we were able to circumvent the procedure normally employed in both aqueous or nonaqueous media by adopting a rather different approach reported recently[13] to be applicable to aliphatic amides. In this modification, the amide is treated at room temperature with iodosobenzene in aqueous acetonitrile containing formic acid.

$$\text{RCOOH} \xrightarrow{a} \text{RCOCl} \xrightarrow{b} \text{RCO}^{15}\text{NH}_2 \xrightarrow{c,d} \text{R}^{15}\text{NH}_3\text{Cl}$$

(a) SOCl$_2$; (b) ^{15}NH$_4$Cl, CHCl$_3$, aq NaOH; (c) PhIO, aq CH$_3$CN, HCOOH; (d) dil HCl

As a precautionary note, our experience is that yields in the final step are most satisfactory, as long as freshly prepared iodosobenzene is used.

NMR Data. Measurements of NMR parameters were performed on substrates with 99% ^{15}N isotopic enrichment.

Chemical Shifts. Carbon-13 chemical shifts in the amines and ammonium salts are collected in Table I. Included also are the substituent chemical shifts (SCS) from which it can be seen that the amino and ammonio groups are responsible for some quite large paramagnetic and diamagnetic shifts of the ring carbons.

Attention is drawn to some of the more interesting observations. First, the magnitude of the α-effect of the NH$_2^+$ group varies quite markedly along the series **1e-5e**; it is noticeable that as the carbon to which the substituent is attached assumes more s character,

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Table I. Carbon-13 and Nitrogen-15 Chemical Shifts in the ^{15}N-Labeled Amines **1d–5d** and Ammonium Compounds **1e–5e**

compd	^{13}C shifts[a,b]					^{15}N shifts[a,c]
	C1	C2,8,9	C3,5,7	C4,6,10		
1d	46.97 (18.27)	46.48 (8.28)	28.12 (−0.58)	36.51 (−1.69)		
1e	54.64 (25.94)	41.27 (3.07)	29.90 (1.20)	35.90 (−2.30)		37.75 (31.45)
	C1	C2,6,7	C3,5,8	C4		
2d	46.27 (22.27)	35.00 (9.00)	27.03 (1.03)	24.43 (0.43)		
2e	53.15 (29.15)	30.17 (4.17)	26.11 (0.11)	24.00 (0.00)		33.31 (28.78)
	C1	C2,6	C3,5	C4	C7	
3d	62.46 (25.86)	37.05 (7.05)	30.82 (0.82)	36.51 (−0.09)	46.27 (7.67)	
3e	62.68 (26.08)	32.99 (2.99)	30.27 (0.27)	36.24 (−0.34)	41.77 (3.17)	21.62 (21.00)
	C1	C2,6	C3	C4	C5,6	
4d	63.04 (23.54)	32.04 (5.74)	29.25 (2.95)	32.04 (−7.46)	46.10 (7.10)	
4e	58.94 (19.44)	28.82 (2.52)[d]	28.28 (1.98)[d]	34.24 (−5.26)	42.15 (3.15)	23.23 (19.78)
	C1	C2,4,5	C3			
5d	53.04 (19.49)	53.31 (2.56)	21.72 (−11.87)			
5e	46.17 (12.58)	52.06 (2.31)	24.28 (−9.31)			25.65 (19.07)

[a] ±0.02 ppm. Shifts determined on **1d–5d** in C_6D_6 solution, and on **1e–5e** in water. [b] Values in parentheses are the substituent-induced chemical shifts (SCS). [c] In aqueous solution, downfield from $^{15}NH_4Cl$. Values in parentheses refer to CH_3–carbon chemical shifts in the corresponding methyl-substituted hydrocarbon in $CDCl_3$ (ref 9). [d] May be interchanged.

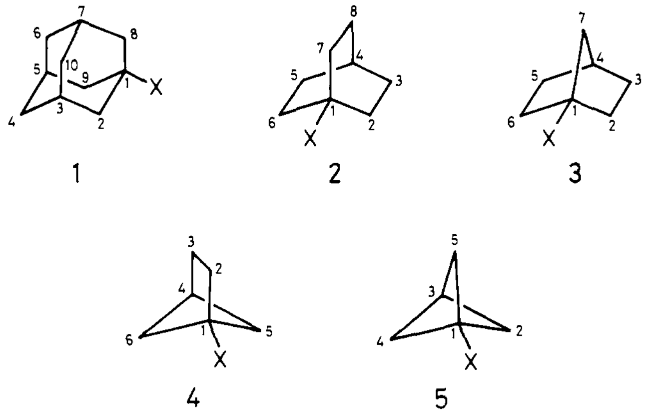

Figure 1. **a**, X = F; **b**, *x* = $SnMe_3$; **c**, X = $^{13}CH_3$; **d**, X = $^{15}NH_2$; **e**, X = $^{15}NH_3^+$.

the deshielding influence of the ammonio group decreases. This behavior was typical also of the fluorides **1a–5a**.[5] Yet, in the free amines **1d–5d**, the deshielding influence of the NH_2 group is consistently large throughout the series.

The chemical shifts of the γ-carbons were found to fluctuate widely. On the one hand the non-bridgehead γ-carbon atoms, C3 in **1d–4d** and **1a–4e**, are shielded only slightly with introduction of the NH_2 and NH_3^+ groups. Similar remarks apply to the bridgehead carbons, C4 in **3d** and **3e**. However, as the systems become more constrained, these highly electronegative antiperiplanar substituents were found to induce large diamagnetic perturbations in the γ-bridgehead carbons. Thus, for example, the SCS of C4 in **4d** and C3 in **5d** is −5.3 and −9.3 ppm, respectively! The effect of the amino group is even more pronounced; in the amines **4e** and **5e** those bridgehead carbons are deshielded by −7.5 and −11.9 ppm. It is tempting to speculate that this phenomenon is a manifestation of through-space orbital interactions associated with the bridgehead carbons in **4** and, more importantly, in **5**. The proximity of the C1 and C3 carbon atoms in bicyclo[1.1.1]pentane, for example, has been suggested[14] to produce favorable rear-lobe overlap of the exocyclic orbitals associated with these carbons, and this is thought[15] to account for the dramatic enhancement of the H1–H3 coupling.[16] The enormous upfield shift of C3 in 1-fluorobicyclo[1.1.1]pentane has also been interpreted[5] as evidence for the operation of such through-space interaction, the existence of which is supported by the results of INDO MO calculations, as discussed below.

^{15}N chemical shifts in the ammonium salts **1e–5e** are also included in Table I. In order to assess chemical-shift behavior of ammonium salts, it has been suggested[17] that the ^{15}N shifts be compared with ^{13}C shifts of the carbons in structurally analogous hydrocarbons. Indeed, a linear correlation between ammonium salts and their hydrocarbon counterparts has been observed[17] to occur in several aliphatic series, suggesting that similar phenomena account for the ^{15}N shifts. From the data in Table I it can be seen that while the ^{15}N and ^{13}C shifts of the substrates **1e–5e** and **1c–5c**[9] are broadly interrelated, there is considerable divergence in the case of the more constrained systems. Whether this is significant or whether it merely reflects the inclusion of solvent effects, for instance, is difficult to say.

Coupling Constants. Spin–spin coupling is a valuable source of information in relation to the types of bonding and structure in organic compounds. Already a fairly extensive tabulation of ^nJ(CN) values exists,[18] and it appears that the magnitude of ^{13}C–^{15}N coupling frequently depends on the hybridization state of the nitrogen atoms as well as the proximity of the nitrogen lone pair to the spin-coupled carbon atom. Values of the coupling constants, ^nJ(CN), in the substrates **1d–5d** and **1e–5e** involved in this study are assembled in Table II. The interesting feature of coupling between directly bonded nuclei is the extent to which such coupling is dominated by Fermi contact. Under those circumstances, ^1J(CX) is directly proportional to the product of the s electron densities of the coupled nuclei. Although a satisfactory correlation between one-bond carbon–nitrogen coupling constants and hybridization has been observed in a limited number of cases,[19] this behavior is by no means general,[20] nor is it supported on theoretical grounds. Certainly, in the case of the substrates **1d–5d** and **1e–5e** which provide a useful array of compounds of increasing s character at the bridgehead, no such relationship exists. In particular, the values of ^1J(CN) in the derivatives of both bicyclo[2.1.1]hexane and bicyclo[1.1.1]pentane show considerable deviation, and this is demonstrated quite comprehensively in the latter system which on the basis of previous experience was expected to display the largest directly bonded coupling. Thus, where ^1J(CN) varies between 3.9 and 4.9 Hz in **1d–4d**, the experimental value of ^1J(CN) in **5d** is 1.33 Hz. The results obtained for the

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Table II. ^{13}C–^{15}N Coupling Constants, $^{n}J(CN)$,[a] in the Amines **1d–5d** and Ammonium Salts **1e–5e**

compd	^1J	^2J	^3J	^4J
1d	3.91	1.64 (C2,8,9)	1.50 (C3,5,7)	ncd (C4,6,10)[b]
1e	3.50	ncd (C2,8,9)	1.47 (C3,5,7)	ncd (C4,6,10)
2d	4.43	1.80 (C2,6,7)	1.50 (C3,5,8)	0.25 (C4)
2e	4.57	0.29 (C2,6,7)	1.54 (C3,5,8)	0.19 (C4)
3d	4.93	2.32 (C2,6); 1.44 (C7)	1.49 (C3,5); 1.37 (C4)	
3e	5.05	0.88 (C2,6); 0.66 (C7)	1.58 (C3,5); 1.99 (C4)	
4d	4.28	3.09 (C2); 1.29 (C5,6)	1.37 (C3); 3.09 (C4)	
4e	3.56	1.26[c] (C2); ncd (C5,6)	1.24[c] (C3); 4.03 (C4)	
5d	1.33	1.46 (C2,4,5)	4.63 (C3)	
5e	ncd	0.31 (C2,4,5)	5.49 (C3)	

[a] In Hz, ±0.02 Hz. [b] ncd ≡ no coupling detected ($J \leq 0.2$ Hz). [c] Could be interchanged.

Table III. Experimental and Calculated Values of Vicinal ^{13}C–^{15}N Coupling Constants[a] in the Salts **1e–5e**

compd	coupled atom	J, Hz exptl	J, Hz calcd[b]	θ,[c] deg	bridgehead C···C dist, Å
1e	C3	1.47		180	
2e	C3	1.54	2.75	180	
3e	C3	1.58	2.71	153.7	
3e	C4	1.99	3.51	180	2.32
4e	C3	1.24	2.52	180	
4e	C4	4.03	4.81	173.6	2.17
5e	C3	5.57	5.63	180	1.85

[a] ±0.02 Hz. [b] INDO SCF MO calculation (see text). [c] N-C-C-C dihedral angle.

(a) 6.11 Hz (b) 8.18 Hz (calc. 18.84 Hz)

Figure 2. Experimental values of $^4J(^{15}N–^1H)$ in (a) 1-[^{15}N]-aminobicyclo[1.1.1]pentane and (b) its hydrochloride, with the calculated value for the latter in parentheses.

hydrochlorides **1e–5e** were even more surprising. The one-bond couplings in **1e–4e** lie in the range 3.5–5.0 Hz, yet in 1-ammoniobicyclo[1.1.1]pentane (**5e**) coupling between C1 and ^{15}N was not detected at all! These results are consistent with the view[20a,21] that the orbital and spin–dipolar terms frequently make a substantial contribution to directly bonded carbon–nitrogen coupling; indeed they are often dominant.[22] Presumably, the absence of any coupling in the case of **5e** represents fortuitous cancellation of the three factors responsible for transmission of spin–spin coupling.

Our interest in the magnitude of vicinal carbon–nitrogen coupling in the amines and their hydrochlorides arose from the possibility that $^3J(CN)$ might conceivably be influenced by through-space interactions involving the bridgehead carbons. We had previously demonstrated such effects to be highly significant in connection with vicinal couplings in the parent hydrocarbons **1–5** (X = H),[10] the bridgehead fluorides **1a–5a**,[5,6] and the ^{13}C-labeled methyl derivatives **1c–5c**.[8-10] For clarity, the values of $^3J(CN)$ in the ammonium salts **1–5e** are reproduced in Table III. Listed with the experimentally determined data are those obtained from MO calculations based on the finite perturbation theroy[23] in the INDO approximation of SCF MO theory,[24] together with other relevant geometric parameters. It is noteworthy that vicinal coupling between ^{15}N and the *non-bridgehead* carbons, C3, in **1e–3e** is essentially constant at ca. 1.5 Hz, with ^3J(C3-N) in **4e** a little smaller (1.24 Hz). In contrast the values of $^3J(^{13}C_{bridgehead}–^{15}N)$ are considerably enhanced, being 1.99 Hz in **3e**, 4.03 Hz in **4e**, and 5.57 Hz in **5e**. In fact, the ratio of these values corresponds to that expected on the basis of the number of vicinal pathways available in the molecules, there being two such pathways in **4e** and three in **5e**. Although calculations were not performed on the amines **1d–5d**, reference to Table II shows that the experimentally determined vicinal coupling constants in the free amines follow similar trends to those observed in their hydrochlorides. For the latter, it is interesting to find that the observed and calculated[25] vicinal couplings are in very good agreement. Furthermore, modified calculations[26] allow an estimate to be made of the contributions to the coupling attributable to through-space interactions, by setting elements of the Fock matrices associated with orbitals centered on the bridgehead carbons equal to zero in each SCF cycle. It is found that the through-space effects determined in this way can be quite large, particularly in the bicyclo[1.1.1]pentyl system. For example, in the bicyclic compounds **3e–5e** the through-bond contribution to $^3J(^{13}C_{bridgehead}–^{15}N)$ is computed to be 3.94, 7.12, and 18.42 Hz, respectively. The component of the coupling calculated to arise from through-space interactions, which for these substrates opposes that transmitted through the σ bond framework, is −1.95, −3.09, and −12.79 Hz.

Finally, an interesting observation in the ^1H NMR spectra of 1-aminobicyclo[1.1.1]pentane (**5d**) and its protonated form **5e** concerns the extent of four-bond coupling between ^{15}N and the proton on the unsubstituted bridgehead carbon (Figure 2). $^{15}N^1H$ couplings beyond three bonds are invariably small and are said[27] to require the intervention of a π-system to be detected. The large values of $^4J(^{15}N–^1H)$ observed in **5d** and **5e** are ascribed to the operation of interorbital interactions between the bridgehead carbons referred to above; MO calculations support this contention. Although the value of $^4J(NH)$ in **5e** so determined is considerably overestimated (18.84 Hz), the calculations suggest that this is predominantly the result of through-space transmission of coupling information; the contribution via this mechanism is estimated to be 16.8 Hz. Interestingly, in this case through-space and through-bond effects are predicted to reinforce each other.

Experimental Section

^1H, ^{13}C, and ^{15}N NMR spectra were measured on a JEOL FX90Q instrument operating at 89.56, 22.53, and 9.04 MHz, respectively. ^1H and ^{13}C NMR spectra were obtained on the amines dissolved in C_6D_6 which also served as internal lock; chemical shifts are referenced to Me_4Si. Samples of the ammonium salts were dissolved in water and placed in 5-mm sample tubes equipped with a coaxial capillary tube

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containing C_6D_6 which provided the lock and which contained Me_4Si as external reference for ^{13}C chemical shift deteminations; $^{15}NH_4Cl$ was added to the aqueous solution for ^{15}N chemical shift referencing. For chemical shift measurements, spectra were run under conditions corresponding to 0.04-ppm digital resolution. Accurate determination of coupling constants was performed by running spectra at 200–400 Hz spectral width with 16K/32K data points, giving 0.02-Hz digital resolution. Mass spectra were obtained on an AEI MS30 spectrometer. [^{15}N]Ammonium chloride (99% enriched) was purchased from Amersham International, U.K.

1-[^{15}N]Aminoadamantane Hydrochloride (1e). A solution of adamantane-1-carboxylic acid[28] (1.65 g) in thionyl chloride (10 mL) was heated under reflux for 2 h. Excess reagent was removed under reduced pressure, and the crude adamantane-1-carbonyl chloride (1.80 g) was dissolved in ethanol-free chloroform (50 mL) and added to a cold (0 °C) solution of [^{15}N]ammonium chloride (0.55 g) in 1.6 M sodium hydroxide (15 mL). The two-phase mixture was stirred vigorously at 0 °C for 2 h and then allowed to warm to room temperature. The organic layer was washed with saturated sodium chloride solution and then dried ($MgSO_4$) and concentrated, giving [^{15}N]adamantane-1-carboxamide (1.40 g, 78%), mp 186–187 °C (sealed tube), after sublimation (lit.[29] mp 189 °C). Freshly prepared iodosobenzene[30] (1.87 g) was added to a solution of the amide (1.32 g) in acetonitrile (12 mL) and water (4 mL). The mixture was stirred vigorously while formic acid (1.1 mL) was added dropwise, and stirring was continued at ambient temperature for 12 h before the mixture was diluted with 1 M hydrochloric acid (30 mL). The mixture was extracted with ether, and the aqueous phase was then concentrated under reduced pressure to dryness. The white solid was recrystallized from ethanol/ether to give 1-[^{15}N]aminoadamantane hydrochloride (0.95 g, 67%) which did not melt below 350 °C (lit.[29] mp > 360 °C).

Treatment of an aqueous solution of **1e** with sodium hydroxide generated the free amine (**1d**) which was extracted with benzene-d_6 and used immediately without isolation for NMR measurements.

1-[^{15}N]Aminobicyclo[2.2.2]octane Hydrochloride (2e). Bicyclo[2.2.2]octane-1-carboxylic acid[31] (2.57 g) was similarly converted into the acid chloride which was purified by distillation (Kugelrohr 130 °C (15 mmHg) (lit.[32] bp 101–103 °C (13 mmHg). Treatment of the acid chloride (1.25 g) in chloroform (70 mL) with 5% sodium hydroxide solution (27 mL) and $^{15}NH_4Cl$ (0.91 g) as described above gave [^{15}N]-bicyclo[2.2.2]octane-1-carboxamide (1.1 g, 83%) which was essentially pure, mp 179–180 °C (sealed tube) (lit.[33] mp 177–178 °C), after recrystallization from benzene/hexane. A solution of the amide (0.93 g) and iodosobenzene (2.4 g) in water (5 mL) containing acetonitrile (15 mL) was treated with formic acid (1.8 mL) as outline above. Workup afforded 1-[^{15}N]aminobicyclo[2.2.2]octane hydrochloride (**2**) (1.05 g, 88%), mp 346–348 °C (lit.[38] mp 350 °C), after recrystallisation from ethyl acetate.

The free base **2d** was generated as described above and isolated with benzene-d_6.

1-[^{15}N]Aminobicyclo[2.2.1]heptane Hydrochloride (3e). Bicyclo[2.2.1]heptane-1-carboxylic acid (1.1 g)[34] was treated with thionyl chloride (15 mL) giving the acid chloride, bp 84–86 °C (14 mmHg), which was dissolved in chloroform (70 mL) and treated with $^{15}NH_4Cl$ (0.36 g) in 1.2 M aqueous sodium hydroxide (10 mL) as above. Workup gave [^{15}N]bicyclo[2.2.1]heptane-1-carboxamide (0.71 g, 64%), mp 233.5–234.5 °C (lit.[34] mp 234–236 °C), after sublimation. The amide (0.70 g) in acetonitrile (15 mL) and water (5 mL) containing iodosobenzene (2.42 g) was treated with formic acid as above. The mixture was worked up as before, yielding 1-[^{15}N]aminobicyclo[2.2.1]heptane hydrochloride (**3e**) (0.53g, 71%), mp > 350 °C.

The free base **3d** was obtained from the hydrochloride in the usual way and taken up into benzene-d_6 for NMR measurements.

1-[^{15}N]Aminobicyclo[2.1.1]hexane Hydrochloride (4e). Bicyclo[2.1.1]hexane-1-carboxylic acid[35] (1.46 g) was treated with thionyl chloride as outlined above, and the derived product was dissolved in dry dichloromethane (20 mL) and added to an ice-cold solution of [^{15}N]ammonium chloride (0.70 g) and 5% sodium hydroxide (20 mL) with stirring as described. Sublimation of the crude product gave [^{15}N]bicyclo[2.1.1]hexane-1-carboxamide (1.3 g, 90%), mp 236–240 °C (lit.[36] mp 236.6–238.4 °C). The amide (110 mg) in acetonitrile (10 mL) and water (4 mL) containing iodobenzene (0.35g) was treated with formic acid (0.2 mL) under conditions referred to above. Workup yielded a solid which upon trituration with ethyl acetate gave 1-[^{15}N]aminobicyclo[2.1.1]-hexane hydrochloride (**4e**) (65 mg, 55%), mp 236–238 °C (lit.[36] mp > 250 °C).

Treatment of **4e** with aqueous sodium hydroxide liberated the amine **4d** which was extracted with benzene-rd_6 and used immediately for spectral measurements.

Bicyclo[1.1.1[]pentane-1-carboxamide. 3-Carbomethoxybicyclo[1.1.1]pentane-1-carboxylic acid[37] was converted into bicyclo[1.1.1]-pentane-1-carboxylic acid as described.[38] Treatment of the latter (1.5 g) with thionyl chloride gave the acid chloride which was dissolved in dichloromethane (20 mL) and added dropwise to concentrated aqueous ammonia (sp. gr. 0.88; 50 mL) at 0 °C with vigorous agitation. The mixture was allowed to attain ambient temperature, and stirring was continued for a further 1 h, after which the organic phase was separated. The aqueous layer was extracted with fresh solvent, the combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was evaporated, giving bicyclo[1.1.1]pentane-1-carboxamide (1.00 g, 67%) which was practically pure. A sublimed sample had mp 202–203 °C. Accurate mass (C_6H_8NO) M - 1 calcd 110.0606, found 110.0604. ^{1}H NMR ($CDCl_3$) δ 5.67 (br s, 2 H) 2.50 (s, 1 H) 2.12 (s, 6 H). ^{13}C NMR: ($CDCl_3$) δ 172.5 (C=O), 51.14 (C2,C4,C5), 44.10 (C1), 26.92 (C3).

1-[^{15}N]Aminobicyclo[1.1.1]pentane Hydrochloride (5e). Bicyclo[1.1.1]pentane-1-carboxylic acid (1.00 g) was converted into the acid chloride, as above, and then treated with a mixture of $^{15}NH_4Cl$ (0.54 g) in 5% aqueous sodium hydroxide (14 mL) under the conditions above. Workup produced [^{15}N]bicyclo[1.1.1]pentane-1-carboxamide (0.56 g, 56%) whose properties were in accord with those of the natural isomer above. The amide was transformed into the salt **5e** by reaction with iodosobenzene under the conditions specified above. 1-[^{15}N]Aminobicyclo[1.1.1]pentane hydrochloride (0.30 g, 60%) had mp > 350 °C after recrystallization from ethanol/ethyl acetate. ^{1}H NMR: (D_2O) δ 2.58 (d, 1 H, J = 8.2 Hz) 2.03 (s, 6 H) (lit.[39] δ 2.61, 2.06).

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