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CONFORMATIONAL STUDIES OF QUATERNARY AMMONIUM IONS—I

^{1}H NMR STUDY OF β-SUBSTITUTED ETHYLTRIMETHYLAMMONIUM HALIDES: IMPORTANCE OF ELECTROSTATIC INTERACTION IN CONFORMATION CONTROL[a]

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Abstract—Conformations of several β-substituted ethyltrimethylammonium halides in deuterium oxide have been studied by ^{1}H NMR spectroscopy. It has been found that acetylcholines (**1a** and **1b**) and cholines (**1c** and **1d**) predominantly adopt the gauche conformation, whereas trimethyl-*n*-propyl- as well as β-phenylethyltrimethylammonium ions (**1h** and **1g**, respectively) have the trans form. The β-cyanoethyl as well as the β-chloroethyl derivatives (**1f** and **1e**, respectively) are almost equally populated by both forms. Factors controlling these conformations are discussed and the importance of electrostatic interaction is proposed.

Conformations of choline analogues have frequently been investigated because of the interesting biological activities of the compounds. The overwhelming predominance of the gauche form of acetylcholine and choline in solutions and the gauche form in crystals were presented on the bases of ^{1}H NMR[1-3] and IR[4] spectroscopic data, and X-ray analyses,[5] contrary to the expectation that a strong steric effect is caused in the gauche form (see Fig 1). On the other hand, thiocholine and acetylthiocholine, which have structures isoelectronic with choline and acetylcholine, respectively, were shown to exist in the trans form in crystals,[6] and predominantly in trans form in D_2O.[2,3] Several authors[4,5,7-10] have hitherto attempted to rationalise these phenomena, but the situation is not a simple one. The conformations of various choline analogues in solutions[10-12] and in crystals[13-15] have been investigated.

Recently, Partington and coworkers have reported a comprehensive ^{1}H NMR study of the conformations of a variety of choline-type molecules in aqueous solutions to discuss the factors controlling their conformations and to examine the correlation between the conformations and the potency of action of the drugs at either the nicotinic or muscarinic receptor.[16] They stated that the gauche conformations depend on the presence of the onium group and the partial negative charge on the β-oxygen.[16] Their paper has prompted us to present here our discussion about the factors controlling their conformations on the basis of the results on population analyses on several β-substituted ethyltrimethylammonium halides by ^{1}H NMR spectroscopy according to a slight modification of the method proposed by Abraham and coworkers.[17] As a result, the importance of electrostatic interaction in the conformation control of this type of molecules will be proposed.

In order to clarify what factors mainly control the conformation of those molecules, we have analysed the 100-MHz ^{1}H NMR spectra of β-cyanoethyltrimethylammonium bromide (**1f**) and trimethyl-*n*-propylamonium bromide (**1h**) as well as those of acetylcholine chloride (**1a**) and bromide (**1b**), choline chloride (**1c**) and bromide (**1d**), chlorocholine chloride (**1e**), and β-phenylethyltrimethylammonium bromide (**1g**) for comparison of their spectra under the same conditions to obtain information about vicinal ^{1}H, ^{1}H spin coupling constants, $J_{H,H(vic)}$. The angular dependence of vicinal spin-coupling constants between ^{14}N and ^{1}H, $J_{^{14}N,H(vic)}$[18] that can be observed in quaternary ammonium ions can also be used to test the validity of results, as has also been employed previously.[11,16] In addition, a comparison of direct coupling constants between ^{13}C and ^{1}H, $J_{^{13}C-H'}$ of the methyl groups on the quaternary nitrogen of the series of molecules under study may give some information about factors controlling their conformation.

In general, ^{14}N,^{1}H spin couplings cannot be observed because of the effect of quadrapolar relaxation of ^{14}N. In some ammonium ions, however, the couplings are clearly observed because the electric-

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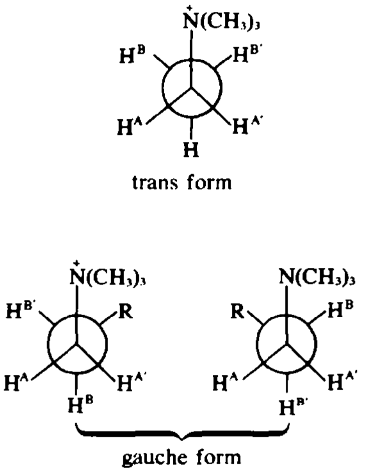

$(CH_3)_3\overset{+}{N}CH_2(A)CH_2(B)R\cdot X^-$
1a: R = OCOCH$_3$, X = CL
1b: R = OCOCH$_3$, X = Br
1c: R = OH, X = Cl
1d: R = OH, X = Br
1e: R = Cl, X = Cl
1f: R = CN, X = Br
1g: R = C$_6$H$_5$, X = Br
1h: R = CH$_3$, X = Br

Figure 1. Newman projection of gauche and trans forms of β-substituted ethyltrimethylammonium ions.

field gradient around ^{14}N is highly symmetrical.[18a] Further, in the ^{1}H NMR spectra of the molecules examined, signals due to the —CH$_2$CH$_2$-groups were found as complicated multiplets owing to observable $J_{^{14}N,H}$'s, as shown in Fig 2. In their ^{1}H,^{14}N-double resonance spectra, however, typical AA'BB' spectral patterns clearly appeared, except in that of **1h** which showed an AA'BB'C$_3$ spectral pattern. Two vicinal coupling constants, $J(J_{AB})$ and $J'(J_{AB'})$, were obtained by computer analysis of these spectral patterns using the LAOCOON II program.[19] Some of the calculated double resonance spectra are reproduced in Fig 2. Thus, $J_{^{14}N,H(vic)}$ values were obtained by first order analysis of the observed spectra by comparing them with the calculated spectral lines for ^{1}H,^{14}N-double resonance spectra.

According to the reported method,[17a] the relationship of Eq (1) was applied in the present calculations. Approximate populations of the gauche and the trans form, P_g and P_t, can easily be estimated by Eqs (3), (4), and (5), if the relationship of Eq (2) is assumed, and if a set of correct values for vicinal ^{1}H,^{1}H coupling constants for CH$_2$CH$_2$ fragments in the gauche and trans relationships, J_g° and J_t° respectively, can be determined for one of the molecules examined.

$$2J + J' = 2J_g + J_t = \text{const} \tag{1}$$

$$\Delta J_g \simeq \Delta J_t \simeq \Delta J_{av} \tag{2}$$

here,

$$\Delta J_g = J_g - J_g^\circ, \quad \Delta J_t = J_t - J_t^\circ,$$

and

$$\Delta J_{av} = \{(2J_g + J_t) - (2J_g^\circ + J_t^\circ)\}/3$$

$$= \{(2J + J') - (2J_g^\circ + J_t^\circ)\}/3 = J_{av} - J_{av}^\circ$$

$$J_g \simeq J_g^\circ + \Delta J_{av} \tag{3}$$

$$J_t \simeq J_t^\circ + \Delta J_{av} \tag{4}$$

$$P_g = 1 - P_t = (J_t - J')/(J_t - J_g) \tag{5}$$

The values for ΔJ_{av} can be understood by considering the electronegativity effect of substituents on the 1,2-disubstituted ethyl fragment.[17] Strictly speaking, ΔJ_g may not be equal to ΔJ_t. But in general, the difference between them is considered to be very small.* Thus, we may use the relationship of Eq (2) to estimate an approximate population. Culvenor and Ham[1] reported that an ^{1}H NMR spectral analysis of acetylcholine in D$_2$O revealed the overwhelming predominance of the gauche conformation, and that this lead to values of 2·5 and 11·4 Hz for J_g and J_t, respectively, assuming that P_g is 1. These values are considered to be correct by comparison with the corresponding J_g and J_t values obtained from a rigid system.[20] We followed this result with **1a** in the manner described above to obtain values of 2·56 and 11·64 Hz for J_g° and J_t°, respectively. Using these values, relative populations of the gauche and the trans forms of the other molecules under study were calculated.†

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*The data used to observe the effect of electronegativity of substituents on $J_{H,H(vic)}$ of rigid molecules indicate the small contribution of dihedral angle on J, to support $\Delta J_g \simeq \Delta J_t$; see for example, N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, Holden-Day, San Francisco, Calif., p. 53 (1964).

†Recently, a similar attempt with analogues of acetylcholine was reported by A. Makriyannis, R. F. Sullivan and H. G. Mautner (see *Proc. Nat. Acad. Sci. USA*, **69**, 3416 (1972)).

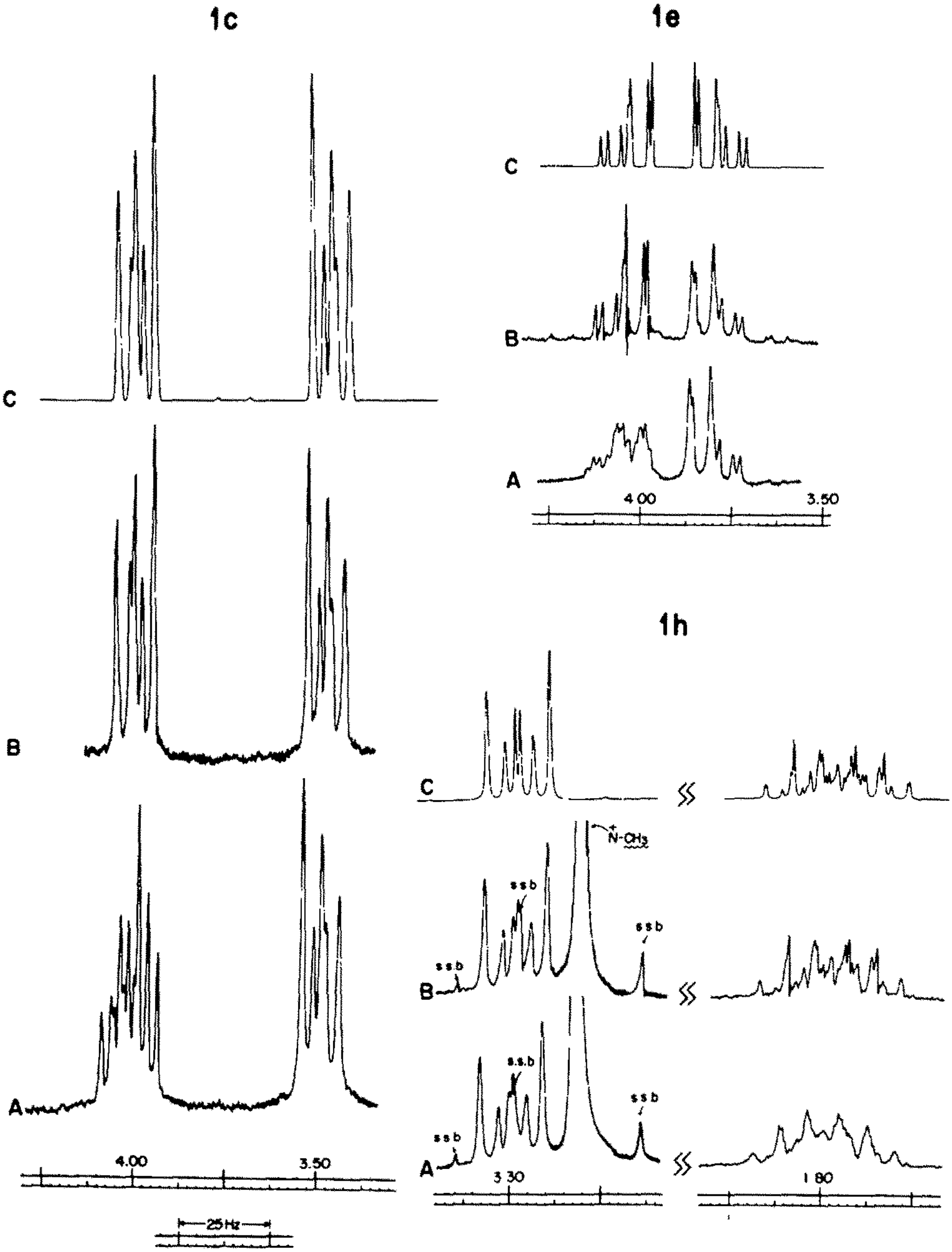

Figure 2. The ^{1}H NMR spectra of **1c**, **1e**, and **1h** in D_2O at 50° at 100 MHz. A: normal spectra B: ^{1}H, ^{14}N-double resonance spectra C: calculated spectra.

The NMR parameters obtained are listed in Table 1 together with the populations estimated.* The $J_{^{13}C-H}$ values of the methyl groups on the quaternary nitrogen were determined by measurements of their ^{13}C-satellite peaks in ^{1}H NMR spectra of the compounds examined.

As seen from Table 1, it was found that **1a–1d** predominantly adopt the gauche forms as reported so far,[16] whereas **1g** and **1h** have predominantly trans conformations, and **1e** and **1f** are almost equally populated by both conformations.

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*The exact method of Abraham and Gatti[17b] gave almost the same results.

Table 1. ^{1}H NMR parameters and estimated populations

Compds.	Solvents	δ_A (ppm)	δ_B (ppm)	$J_{AA'}$ (Hz)	$J_{BB'}$ (Hz)	J (Hz)	J′ (Hz)	$J_{^{14}N,H(vic)}$ (Hz)	$J_{^{13}C-H}$ (Hz)	P_g (%)	P_t (%)
1a	D_2O	3·74	4·55	−11·4	−11·5	$7{\cdot}1_0$ $(6{\cdot}9_3)^b$	$2{\cdot}5_6$ $(2{\cdot}3_5)^b$	2·5 $(2{\cdot}6)^b$	144·5	100^a $(100)^b$	0^a $(0)^b$
1a	CF_3COOD	3·80	4·72	−11·0	−11·3	$7{\cdot}0_1$	$2{\cdot}6_3$	2·5	144·5	99·6	0·4
1b	D_2O	3·74	4·55	−11·4	−11·5	$7{\cdot}1_0$	$2{\cdot}5_6$	2·5	144·5	100^a	0^a
1c	D_2O	3·50	4·03	−11·2	−11·3	$6{\cdot}8_1$ $(6{\cdot}56)^b$	$3{\cdot}3_7$ $(3{\cdot}55)^b$	2·3 $(2{\cdot}7)^b$	144·7	92·0 $(89{\cdot}0)^b$	8·0 $(11{\cdot}0)^b$
1d	D_2O	3·50	4·03	−11·2	−11·3	$6{\cdot}8_1$	$3{\cdot}3_7$	2·3	144·7	92·0	8·0
1e	D_2O	3·81	4·05	−11·4	−11·6	$6{\cdot}7_9{}^c$ or $6{\cdot}3_4$ (6·42 and 6·53)^b	$6{\cdot}3_4{}^c$ or $6{\cdot}7_9$	1·3 $(1{\cdot}8)^b$	144·5	$69{\cdot}8^c$ or 63·3 $(64)^b$	$30{\cdot}2^c$ or 36·7 $(36)^b$
1f	D_2O	3·79	3·21	−11·6	−11·6	$7{\cdot}0_1{}^c$ or $6{\cdot}9_3$	$6{\cdot}9_3{}^c$ or $7{\cdot}0_1$	$\sim 1{\cdot}0^d$	144·5	$66{\cdot}9^c$ or 65·7	$33{\cdot}1^c$ or 34·3
1g	D_2O	3·56	3·15	−10·7	−10·7	$4{\cdot}8_2$ $(4{\cdot}68)^b$	$11{\cdot}7_5$ $(11{\cdot}50)^b$	$\leqslant 1{\cdot}0^d$ $(0{\cdot}7)^b$	144·5	15·7 $(17)^b$	84·3 $(83)^b$
1h	D_2O	$3{\cdot}27^e$	$1{\cdot}80^e$	$-11{\cdot}5^e$	$-11{\cdot}3^e$	$4{\cdot}7_7{}^e$	$12{\cdot}1_2{}^e$	$\leqslant 1{\cdot}0^e$	144·6	12·3	87·7

[a] Assumed values.
[b] Reported values (see Ref 16).
[c] Two values are possible because J and J′ cannot be distinguished (see Ref 17*a*).
[d] Estimated from the half-height band-width of signals because of lack of clear splitting.
[e] Obtained from analysis of a seven spin $AA'BB'C_3$ system.

From the fact that angular dependence of $J_{^{14}N,H(vic)}$ is found and rationalised theoretically,[18] it is expected that the $J_{^{14}N,H(t)}$ value is much larger than the $J_{^{14}N,H(g)}$ value, and hence, the $J_{^{14}N,H(obs)}$ value may be increased by an increase of P_g as represented by Eq (6).[16] The tendency of variation in $J_{^{14}N,H(vic)}$

$$J_{^{14}N,H(obs)} = P_g\{J_{^{14}N,H(g)} + J_{^{14}N,H(t)}\}/2 + P_t J_{^{14}N,H(g)} \qquad (6)$$

values in the series of molecules examined is in good agreement with the results of the population analyses described above and generally supports the validity of the present analyses. When we take account of the effect of the electronegativity of a substituent on the $J_{^{14}N,H(vic)}$ values, a decrease in $J_{^{14}N,H(vic)}$ value with an increase in electronegativity is expected because the sign of $J_{^{14}N,H(vic)}$ is believed to be positive.[21] Even if this effect is strong, this should not alter the result that there is a predominance of the gauche form in **1a**–**1d** and of the trans form in **1g** and **1h**.

The predominance of the trans form in a molecule having a non-polar substituent, and that of the gauche form or comparable stability of both conformers in a molecule having a polar substituent have been indicated by population analyses. The order of the predominance of the gauche form, however, does not simply correspond to the polarity of substituents. Other main contributors to the conformation energy and the balance among them should also be taken into consideration.

The above results also show that there is no observable effect by counter anions, i.e. halogen anions, in the solution examined. This is reasonable if we can assume that the conformation is mainly controlled by factors in the solvated organic cation, and is almost independent of its counter anion because of almost complete dissociation of the salt form.

Several authors have suggested that hydrogen bonding between a hydrogen atom of the N^+-methyl group and the oxygen atom is an important cause of the stability of the gauche forms of acetylcholine and choline.[7,9b] However, all N^+-methyl signals in the series of molecules examined here appeared as sharp singlets, collapsing by ^{14}N-spin-decoupling ($J_{^{14}N,H(gem)} = 0{\cdot}6$ Hz for **1c** and **1d**), and the absence of observable differences in chemical shifts between the three methyl groups on the quaternary nitrogen in these molecules suggests that strong hydrogen bonding is unlikely, as reported for acetylcholine isologues.[3] The $J_{^{13}C-H}$ values and the solvent effects observed further underline the improbability of hydrogen bonding. If hydrogen bonding strong enough to stabilise the gauche form of choline or acetylcholine exists, some differences between the $J_{^{13}C-H}$ values of the methyl groups in **1a**–**1d** and those for the other molecules would be expected, while in fact the $J_{^{13}C-H}$ values are almost equal (see Table 1). Again, if hydrogen bonding is an important factor, then the population distributions in acetylcholine and choline should be very different in acidic or basic media from those in neutral medium. Examination of **1a** in CF_3COOD (since the acetoxy group would be hydrolysed under basic conditions) showed that there is essentially no difference between their populations in D_2O and those in CF_3COOD.

Conformation energy is usually discussed in terms of van der Waals' interaction energy, E_v, torsional energy, E_t, stretching and compression energy, E_l, and bending energy, E_θ, etc. In our straight chain molecules, the contribution of E_l and E_θ should be very small because of freedom of rotation; the contribution of E_t is also considered to be small so far as the staggered form is assumed as a stable conformer; and, since the contribution of hydrogen bonding is believed to be very small, the remaining term E_v cannot explain the phenomena, except for molecules having non-polar substituents such as **1g** and **1h**. Thus the electrostatic interaction energy, E_e, may be considered as an important contributor besides E_v, as has been suggested by several workers.[7,8b,8c] If the contribution of E_e is large enough to cover the energy difference in E_v between the gauche and the trans forms, then higher or comparable stability of the gauche form is possible.

We agree with the suggestion of previous workers[8b,8c,22] that the E_e term can be calculated from the sum of Coulomb interaction energies between net charges of non-bonded atoms by Eq (7),

$$E_e = \Sigma\, Ce_ie_j/Dr_{ij} \qquad (7)$$

where C is a constant, D is the effective dielectric constant, e_i and e_j are electric charges of the ith and jth atom, respectively, and r_{ij} is the internal distance between them.

Cushley and Mautner[3] suggested that the dipole–dipole interaction between the C—N$^+$ and C—R bonds is one of the important contributors to conformation. However, this concept brings up the difficult problem of how to imagine the dipole of the C—N$^+$ bond, because, in the usual sense, the negative charge at one side of a dipole is balanced by a similar positive charge at the other side. The bond length of C—N$^+$ in ammonium ions is reported to be almost the same as that of C—N in amines,[23] contrary to the expectation that the electronegativity of the quaternary nitrogen should be much higher than that of a neutral nitrogen,[24] and the bond length of C—N$^+$ consequently shorter than that of C—N. This fact suggests a high possibility of delocalisation of positive charge on atoms close to the quaternary nitrogen, causing an increases of the bond length by repulsive forces among the positive charges distributed. The results of molecular orbital calculations on the acetylcholine ion[9] support this consideration.

Using the assumption that E_v and E_e are the main contributing factors to the conformation, we can now make a straightforward interpretation of the results of the population analyses. The results with **1e** and **1f** indicate that they have almost free rotation, the gauche and trans forms having almost equal stability. With **1e**, the chlorine atom is a polar substituent and E_e contributes to the higher stabilisation of the gauche form, but E_v contributes to that of the trans form, and the balance between E_v and E_e may give the result observed. For **1f**, the CN group is undoubtedly polar and the nitrile nitrogen may possess a negative charge. However, it is rather far from the cationic head, while the positively charged nitrile carbon is situated close to the cationic head. Even if there is a considerable difference in charge between the nitrile nitrogen and nitrile carbon, E_e stabilisation of the gauche form cannot be expected to be very strong because electrostatic interaction energy is in an inverse proportion to distance. The E_e value in combination with E_v can therefore lead to the result observed.

With cholines **1c** and **1d**, the negatively charged hydroxyl oxygen can occupy a position close to the cationic head and the positively charged hydroxyl hydrogen will twist to the reverse side of the cationic head or be easily detached by exchange. Since the van der Waals' repulsive interaction between the oxygen and the bulky cationic head will be not so large as that towards chlorine or carbon in the gauche form,* the predominance of the gauche form of the choline ion will be made possible by the electrostatic interaction effect. The two oxygens of acetylcholine ion can strongly stabilise the gauche form by their negative charges, and rotational freedom of each bond except the carbonyl double bond may allow that in the gauche form each atom can occupy a position such as not to increase van der Waals' interaction energy so much. Thus the predominance of the gauche form of these molecules, **1a**–**1d**, can also be rationalised by the contribution of E_e.

Apparent increases in population of the trans forms in modified cholines or acetylcholines, in which an N-methyl group is replaced by a bulkier substituent,[10,12] or which have a substituent at the α-position,[11,16] can simply be explained by an increased steric interaction with the substituents.

The predominance of the trans conformation in a molecule having a non-polar substituent, such as **1g** and **1h**, is understood reasonably in terms of steric interaction and the lack of a stabilising effect of E_e on the gauche form.

By analogy with these explanations, the predominance of the trans forms of choline or acetylcholine isologues such as thiocholine and acetylselenocholine[2,3,6] may be understood, since the electronegativities of sulfur and selenium are considerably smaller than that of oxygen,[23] while on the other hand, their van der Waals' repulsive forces against other atoms or groups are undoubtedly larger than that of oxygen.

In order to confirm the validity of the present considerations, conformation energy calculations have been made on some of the ammonium ions described here, taking E_e into account and will be reported in a forthcoming paper.[25]

EXPERIMENTAL

Measurements. The 100-MHz ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer in the frequency-swept and external-Me_4Si locked mode with a variable temperature probe at 50°. Concentrations of the compounds were about 1 M in D_2O and/or CF_3COOD. The ^{14}N-spin decoupling experiments were performed using an NMR Specialties HD-60B heteronuclear spin decoupler operating at about 7·229 MHz.

Materials. Acetylcholine chloride (**1a**) and bromide (**1b**), choline chloride (**1c**) and bromide (**1d**), chlorocholine chloride (**1e**), and trimethyl-*n*-propylammonium bromide (**1h**) were commercially available.

β-Cyanoethyltrimethylammonium bromide (**1f**). β-Cyanoethylbromide (500 mg) was dissolved in 5 ml of MeOH, and 3 ml of Me_3N was added under cooling with dry ice–acetone. The solution was allowed to stand at room temperature overnight. After evaporation of the solvent, a crystalline residue was obtained in an almost quantitative yield. This was recrystallised from EtOH to give a colourless crystalline product, m.p. 203–204° (decomp.). (Found: C, 37·16; H, 6·91; N, 14·51. $C_6H_{13}BrN_2$ requires: C, 37·32; H, 6·79; N, 14·55%).

β-Phenylethyltrimethylammonium bromide (**1g**). Phenethylbromide was treated in the same way as described above to obtain a colourless crystalline product. The physical data were identical with those reported.[26]

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*Comparison of the coefficients a_{ij} and b_{ij} of the potential function for van der Waals' interaction energy $[E_v = \Sigma (a_{ij}r_{ij}^{-12} + b_{ij}r_{ij}^{-6})]$ and the r_{ij}^{min} value for interacting atoms leads us to this conclusion; see R. A. Scott and H. A. Sheraga, *J. Chem. Phys.*, **42**, 2209 (1965).

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