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Chemistry

Substituent effects on the nitrogen-15 and carbon-13 shieldings of some *N*-arylguanidinium chlorides

(nuclear magnetic resonance spectroscopy/electrical effects/guanidine tautomers)

ROBERT E. BOTTO, JOSEPH H. SCHWARTZ, AND JOHN D. ROBERTS

Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

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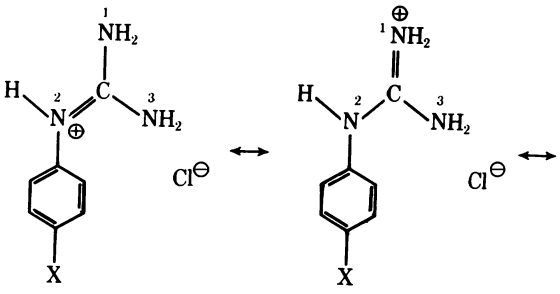
ABSTRACT The ^{13}C and ^{15}N chemical shifts of five *N*-arylguanidinium chlorides carrying polar substituents, ranging in character from 4-methoxy to 4-nitro groups, have been determined by NMR spectroscopy at the natural-abundance level of ^{13}C and ^{15}N in dimethyl sulfoxide solution. Comparison of the ^{13}C shifts of these salts with those of monosubstituted benzenes shows that the guanidinium group induces an average downfield shift of −5.8 ppm of the resonance of the aryl carbon to which it is attached (C1), an average upfield shift of +4.2 ppm for C2 and C6, and a small upfield shift of +1.9 ppm for C4. The shifts of C3 and C5 are small and erratic relative to the corresponding carbons in monosubstituted benzenes. The ^{15}N resonances of the guanidinium nitrogens are quite sensitive to electric effects resulting from substitution of polar groups at C4. The ^{15}N shift of the =NAr nitrogen relative to that of the salts suggests that the predominant tautomer for *N*-arylguanidines is $(H_2N)_2C{=}NAr$. The ^{15}N shifts of the $(NH_2)_2$ nitrogens correlate rather well with σ_p^- parameters, whereas the shifts of the −NHAr nitrogens seem to correlate only with *R* values derived from the σ_p^- substituent constants.

Guanidine is the strongest known organic base, its remarkable basicity being ascribed to substantially increased electron delocalization made possible by addition of a proton (for review, see ref. 1). To assess the influence of polar substituents on the ^{13}C and ^{15}N NMR shifts of guanidinium ions, we have investigated the effects produced by a substituent, X, for several *N*-arylguanidinium chlorides for which the resonance structures **1–3** are usually written to account for their reluctance to lose a proton relative to ammonium salts.



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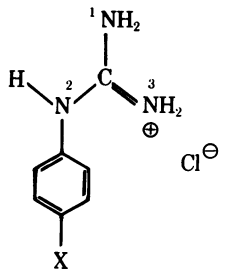

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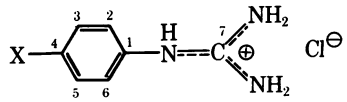
RESULTS AND DISCUSSION

The ^{13}C NMR chemical shifts of *N*-arylguanidinium chlorides are listed in Table 1. The resonances of the ring carbons were assigned on the basis of shift data for the corresponding substituted benzenes (2, 3) and *N*-(arylmethylidene)amines (4) as well as spin–spin splittings in the coupled spectra. There is a reasonable parallelism between the shifts of most of the ring carbons and those of the corresponding carbons in monosubstituted benzenes (2, 3). For C1, there is an average deshielding of −5.8 ± 0.6 ppm; for C2 and C6 the average shielding is 4.2 ± 0.4 ppm, and for C4 the average shielding is 1.9 ± 1.1 ppm resulting from substitution of a guanidinium group. The effects at C3 and C5 are relatively smaller and erratic.

The C7 chemical shifts are virtually insensitive toward substitution of polar groups at C4. This is surprising, considering the sensitivity of β-carbon shieldings in 4-substituted cyclopropylbenzenes (5), 4-substituted ethenylbenzenes (6), and *N*-(benzylidene)arenamines (7) and the β-nitrogen shieldings of *N*-(arylmethylidene)amine hydrochlorides (8). Apparently, the electrical effects of the polar groups, X, are transmitted primarily to the nitrogens of the guanidinium groups because, as we will show, the effects are much larger on the ^{15}N chemical shifts than on the ^{13}C shifts of the C7 carbons.

The ^{15}N chemical shifts of the *N*-arylguanidinium chlorides are given in Table 2. The N1 and N3 chemical shifts cover from 291.5 to 297.1 ppm; the N2 shifts are at lower fields, between 271.2 and 276.9 ppm. The equivalence of the N1 and N3 chemical shifts indicates that rotation about the C—N2 bond in these compounds is fast on the NMR time scale. This observation is in accord with studies by Bally and coworkers (9) and also by Kessler and Leibfritz (10), who have shown that the activation energy for rotation about the C—N2 bond is 10–13 kcal/mol (42–54 kJ/mol) for closely related guanidinium analogs.

Table 1. ^{13}C NMR chemical shifts of 4-substituted phenylguanidinium chloride in dimethyl sulfoxide solution



X	Chemical shift*				
	C1	C2, C6	C3, C5	C4	C7
CH_3O	126.9	126.3	114.4	157.6†	156.3†
CH_3	131.8	123.9	129.6	135.5	155.9
H	134.7	123.8	129.1	128.8	155.7
Cl	130.3	125.6	129.0	133.5	155.7
NO_2	141.8	124.6	122.3	143.6	155.3

* All chemical shifts are reported in ppm downfield from external tetramethylsilane.

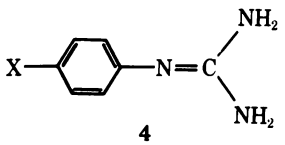
† Assignments are uncertain.

Table 2. ^{15}N NMR chemical shifts of 4-substituted phenylguanidinium chlorides in dimethyl sulfoxide solutions*

X	Conc., mol %	^{15}N chemical shift N1, N3	N2
CH_3O	16	297.1	276.9
CH_3	14	296.5	275.2
H	20	296.2	274.2
Cl	20	295.3	275.5
NO_2†	6	291.5	271.2

* Chemical shifts reported in ppm upfield from external $^2H^{15}NO_3$ capillary.
† $\delta^{15}N(NO_2) = 5.5$.

When the shifts in Table 2 are compared with the ^{15}N shifts of *N*-arylguanidines themselves (unpublished results), it is evident that protonation produces a large diamagnetic shift of ≈50 ppm in the N2 resonances and a somewhat smaller paramagnetic shift of ≈8 ppm in the N1 and N3 resonances. A parallel pattern of nitrogen shift changes occurs in the protonation of imidazole—the large upfield shift being typical of the protonation of a C=N— nitrogen, and the smaller downfield shift corresponding to increased charge through the change of $—NH_2$ to $—NH_2^{\delta\oplus}$ (8, 11). Because on protonation the resonance of N2 makes a large upfield shift, the preferred tautomer for *N*-arylguanidines, like sulfaguanidine (12), must have the C=N double bond conjugated with the aryl group, as in **4**.



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In general, the ^{15}N chemical shifts for both the N1 and N3 and the N2 nitrogens of *N*-arylguanidinium chlorides are sensitive to the polar effects of substituents at C4 on the benzene ring. Electron-withdrawing substituents cause downfield shifts; electron-donating substituents produce the opposite effect. The range of N2 chemical shifts from 4-nitro to 4-methoxy is 5.7 ppm, which is much smaller than the 25.5-ppm difference between the same substituents for benzenamines (13) and the 14.9- to 23.8-ppm difference observed for various *N*-(arylmethylene)amines (4), but it is much larger than the range of shifts reported for benzenammonium salts (14).

Table 3 summarizes correlations of the N2 shifts with various substituent parameters. The N2 shifts correlate relatively poorly with σ_p^- (15) and σ_p (16, 17) values. However, there is a much better correlation of the N2 shifts with *R* values derived from σ_p^- substituent constants (18). Thus, a substantial conjugative component can be inferred for substituent effects on the N2 chemical shifts and has a parallel in ^{15}N shifts for *N*-arylethanamides (19). In fact, a good linear correlation exists between the N2 shifts and those found for *N*-arylethanamides (19), with a slope of 1.14, an intercept of 0.17, and $r = 0.998$.

Table 3. Correlations of N2 chemical shifts with substituent constants

Substituent constant*	ρ	Intercept	r†
R	−5.07	274.4	0.996
σ_p^-	−3.84	275.4	0.912
σ_p	−5.75	275.3	0.890

* Values of σ_p^- are from ref. 15; those for σ_p are from refs. 16 and 17. The *R* values are calculated from σ_p^- values according to ref. 18.
† Correlation coefficient.

The N1 and N3 chemical shifts give a good linear correlation with σ_p^-, having a slope of −3.66, intercept of 296.1, and $r = 0.998$. Because substituent effects usually fall off rapidly with distance, the N1 and N3 shifts might be expected to be less sensitive than the N2 shifts to changes in X, but this is not the case. Apparently, the contributions of the resonance structures **1–3** to the hybrid structure are such that an electrical effect at N2 is transmitted essentially equally to N1 and N3. This is as it should be, considering the large stabilization energies of guanidinium cations, 24–26 kcal/mol (9).

EXPERIMENTAL SECTION

Each of the *N*-arylguanidinium chlorides was prepared by procedures based on those of Braun *et al.* (20) and Ainley *et al.* (21), with the exception of the 4-nitrophenyl derivative, which has a low solubility in the organic reaction media. 4-Nitrobenzenammonium chloride was prepared by dissolving 4-nitrobenzenamine in hot concentrated hydrochloric acid and allowing the solution to cool slowly. The resulting crystals were collected and dried under reduced pressure. The hydrochloride (10 g) was combined with a 10% molar excess of cyanamide in 250 ml of dry ethanol (distilled from calcium oxide) and the mixture was heated under reflux for 50 hr. At no time did all of the solid material dissolve. The reaction mixture was cooled, and the solid was collected and dried under reduced pressure. The yield was 3.6 g (29% yield) of 4-nitrophenylguanidinium chloride as a buff-colored solid, mp 298–300°C (lit. mp, 290–293°C) (22). The identity of the product was verified by its infrared and proton NMR spectra.

The ^{13}C NMR spectra were recorded on a Varian DFS-60 spectrometer operating at 15.1 MHz. Each spectrum was obtained of a 13 mol % solution in dimethyl sulfoxide with a repetition rate of 5.0 sec, 40-μsec pulse width, and accumulations of 1000 transients. Internal dimethyl sulfoxide-d_6 provided the field-frequency lock signal, and the shifts were measured with the solvent as reference. The resonances were subsequently referenced to external tetramethylsilane (TMS) by using $\delta^{TMS} = \delta^{(CH_3)_2SO} + 40.0$ ppm. The proton-noise decoupled ^{15}N NMR spectra were recorded at the natural-abundance level of ^{15}N with a Bruker WH-180 spectrometer operating at 18.25 MHz. The operating parameters were: repetition rate, 10 sec; acquisition time, 0.819 sec; typical total accumulation, 1000 transients. The pulse angle was 20° (20-μsec pulse width), and 8 W of proton-decoupling power was used only during the acquisition of the free-induction decays so that the sample remained at ambient probe temperature (≈28°C). Dimethyl sulfoxide was used as the solvent.

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1. Gund, P. (1972) *J. Chem. Educ.* 100–103.
2. Stothers, J. B. (1972) *Carbon-13 NMR Spectroscopy* (Academic, New York), p. 197.
3. Breitmaier, E. & Voelter, W. (1974) *^{13}C-NMR Spectroscopy*, (Verlag Chemie, Mannheim, Germany), p. 171.
4. Westerman, P. W., Botto, R. E. & Roberts, J. D. (1978) *J. Org. Chem.* 43, 2590–2596.
5. Kusuyama, Y., Dyllick-Brenzinger, C. & Roberts, J. D. (1979) *Org. Magn. Reson.*, in press.
6. Dhami, K. S. & Stothers J. B. (1965) *Can. J. Chem.* 43, 510–520.
7. Inamoto, N., Kushida, K., Masuda, S., Ohto, H., Satoh, S., Tamura, Y., Tokumaru, K., Tori, K. & Yoshida, M. (1974) *Tetrahedron Lett.* 3617–3620.

8. Botto, R. E. & Roberts, J. D. (1979) *J. Org. Chem.* **44,** 140–141.
9. Bally, T., Diehl, P., Haselbach, E. & Tracey, A. S. (1975) *Helv. Chim. Acta* **58,** 2398–2402.
10. Kessler, H. & Leibfritz, D. (1971) *Chem. Ber.* **104,** 2158–2169.
11. Schuster, I. I. & Roberts, J. D. (1979) *J. Org. Chem.* **44,** 3864–3867.
12. Sullivan, G. R. & Roberts, J. D. (1977) *J. Org. Chem.* **42,** 1095–1096.
13. Axenrod, T., Pregosin, P. S., Wieder, M. J., Becker, E. D., Bradley, R. B. & Milne, G. W. A. (1971) *J. Am. Chem. Soc.* **93,** 6536–6541.
14. Axenrod, T. & Wieder, M. J. (1976) *Org. Magn. Reson.* **8,** 350–353.
15. Hine, J. (1962) *Physical Organic Chemistry* (McGraw-Hill, New York), 2nd Ed.
16. McDaniel, D. H. & Brown, H. C. (1958) *J. Org. Chem.* **23,** 420–427.
17. Lewis, E. S. & Johnson, M. D. (1959) *J. Am. Chem. Soc.* **81,** 2070–2072.
18. Swain, C. G. & Lupton, E. C., Jr. (1968) *J. Am. Chem. Soc.* **90,** 4328–4337.
19. Westerman, P. W. & Roberts, J. D. (1978) *J. Org. Chem.* **43,** 1177–1179.
20. Braun, C. E., Erit, J. D. & Crooks, G. C. (1938) *J. Org. Chem.* **3,** 146–152.
21. Ainley, A. D., Curd, F. H. S. & Rose, F. L. (1949) *J. Chem. Soc.* 98–106.
22. Backer, H. J. & Moed, H. D. (1947) *Recl. Trav. Chim. Pays-Bas* **66,** 689–704.