Carbon-13 Magnetic Resonance. XXII.[1a] The *N*-Methylpurines

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Abstract: Carbon-13 magnetic resonance shift data are reported for *N*-methylimidazole and the four *N*-methylpurines in order to evaluate the effects of *N*-methyl substitution as opposed to nitrogen protonation. The resulting chemical shifts are compared to imidazole and purine anions and the N-methylation shifts are found to be comparable to the protonation shifts noted previously in various azines. The CNDO–SCF molecular orbital theory coupled with a modified Karplus–Pople shielding tensor is used to rationalize the experimental data. The dependence of carbon-13 chemical shifts on both charge densities and bond order terms is also noted.

Previous work on the five- and six-membered nitrogen heterocycles and their charged species[2] has demonstrated that highly predictable protonation parameters can be expected when nitrogen lone-pair electrons are bonded to a proton. The extension of these results to benzimidazole and to purine[3] indicated that protonation parameters similar to those noted previously for the simple azine systems[2] could also be expected in the more complex fused-ring heteroaromatic systems. The observed substituent parameters have been used to determine the preferred positions of the labile protons in purine and its cationic species.[3] However, the dynamic proton exchange between the various tautomeric forms limits a definitive interpretation of the protonation shifts in terms of concomitant changes in the electronic structure.

N-Methylation of the nitrogen heterocycles eliminates the problem of rapid tautomeric exchange and simplifies a structural interpretation of the data. *N*-methylimidazole is taken as a model compound for establishing the relationship between protonation and methylation parameters. In this instance, the imidazole anion is the common reference. The chemical shift trends thus established in this simple molecular species form the basis for interpreting the changes in the carbon-13 chemical shifts for the 7- and 9-methylpurines. No direct analog is proposed for the 1- and 3-methylated species, but the substituent effects are discussed in terms of other similar data.

The CNDO molecular orbital theory[4–6] is employed to generate approximate wave functions for use in a modified form[2] of the Karplus–Das paramagnetic shielding expression.[7] Correlations between such MO parameters and the observed chemical shifts are then taken as a vindication of the validity of the theoretical estimates of the electronic structure.

Experimental Section

A. Equipment. A Varian high-resolution spectrometer (AFS-60) equipped with a V-4311 transmitter operating at 15.085 Mcps was used to observe the carbon-13 magnetic resonance spectra. Proton decoupling was accomplished with a Varian V-4320 spin decoupler operating at 60 MHz in the manner described previously.[8,9] A Varian C-1024 time-averaging device was used to enhance the signal-to-noise ratio in the slightly soluble compounds.

B. Spectroscopic Details. 9-Methylpurine was run in a saturated (10 mol %) water solution and the chemical shifts were obtained as previously described.[8] 7-Methylpurine was run as a saturated solution in a water–*p*-dioxane mixture to facilitate solubility. The *p*-dioxane peak was used as an internal standard for determining the carbon-13 chemical shifts. The 1- and 3-methylpurines were run as saturated solutions in DMSO and the solvent peak was used again as an internal reference. *N*-Methylimidazole was obtained from commercial sources and run as a neat liquid. In the case of 1-, 3-, and 7-methylpurine the decoupling and transmitter frequencies of the carbon-13 singlet arising from the solvent peak were obtained, and the chemical shifts from benzene determined[8] from the equation

$$\delta_{^{13}C} = \frac{\Gamma_i - \Gamma_0}{\Gamma_i} + \frac{\Gamma_0}{\Gamma_i}\delta_H \cong \frac{\Gamma_i - \Gamma_0}{\Gamma_i} + \delta_H \qquad (1)$$

where Γ_i is the ratio of the decoupler frequency to that of the transmitter (f_i/ν_i). Thus, the solvent peak serves as a fiducial mark in the spectra of the 1-, 3-, and 7-methylpurines. Peak identification for all compounds studied is made by associating the carbon peak with the directly bonded proton by means of the selective decoupling technique described elsewhere.[9]

All samples for carbon-13 analysis were run in 10-mm glass tubing while the proton samples were contained in 5-mm glass tubes. DSS was added as an internal standard to all samples for proton analysis.

C. Sample Preparation. 1- and 3-Methylpurine were prepared in 2-g quantities by previously reported procedures.[10,11] 7-Methylpurine was prepared by the method reported by Albert and Brown[12] with the following modification: 2,6-dichloro-7-methylpurine was hydrogenated catalytically on palladium/carbon (5%) in aqueous NH_4OH (3%). The product was isolated by lyophilization and then recrystallized. 9-Methylpurine was prepared as previously described[12] except that 6-chloro-9-methylpurine was catalytically hydrogenated, lyophilized, and recrystallized.

Results

A. Proton Shifts. The proton shifts of the com-

(1) (a) Previous paper in this series: D. K. Dalling and D. M. Grant, submitted for publication; (b) University of Utah; (c) Nucleic Acid Research Institute.
(2) R. J. Pugmire and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 697, 4232 (1968).
(3) R. J. Pugmire and D. M. Grant, *ibid.*, **93**, 1880 (1971).
(4) J. A. Pople and D. P. Santry, *J. Chem. Phys.*, **43**, S129 (1965).
(5) J. A. Pople and G. A. Segal, *ibid.*, **43**, S136 (1965); **44**, 3289 (1966).
(6) J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).
(7) M. Karplus and T. P. Das, *J. Chem. Phys.*, **34**, 1683 (1961).
(8) W. R. Woolfenden and D. M. Grant, *J. Amer. Chem. Soc.*, **88**, 1496 (1966).
(9) R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *ibid.*, **91**, 6381 (1969).
(10) L. B. Townsend and R. K. Robins, *J. Org. Chem.*, **27**, 990 (1962).
(11) L. B. Townsend and R. K. Robins, *J. Heterocycl. Chem.*, **3**, 241 (1966).
(12) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1960).

Table I. Carbon-13 Chemical Shifts of the *N*-Methylpurines

Compound	Position	δ_H, ppm[a]	$\delta^{13}C$, ppm[a]	$\delta^{13}C$, ppm[b]	$\Delta\delta^{13}C$[c]
Imidazole anion	2	−0.42	−16.55	145.09	
	4,5	0.02	1.78	126.76	
Imidazole	2	−0.68	−7.69	136.23	+8.86[d]
	4,5	−0.02	+6.21	122.33	+4.43[d]
N-Methyl-imidazole	CH_3	3.68	96.30	32.24	
	2	−0.35	−9.37	137.91	+7.18[d]
	4	~0.19[e]	−0.03	128.57	−1.81[d]
	5	~0.19[e]	+8.00	120.54	+6.22[d]
1-Methylpurine	CH_3	2.94	84.98	43.56	
	2	−1.73	−16.17	144.71	+4.81
	4		−36.83	142.37	−4.67
	5		−6.41	134.95	−0.48
	6	−1.91	−7.93	136.47	+7.20
	8	−1.38	−37.74	166.28	−9.37
3-Methylpurine	CH_3	2.79	90.11	38.43	
	2	−1.83	−15.24	143.78	+5.74
	4		−27.39	155.93	+4.77
	5		−12.35	140.89	−6.42
	6	−1.91	−17.18	145.72	−2.05
	8	−1.25	−33.77	162.31	−5.40
7-Methylpurine	CH_3	3.12	96.38	32.16	
	2	−1.63	−23.57	152.11	−2.59
	4		−30.73	159.27	+1.43
	5		2.40	126.14	+8.33
	6	−1.75	−12.37	140.91	+2.76
	8	−1.31	−22.11	150.65	+6.26
9-Methylpurine	CH_3	2.89	97.98	30.56	
	2	−1.91	−23.35	151.89	−2.37
	4		−22.39	150.93	+9.77
	5		−4.35	132.89	+1.58
	6	−2.03	−18.88	147.42	−3.75
	8	−1.73	−20.23	148.77	+8.16
Purine anion	2	−1.85	−20.98	149.52	
	4		−32.16	160.70	
	5		−5.93	134.47	
	6	−2.00	−15.13	143.67	
	8	−1.66	−28.37	156.91	
Purine	2	−1.98	−23.46	152.00	−2.48
	4		−26.32	154.86	+5.84
	5		0.14	128.40	+6.07
	6	−2.10	−16.30	144.84	−1.17
	8	−1.81	−19.33	147.87	+9.04

[a] Taken with respect to benzene, negative values are downfield from benzene. [b] Taken with respect to TMS, positive values are downfield from TMS. [c] Taken with respect to purine anion. [d] Taken with respect to imidazole anion. [e] Peaks could not be resolved at 60 MHz.

pounds studied are given in Table I. The proton assignments in the methylpurines were made assuming the same relative ordering of the H-2, H-6, and H-8 protons reported previously[13] for purine and its charged species. As the structural changes (protonation and deprotonation) induced in purine under strongly acidic and basic conditions do not change the relative ordering of the proton shifts (H-6 < H-2 < H-8), it was assumed that methyl substitution likewise does not change the relative order. This assumption was verified as described in the following section.

B. Carbon-13 Chemical Shifts. The carbon-13 chemical shifts in *N*-methylimidazole are presented in Table I along with the values of imidazole and its anionic species for purposes of comparison. While chemical shifts relative to both TMS and benzene are given for convenience in Table I, this discussion uses the benzene scale. The methyl group is readily identified since it appears at high field as compared to the remainder of the resonance positions and position C-2 may be identified by the selective decoupling technique.[9] It is noted that N-methylation produces an upfield shift of +7.18 ppm at C-2 relative to the imidazole anion and this shift change corresponds to a value of +8.86 ppm found in imidazole.[2] Positions C-4 and C-5 could not be readily distinguished by selective decoupling but C-5 was assigned at +8.00 ppm since, like C-2, it is adjacent to the methylated heteroatom and is expected to exhibit an upfield resonance shift as compared to imidazole anion.[14] This assignment yields a positive shift of +6.22 ppm while the alternative assignment of −0.03 ppm would require a negative shift with respect to the anion (−1.81 ppm), and there is no precedent for such an assignment.[2,3] Hence, C-4 is assigned a value of −0.03 ppm which is −1.81 ppm downfield from the corresponding position in imidazole anion and is within the experimental error of the previously observed (−1.59 ± 0.4 ppm) protonation induced β-shift parameter.

The carbon-13 chemical shifts for the methylpurines are also given in Table I. The bridgehead carbons, C-4 and C-5, are readily identified in each molecule by the absence of the large C–H splittings. The resonance positions of C-4 and C-5 in every case were assigned the same relative order, *e.g.*, C-4 downfield from C-5 as noted previously for various other purines.[3,15] The methylation values relative to purine anion are also given in Table I.

The chemical shift assignments for C-2, C-6, and C-8 were made by the selective decoupling techniques employing the proton shifts discussed in section A. As this method of assignment only establishes the connecting pairs of hydrogen and carbons, further confirmatory evidence of the assignment was sought. This was accomplished by taking all possible combinations of experimental shift values relative to those in the purine anion to produce four different sets of methylation parameters for each carbon position. Comparing these sets with the protonation values previously reported for purine anion[3] as well as the N-methylation values observed for *N*-methylimidazole, only a single set of C-13 methylation shifts was found to be consistent with these previous data. This approach confirmed the carbon assignments based on the assumed proton shifts in each case. The methyl groups in the compounds studied are easily identified as the only peaks found in the aliphatic region of the spectra. The observed values with respect to benzene are presented in Table I.

Discussion

As was pointed out in the Results section (B), the methylation shifts observed in *N*-methylimidazole closely parallel the results of protonation of the imidazole anion. In fact, the sum of the α- and β-N-methylation parameters reproduces the shift change found at C-4, C-5 in imidazole (+4.41 ppm this study *vs.* 4.43 ppm noted previously[2]). These results indicate that the chemical shifts observed for *N*-methyl-

(13) M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **86**, 696 (1964).

(14) It should be noted that the positive "α-methylation parameter" of +7.18 ppm at C-2 is analogous to the α-protonation parameter (+9.02 ± 0.4 ppm) noted previously for the simple five-member heterocycles. Protonation of imidazole anion also produces a negative β shift of −1.59 ± 0.4 ppm.

(15) R. J. Pugmire, D. M. Grant, R. K. Robins, and G. W. Rhodes, *J. Amer. Chem. Soc.*, **87**, 2275 (1965).

imidazole may be used to rationalize the chemical shifts found in both the 7- and the 9-methylpurines. The chemical shift changes observed at positions C-8 are +6.26 and +8.16 ppm in the 7- and 9-methyl derivatives, respectively, and reflect the expected upfield shifts. Likewise, at the bridgehead carbons adjacent to the substituted nitrogen, one notes upfield shifts of +8.33 and +9.77 ppm respectively for C-5 and C-4. On the basis of the *N*-methylimidazole data, a downfield shift is expected for C-4 in 7-methylpurine and C-5 in 9-methylpurine, but the peaks move upfield +1.43 and +1.58 ppm, respectively. The reason for this reversal in trend is not presently clear but is probably associated with the existence of the second ring and the unusual characteristics of bridgehead carbons as compared with the other carbons in imidazole.[16] Hence, the data confirm that in a fused ring system, a carbon atom adjacent to a methylated nitrogen atom in the five-membered ring experiences an upfield shift of comparable magnitude to that of the α-protonation parameter. On the other hand, the β shift is not preserved at the bridgehead positions, but in any event the magnitude of the shift is reduced.

The long-range cross-ring effects noted at position C-2 in purine[2] are faithfully preserved in the system under study (−2.48, −2.59, and −2.37 ppm for purine, 7-methylpurine, and 9-methylpurine, respectively) and reflect comparable long range electronic effects. These long-range effects are also observed in the chemical shift at C-6 in purine (−1.17 ppm) as well as the 9-methyl derivative (−3.75 ppm), but for 7-methylpurine the methylation shift is upfield (+2.76 ppm), exhibiting the usual positive steric effect of proximate 1,4 carbon atoms. It should be borne in mind that the negative C-6 protonation parameter in purine (−1.17 ppm) is accompanied by proton exchange between the two tautomeric (N-7 and N-9) forms and provides no information as to the effects produced by each tautometic form taken separately. It is interesting to note, however, that the average of the methylation shift at C-6 for the 7- and 9-methyl species is −0.5 ppm which approximates the corresponding purine protonation parameter. The reduction in magnitude is undoubtedly due to large upfield steric shifts for the methyl group. Having established the general equivalence of 7- and 9-protonation and methylation shifts upon all carbon resonance positions in the six-membered rings, it may be concluded that the mechanism responsible for the similar long-range substituent parameters is probably due to common inductive effects. Protonation and methylation, to the same degree, appear to localize the electronic charge as compared with the purine anion.

The directions of the upfield α and downfield β- and γ-shift changes observed in the protonated six-membered azines[2] are preserved by methyl substitution in the six-membered ring of purine. In 1-methylpurine, C-2 and C-6 are shifted upfield +4.81 and +7.20 ppm, respectively, while C-4 and C-5, which are in γ and β positions, respectively, move downfield −4.67 and −0.48 ppm. It is significant to note that the methylation shift parameters for 1-methylpurine are in reasonable agreement with the protonation parameters found in purine cation[3] (Table II). Hence, the methylation data independently substantiate the previous conclusion[3,17,18] that cation formation in purine occurs primarily with protonation at N-1.

Table II. Comparison of Methylation Parameters in 1-Methylpurine with the Protonation Parameters in Purine Cation

Position	Chemical shift changes, ppm	
	Purine cation[a]	1-Methylpurine[b]
2	+3.76	+4.81
4	−3.24	−4.67
5	−0.02	−0.48
6	+4.98	+7.20
8	−5.12	−9.37

[a] Taken with respect to neutral purine (see ref 3). [b] Taken with respect to purine anion.

The methylation shift changes observed in 3-methylpurine are also similar to those noted in the 1-methyl species. Those carbons adjacent to the methylated nitrogen, C-2 and C-4, are shifted +5.74 and +4.77 ppm, respectively, to higher field than the corresponding positions in purine anion. However, the β carbon, C-5, experiences a greater downfield shift (−6.42 ppm) than observed at the γ position (C-6; −2.05 ppm). This reversal of magnitude of the β- and γ-shift parameters has not been previously observed.

The data in Tables I and II also indicate that long-range inductive effects are experienced at C-8 as a result of methylation at N-1 or N-3. Position C-8 experiences −9.37 and −5.40 ppm downfield shifts as the result of methylation at N-1 and N-3, respectively. While the latter chemical shift change is less than the corresponding value in the 1-methyl derivative, the magnitude is indicative of the apparent long range inductive effects induced by methylation at either N-1 or N-3.

In previous protonation studies on purine[3] the long-range substituent effects were observed to be more pronounced as a result of protonation in the six-membered than in the five-membered ring.[19] Similar trends are preserved in the *N*-methylpurines where methylation at N-7 and N-9 shift C-2 downfield −2.59 and −2.37 ppm, respectively, whereas C-8 is shifted −9.37 and −5.40 ppm to lower field by methylation at N-1 and N-3, respectively.

The carbon-13 chemical shifts for the methyl groups in the *N*-methylpurines fall into two general groups: the 1- and 3-methylpurines at +84.98 and +90.11 ppm, respectively, from benzene and the 7- and 9-methyl derivatives at +96.38 and +97.98 ppm. It is noted that the resonance positions of the methyl groups located at positions N-7 and N-9 fall at higher field than those at N-1 and N-3 and reflect the expected excess charge present in the five-membered aromatic ring systems. (It should be noted that the methyl

(16) For a discussion of the theoretical problems associated with, interpreting the chemical shifts at bridgehead carbons, see T. D. Alger, D. M. Grant, and E. G. Paul, *J. Amer. Chem. Soc.*, **88**, 5397 (1966); R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *ibid.*, **91**, 6381 (1969); A. J. Jones, T. D. Alger, D. M. Grant, and W. M. Litchman, *ibid.*, **92**, 2386 (1970); A. J. Jones, P. D. Gardner, D. M. Grant, W. M. Litchman, and V. Boekelheide, *ibid.*, **92**, 2395 (1970).

(17) S. I. Chan, M. P. Schweizer, P. O. Ts'o, and G. K. Helmkamp, *ibid.*, **86**, 4182 (1964).

(18) J. M. Read, Jr., and J. H. Goldstein, *ibid.*, **87**, 3440 (1965).

(19) Protonation of purine anion at N-7, N-9 shifts C-2 downfield −2.48 ppm, while protonation of purine at N-1 moves the C-8 resonance position −5.12 ppm to lower field.

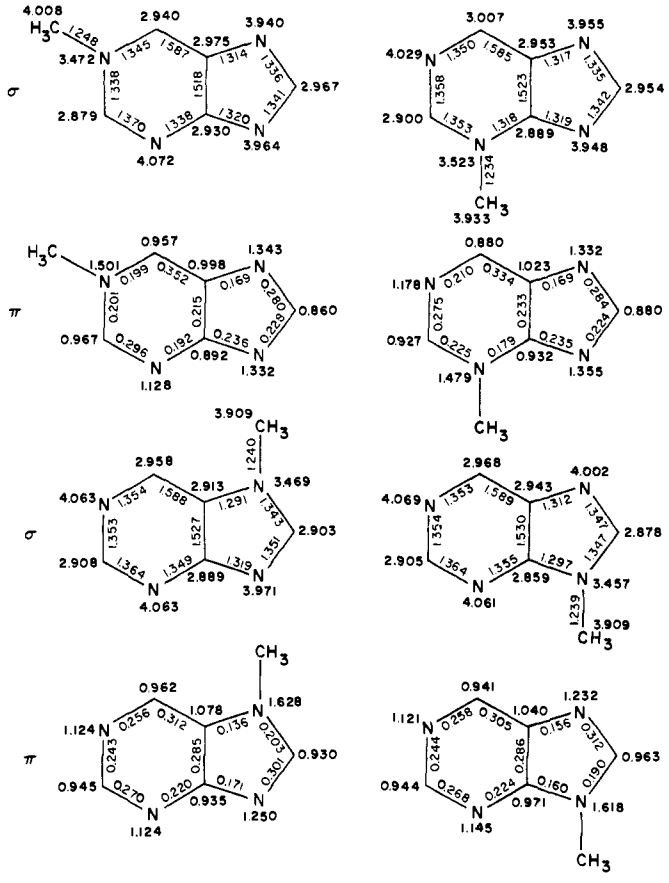

Figure 1. Molecular orbital parameters obtained from the CNDO program include both σ and π charge densities (outside of ring) and bond orders (inside of ring). Test calculations have been made on purine to compare the theoretical values obtained assuming idealized geometry with calculated values obtained from X-ray structural data. While the shielding values at all carbons are affected by the geometry chosen, the chemical shift change at C-8 is greatest and exhibits a 5-ppm change while the other positions are only 1-2 ppm. Since the scatter in the data is greater than even the largest correction and since exact geometries are not available for all species involved, a consistent set of idealized geometry was used throughout the calculations.

carbon in *N*-methylimidazole comes at 96.30 ppm with respect to benzene, a value almost identical with that found in 7-methylpurine, *i.e.*, 96.38 ppm.) In addition, one also observes an apparent upfield shift in the 3- and 9-methyl resonance position due to the proximity of the 9 and 3 nitrogens, respectively (*i.e.*, the methyl resonance line for 3-methylpurine is 5.13 ppm upfield from that for the 1-methyl compound, and the methyl resonance line for 9-methylpurine is 1.60 ppm upfield from that for the 7-methyl species). Thus, steric effects[20] are proposed to explain changes in the methyl shifts.

Theoretical Considerations

The electronic structures of the *N*-methylpurines have been investigated by means of the CNDO–SCF–MO technique,[4-6] and the resulting charge densities and bond orders for both σ and π electrons are presented in Figure 1. The wave functions obtained were

(20) The effects of steric interactions on carbon-13 chemical shifts have been discussed previously: D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967); D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967); and ref 8. While a nitrogen free pair had less directional character than a CH bond, the oblate nature of the free pair can still affect proximate bond centers.

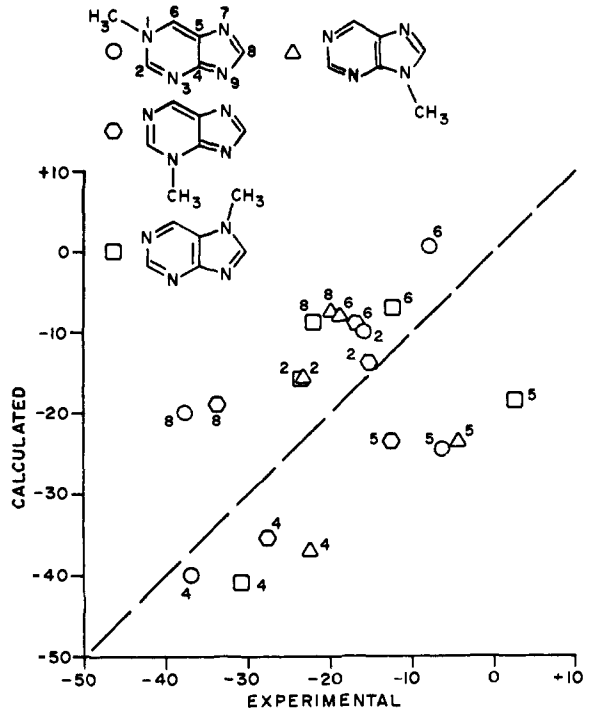

Figure 2. CNDO predicted chemical shifts are plotted *vs.* experimental values for the *N*-methylpurines. Both predicted and experimental values have been referenced to benzene and the average excitation energy is assumed to be 10 eV.

used to calculate the paramagnetic contribution to the carbon-13 shielding tensor in the manner previously described.[2] The results of these calculations are presented in Table III. Using benzene as reference, the theoretical results are plotted against the experimental values in Figure 2. The theoretical results place the

Table III. Theoretical Estimates of ^{13}C Chemical Shifts in the *N*-Methylpurines

Compd	Position[a]	Theoretical estimates: σ^{total}, ppm	f	σ^{total}, ppm[b]	$\delta^{13}C$ (exptl), ppm[c]
Indenyl anion		0	1.000		0
1-Methylpurine	2	−18.0	0.968	−27.9	−30.8
	4	−19.6		−33.2	−37.3
	5	−3.7		−16.7	−6.9
	6	−5.8		−18.0	−17.1
	8	−34.7		−47.6	−51.3
3-Methylpurine	2	−21.7	0.971	−32.9	−29.9
	4	−14.7		−26.6	−27.9
	5	−2.6		−14.1	−12.8
	6	−15.3		−26.4	−26.3
	8	−33.5		−45.0	−47.3
7-Methylpurine	2	−23.7	0.973	−34.1	−38.2
	4	−20.2		−31.3	−31.2
	5	+2.1		−8.3	+1.9
	6	−13.4		−23.5	−21.5
	8	−23.3		−33.5	−35.7
9-Methylpurine	2	−23.7	0.974	−33.7	−38.0
	4	−16.1		−26.6	−22.9
	5	−2.9		−13.1	−4.8
	6	−14.4		−24.1	−28.0
	8	−22.0		−31.7	−33.8

[a] See Figure 2 for numbering scheme. [b] Values are calculated using a corrected ΔE value (see ref 25) as described in ref 1a, 2, and 3. These theoretical values are plotted in Figure 4. [c] Values relative to the corresponding positions in indenyl anion; see ref 1a.

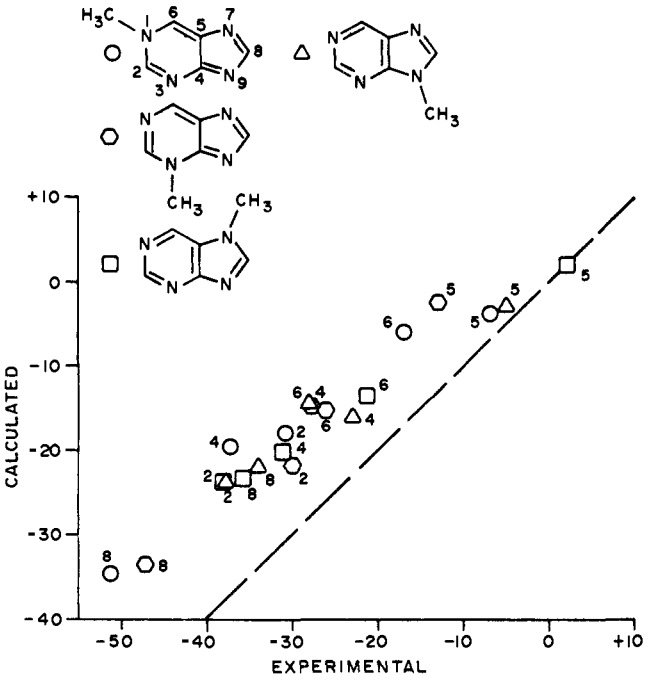

Figure 3. CNDO predicted chemical shifts are plotted *vs.* experimental values. Both predicted and experimental values were referenced to the corresponding position in indenyl anion.

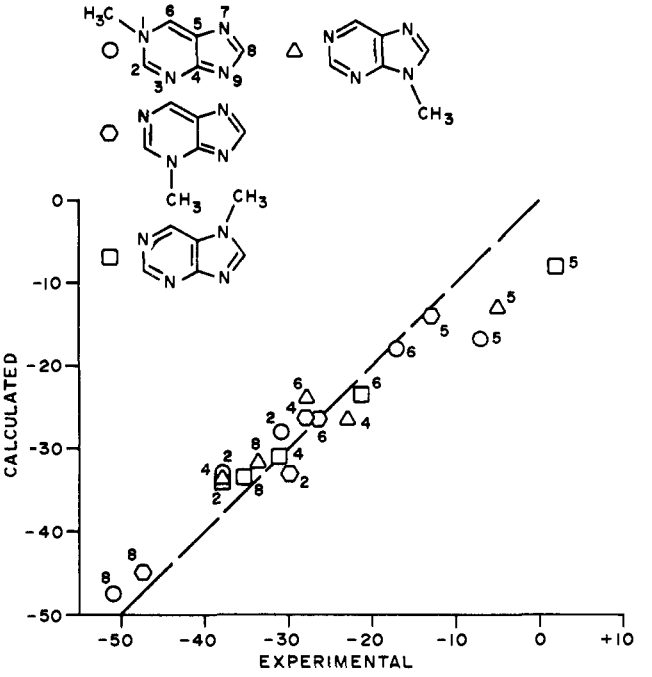

Figure 4. CNDO predicted chemical shifts are plotted *vs.* experimental values where indenyl anion has been used as reference and the average excitation energy for each species studied is $f \times \Delta E$ in eV.

C-2, C-6, and C-8 resonance values for each species above the correlation line. On the other hand, theory predicts the bridgehead carbons (C-4 and C-5) to be shifted to lower field than is found experimentally and the corresponding points fall below the correlation line. Previous investigations have also noted that the theory predicts inordinately large paramagnetic shifts at the bridgehead carbons in aromatic and heteroaromatic compounds.[1a,3,9,21-24] Pugmire and Grant[3] have pointed out that the theoretical discrepancies appearing at bridgehead carbons can be obviated when the appropriate molecular structure (in the present case indenyl anion) is employed to reference experimental and theoretical values. In Figure 3 all values are referred to the appropriate position in indenyl anion resulting in a significant improvement in the fit of the data. The bridgehead positions now correlate with the general body of data and although all positions are displaced above the perfect correlation line, only moderate scattering occurs among the data points. It may well be that the discrepancy at the bridgehead carbons between theoretical and experimental shifts is due to the failure to include the appropriate diamagnetic corrections. Mason[25] and Sadleg[26] have suggested that the diamagnetic term should vary by an amount comparable with the discrepancy between the two different types of carbon atoms as is readily seen in Figure 2.

The fact that the data fall along a line which closely parallels the perfect correlation line is indicative of a poor choice of the average excitation energy, ΔE.[24,27] In order to partially compensate for the errors induced by employing a constant value of ΔE for each species studied, the average separation between the occupied and unoccupied energy levels as calculated in the manner previously described[1a,2,3] and the computed f values[28] for each species are given in Table III. Applying this correction to ΔE (it is noted that the correction is approximately constant among all species studied, varying by only 6%), a slightly modified paramagnetic shielding term is calculated for each carbon and these values, referenced to indenyl anion, are plotted against the experimental values in Figure 4. Although little overall reduction in the scatter in the data is apparent, the data fall along the correlation line, and, in view of the many simplifying approximations employed in a calculation of this type, the correlation obtained in Figure 4 is considered to be unusually good.

A detailed comparison of the predicted and experimental N-methylation shifts portrayed in Figure 4 is presented in Table IV. Although perfect correlation is not obtained for all data points, the correct sign is predicted for the shift parameters in all but two of 20 pieces of data, *i.e.*, C-5 and C-6 in 3-methyl- and 9-methylpurine, respectively. However, these two discrepancies are only minor in light of the overall correlation obtained. Two major factors are to be noted as a result of the theoretical predictions. (1) Each carbon adjacent to a methylated nitrogen atom is predicted to move upfield in concert with the experi-

(21) T. D. Alger, D. M. Grant, and E. G. Paul, *J. Amer. Chem. Soc.*, **88**, 5397 (1966).
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(28) Using the average separation of the energies of the occupied and unoccupied molecular orbitals in indenyl anion as a reference, the f values are computed as the average separation in energy levels of each species in question divided by the value for indenyl anion. The corrected ΔE value is equal to $f \times 10$ eV for each species (see ref 24 for additional details).

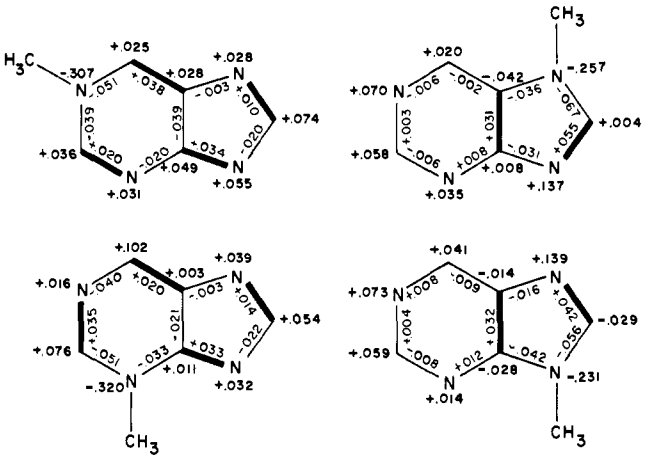

Figure 5. CNDO net π charges and mobile bond orders for the *N*-methylpurine using purine anion as reference. The positive and negative signs on the bond order terms indicate net increase or decrease of the mobile bond order terms. The heavy lines indicate those bonds where the net bond order change is +0.10 or greater.

Table IV. Experimental and Theoretical Methylation Shifts in *N*-Methylpurines

Compd	Position	—Chemical shift changes[a]— Pred, ppm	Exptl, ppm
1-Methyl-purine	2	+5.7	+4.8
	4	−1.0	−4.7
	5	−0.6	−0.5
	6	+6.3	+7.2
	8	−3.5	−9.4
3-Methyl-purine	2	+0.7	+5.7
	4	+5.6	+4.8
	5	+2.0	−6.4
	6	−2.1	−2.0
	8	−0.9	−5.4
7-Methyl-purine	2	−0.5	−2.6
	4	+0.9	+1.4
	5	+7.8	+8.3
	6	+0.8	+2.8
	8	+10.6	+6.3
9-Methyl-purine	2	−0.1	−2.4
	4	+5.6	+9.8
	5	+3.0	+1.6
	6	+0.2	−3.7
	8	+12.4	+8.1

[a] Taken with respect to purine anion.

mental results. (2) The long-range electronic effects are preserved at C-2 and C-8 and theory predicts that these effects are more pronounced as a result of N-methylation in the six- than in the five-membered ring. Similar results were obtained in the protonated purine species.[3] These results indicate that the electronic structure in purine is affected by N-methylation in a manner similar to that observed for N-protonation.[2,3]

Figure 5 presents the π-electronic structure of the *N*-methylpurines as compared to purine anion. It is noted that significant change occurs in the electronic charges as well as bond orders, especially at those carbons experiencing long-range shift effects (*i.e.*, C-2 and C-8). The theory also predicts that significant bond localization occurs as indicated in Figure 5. While one can write resonance forms including charge separation for the 1- and 3-methyl species, the theory predicts notable increases in bond order character at those locations where classical double bonds can be written. Although these findings should not be construed as evidence that only a single structure contributes to the ground-state electronic structure of these two molecules, the data indicate that the enhanced classical double bond structure can make a major contribution in long-range shift effects. The localized double bonds in the five-membered rings will partially explain the large downfield chemical shifts observed at C-8,[29] but the net charge decrease must also be considered. It is significant to note that the predicted electronic structure in 1-methylpurine places the double bonds in the para-quinoid structure while substitution in the 3 position enhances the less stable ortho-quinoid structure. Therefore, changes in bond orders as well as charge densities both affect the chemical shifts. In the case of C-8 in the 1- and 3-*N*-methylpurines, theory suggests that inductive effects are more dominant in the 1-*N*-methyl species than in 3-*N*-methylpurine, since in both cases the bond order changes are comparable, but in the latter molecule the change in net charge density is considerably less.

For the 7- and 9-methyl species, the theory predicts significant changes in double bond character in the five-membered rings corresponding to classical localized bond structures. No large changes, however, are observed in the double bond character of the pyrimidine ring as a result of methylation at N-7 or N-9. On the other hand, the charge polarization effects at C-2 are similar to those found at C-8 in the 1- and 3-methyl species. Thus, as the long-range methylation shifts at C-2 in the 7- and 9-methyl species are considerably smaller than the corresponding long-range shifts observed at C-8 in the 1- and 3-methyl compounds, it is concluded that alteration of the bonding patterns is of more importance in the long-range shift effects.

The significance of the theoretical results lies not so much in the success of predicting the measured shifts exactly but in the fact that the general trends and overall correlations are found between the shifts and MO parameters. Thus, the theoretical calculations indicate that the CNDO method is useful for predicting gross electronic properties in complex aromatic systems. Furthermore, this study illustrates the sensitivity and importance of carbon-13 chemical shift data as a means for characterizing and verifying important electronic structural features.

Acknowledgment. This work was supported by the National Institutes of Health under Grant No. GM-08521 and Grant No. CA-08109 from the National Cancer Institute, National Institutes of Health, Public Health Service.

(29) An increase in spin pairing enhances the paramagnetic shielding term. For a complete discussion of the effects of bond order changes see ref 2.