Correlation of the Proton Magnetic Resonance Chemical Shifts of Substituted Purines with Reactivity Parameters. II. 6-Substituted Purines

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The proton magnetic resonance spectra of eight 6-substituted purines plus purine itself in dimethyl sulfoxide yielded a linear correlation of the chemical shift of the 8-proton with Brown's electrophilic substituent constants: δ_{H-8} (parts per million downfield from internal tetramethylsilane) = $(8.653 \pm 0.013) + (0.359 \pm 0.019)\sigma_{p_6}{}^+$, with a standard deviation in δ_{H-8}, $s_{\delta_{H-8}} = \pm 0.035$ p.p.m., and a correlation coefficient, $r = 0.991$. δ_{H-8} was assigned with the help of deuterated compounds in two cases and on the basis of a previously established correlation for 2,6-disubstituted purines. δ_{H-8} was found to be fairly well correlated with Taft's σ_{R_6}. δ_{H-8} for 27 compounds—16 2,6-di-, eight 6-, and two 2-substituted purines, and purine—in dimethyl sulfoxide solution was found to give a good correlation with $\underset{2,6}{\Sigma}\sigma_p{}^+$: $\delta_{H-8} = (8.655 \pm 0.013) + (0.347 \pm 0.013)\underset{2,6}{\Sigma}\sigma_p{}^+$, with $r = 0.984$ and $s_{\delta_{H-8}} = \pm 0.064$ p.p.m. In trifluoroacetic acid solutions compounds other than amino-substituted ones could also be correlated with $\underset{2,6}{\Sigma}\sigma_p{}^+$, $r = 0.995$.

In paper I[1] we reported a linear correlation between the chemical shift of the proton in the 8-position of 2,6-disubstituted purines and the sum of the $\sigma_p{}^+$ constants[2] for the substituents in the 2- and 6-positions, eq. 1.[3]

$$\delta_{H-8} = (8.658 \pm 0.017) + (0.342 \pm 0.016)\underset{2,6}{\Sigma}\sigma_p{}^+ \qquad (1)$$

This paper reports our results for eight 6-substituted purines.

With substitution in the 6-position only, two aromatic-ring proton bands are observed in the 8- to 9-p.p.m. region. Which of these to assign to H-2 and which to H-8 is not immediately obvious. We initially resolved this problem by plotting both chemical shifts against $\sigma_{p_6}{}^+$. For each pair of points one was found to lie close to the line predicted from the data for 2,6-disubstituted purines, eq. 1. The ordinates of these points, then, were assumed to be δ_{H-8}. Since, in some cases the values of δ_{H-2} and δ_{H-8} were close together, the wrong choice for δ_{H-8} would not lead to a large error in correlation with $\sigma_p{}^+$. However, in the cases of 6-methyl- and 6-methoxypurine a significant error would result from a wrong choice. Therefore, we synthesized 6-methylpurine-2-*d* and 6-methoxypurine-2-*d* and proved the validity of the initial assignment from the values of δ_{H-8} observed for these two compounds, where the assignment is unambiguous.

Experimental

The proton magnetic resonance (p.m.r.) spectra were recorded at 60 Mc./sec. on a Varian Associates A-60 spectrometer. The procedures and solvents were the same as described previously.[1]

The preparations of most of the substituted purines have already been reported in the literature. The two deuterated compounds, 6-methylpurine-2-*d* and 6-methoxypurine-2-*d*, were made by deuterolysis of the corresponding 2-chloropurines by the procedure described in part I.[1] The deuterolysis of 2-chloro-6-methylpurine required 4.5 hr. at 35–40° and gave an 81% yield of 6-methylpurine-2-*d*. The deuterolysis of 2-chloro-6-methoxypurine required 6 hr. at 45–50° and gave a 68% yield of 6-methoxypurine-2-*d*. In this case the product crystallized from deuterium oxide on concentration to one-tenth volume; it was collected by filtration and washed with fresh deuterium oxide. In both cases some exchange of the 8-proton also occurred.

Results and Discussion

The chemical shifts of the two ring protons of eight 6-substituted purines and purine-d_0 are given in Table I, and δ_{H-8} is plotted against $\sigma_{p_6}{}^+$ in Figure 1. The least-squares equation of this line, eq. 2, gives a correlation coefficient, r, of 0.991 and a standard deviation of δ_{H-8} from the least-squares line, $s_{\delta_{H-8}}$ of ± 0.035 p.p.m., equal to the estimated experimental error in δ_{H-8}. Point 6, corresponding to 6-iodopurine, shows the largest deviation. The predicted value of δ_{H-8} for this compound, from eq. 2, is 8.70 p.p.m., a difference of 0.07 p.p.m. downfield from the observed shift. This failure of $\sigma_p{}^+$ to properly predict the chemical shift for 6-iodopurine is paralleled by the behavior of 2,6-dibromopurine[1] where H-8 is more shielded by 0.06 p.p.m. than predicted by eq. 1. On the other hand 2-chloro-, 6-chloro-, and 2,6-dichloropurine are all observed to be slightly less shielded than predicted. Since 2,6-dibromo substitution shows little effect and 6-iodo substitution appears to be electron donating, we can only conclude that the resonance effect neutralizes or outweighs the inductive effect for these larger and more polarizable halogens when they are substituents on such a strongly electrophilic ring system as that of purine.

$$\delta_{H-8} = (8.653 \pm 0.013) + (0.359 \pm 0.019)\sigma_{p_6}{}^+ \qquad (2)$$

TABLE I

CHEMICAL SHIFTS OF 6-SUBSTITUTED PURINES IN DIMETHYL SULFOXIDE

Compound	Substituent	Concn., g./dl.	δ_{H-2}	δ_{H-8}
1	$-NMe_2$	5.0	8.19	8.07
2	$-NH_2$	5.0	8.11	8.14
3	–OMe	5.0	8.51	8.38 (8.41)[a]
4	–SMe	6.0	8.73	8.47
5	–Me	4.0	8.76	8.53 (8.57)[a]
6	–I	5.0	8.60	8.63
7	–H	5.0	8.99	8.68
8	–Cl	7.5	8.76	8.71
9	–CN	5.0	9.08	8.91

[a] Chemical shift of the corresponding 2-deuteriopurine.

The chemical shift observed for purine-d_0, δ_{H-8} = 8.68 p.p.m., lies within 0.03 p.p.m. of the line. A further proof of the validity of the choice of assignment of

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[1] W. C. Coburn, Jr., M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, **30**, 1110 (1965).

[2] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

[3] δ_{H-8} is the chemical shift of the 8-proton in parts per million downfield from internal tetramethylsilane (TMS), measured in dimethyl sulfoxide (DMSO) solutions at solute concentrations near 5 g./dl.

δ_{H-8} is provided in the cases of 6-methyl- and 6-methoxypurine by the observed chemical shifts of H-8 in the corresponding 2-deuteriopurines, also shown in Table I. In neither case could these shifts be mistaken for those of δ_{H-2}.[4] Although the choice of δ_{H-8} for the five remaining compounds was not confirmed in this way, we feel that the excellent fit to eq. 2 and the agreement with our previous results for 2,6-disubstituted purines constitute sufficient validation.

We also attempted to correlate δ_{H-8} with separated inductive and resonance parameters,[5] employing an equation having the form shown in eq. 3. Here, b_0

$$\delta_{H-8} = b_0 + \sum_{i=1}^{n} b_i X_i \qquad (3)$$

is the intercept, and the b_i are the coefficients of the n parameters, X_i, to be linearly correlated with δ_{H-8}. Table II shows the results for several cases computed by the method of least squares. Neither σ_{R_6} nor $\sigma_{R_6}{}^0$ yields as good a correlation as does $\sigma_{R_6}{}^+$, and the separation of $\sigma_p{}^+$ into σ_I plus $\sigma_R{}^+$ makes no improvement over eq. 2.

Table II

Least-Squares Parameters for Eq. 3

X_1	X_2	b_0	b_1	b_2	r	$s\delta_{H-8}$
σ_{I_6}	σ_{R_6}	8.626	0.398	0.662	0.984	0.045
σ_{I_6}	$\sigma_{R_6}{}^+$	8.657	0.346	0.363	0.990	0.037
σ_{I_6}	$\sigma_{R_6}{}^0$	8.654	0.402	1.088	0.982	0.048

As may be seen from Table I, δ_{H-2} shows a rough correlation with δ_{H-8} and, hence, with $\sigma_{p_6}{}^+$. However, of the various measures of substituent effects commonly employed, δ_{H-2} is best correlated with Taft's σ_{R_6},[5] according to eq. 4. The value of r is 0.967 and the

$$\delta_{H-2} = (8.928 \pm 0.030) + (0.899 \pm 0.090)\sigma_{R_6} \qquad (4)$$

standard deviation in δ_{H-2} is ±0.079 p.p.m. Figure 2 shows a plot of δ_{H-2} *vs.* σ_{R_6} for the eight 6-substituted purines and purine-d_0. The inclusion in eq. 4 of another term on the right-hand side linear in σ_{I_6} does not improve the correlation significantly. Both the value of r and the standard deviation in δ_{H-2} remain unchanged. Evidently the 6-substituent exerts primarily a resonance effect on the electron density at the 2-position. This result is surprising since the 2- and 6-positions are *meta* to one another by analogy with benzene, and yet δ_{H-2} is not so well correlated with σ_I, σ_{R_m}, $\sigma_{R_m}{}^+$, or combinations of these. The fact that the inclusion of a term linear in σ_I in eq. 4 does not improve the correlation is further evidence that the resonance effect of the 6-substituent predominates.

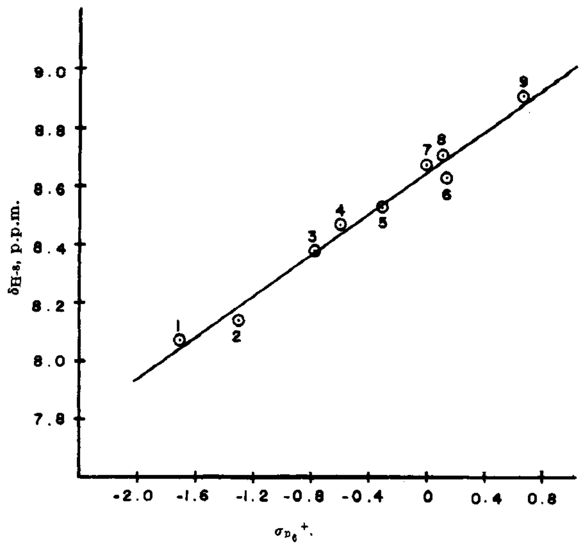

Figure 1.—δ_{H-8} of 6-substituted purines in dimethyl sulfoxide as a function of $\sigma_{p_6}{}^+$. To identify points see compound numbers given in Table I.

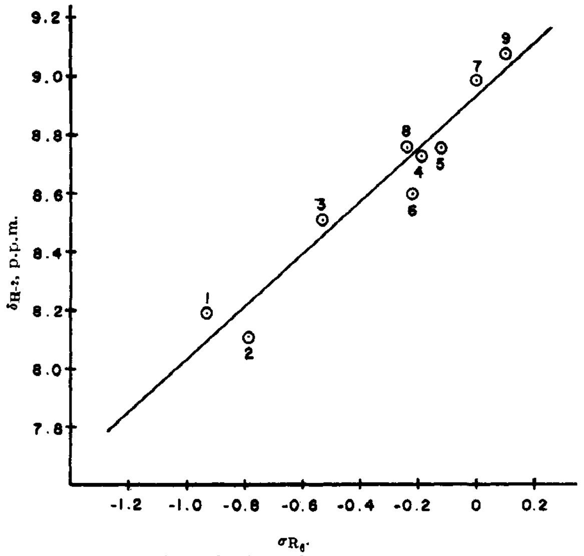

Figure 2.—δ_{H-2} of 6-substituted purines in dimethyl sulfoxide as a function of σ_{R_6}. To identify points see compound numbers given in Table I.

In part I[1] δ_{H-8} was found to be well correlated with $\sum\limits_{2,6}\sigma_p{}^+$ for sixteen 2,6-disubstituted purines and purine by eq. 1, with $r = 0.984$ and $s_{\delta H-8} = \pm 0.066$ p.p.m. The magnitudes of the slope and intercept in this equation compared with the corresponding quantities in eq. 2, together with the fact that the attempt to separate the effects of the 2- and 6-substituents in the case of the 2,6-disubstituted purines, eq. 5, gave equal coefficients

$$\delta_{H-8} = (8.655 \pm 0.018) + (0.353 \pm 0.029)\sigma_{p_2}{}^+ + (0.332 \pm 0.029)\sigma_{p_6}{}^+ \qquad (5)$$

within experimental error to $\sigma_{p_2}{}^+$ and $\sigma_{p_6}{}^+$, indicate that the effects of the 2- and 6-substituents on δ_{H-8} are nearly equal. We, therefore, gathered all the available data on 2-, 6-, and 2,6-disubstituted purines in DMSO, summarized in Table III, and plotted the values of δ_{H-8} for these 27 compounds against $\sum\limits_{2,6}\sigma_p{}^+$, Figure 3. The resulting least-squares line, represented by eq. 6,

$$\delta_{H-8} = (8.655 \pm 0.013) + (0.347 \pm 0.013) \sum_{2,6} \sigma_p{}^+ \qquad (6)$$

yields a correlation coefficient, r, of 0.984, identical with that for eq. 1 and 5, and gives about the same standard deviation in $s_{\delta H-8}$, $\delta_{H-8} = \pm 0.064$ p.p.m. Although data for only two 2-substituted purines,

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(4) The small differences in δ_{H-8} between the deuterated and undeuterated compounds apparently merely reflect experimental error rather than an isotope effect. A solution containing both 6-methylpurine and 6-methylpurine-2-*d* showed only one peak in the 8.5-p.p.m. region, at 8.55 p.p.m.

(5) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963). Values of σ_R were obtained by taking the difference between the σ_p values of McDaniel and Brown[6] quoted in Wells' Table V and the σ_I values of Taft quoted in Wells' Table VII. Values of $\sigma_R{}^+$ were calculated from $\sigma_R{}^+ = \sigma_p{}^+ - \sigma_I$. Values of $\sigma_R{}^0$ were taken from ref. 7.

(6) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(7) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

TABLE III

CHEMICAL SHIFTS OF THE 8-PROTON OF 2-, 6-, AND 2,6-DISUBSTITUTED PURINES IN DIMETHYL SULFOXIDE

Compound	Substituent 2	Substituent 6	$\sigma_{p_2}{}^{+\,a}$	$\sigma_{p_6}{}^{+\,a}$	$\Sigma_{2,6}\sigma_p{}^+$	$\delta_{H\text{-}8}$, p.p.m.	d^b
1	$-NMe_2$	$-NH_2$	−1.7	−1.3	−3.0	7.72	0.11
2	$-NH_2$	$-NH_2$	−1.3	−1.3	−2.6	7.76	0.01
3	$-NH_2$	-SMe	−1.3	−0.604	−1.9	7.93	−0.06
4	-SMe	$-NMe_2$	−0.604	−1.7	−2.3	7.97	0.11
5	$-NH_2$	-Me	−1.3	−0.311	−1.6	7.98	−0.12
6	-SMe	$-NH_2$	−0.604	−1.3	−1.9	8.02	0.03
7	-F	$-NMe_2$	−0.073	−1.7	−1.8	8.03	−0.01
8	-H	$-NMe_2$	0.000	−1.7	−1.7	8.07	0.00
9[c]	$-NH_2$	-H	−1.3	0.000	−1.3	8.08	−0.12
10	-Cl	$-NH_2$	0.114	−1.3	−1.2	8.13	−0.11
11	-H	$-NH_2$	0.000	−1.3	−1.3	8.14	−0.06
12	-F	$-NH_2$	−0.073	−1.3	−1.4	8.16	−0.02
13	-SMe	-SMe	−0.604	−0.604	−1.208	8.32	0.08
14	-H	-OMe	0.000	−0.778	−0.778	8.38	−0.01
15	-Cl	-OMe	0.114	−0.778	−0.664	8.45	0.03
16	-H	-SMe	0.000	−0.604	−0.604	8.47	0.02
17	-H	-Me	0.000	−0.311	−0.311	8.53	−0.02
18	-Et	-Cl	−0.295	0.114	−0.181	8.58	−0.01
19	-H	-I	0.000	0.135	0.135	8.63	−0.07
20	-Cl	-Me	0.114	−0.311	−0.197	8.64	0.05
21	-H	-H	0.000	0.000	0.000	8.68	0.03
22	-Br	-Br	0.150	0.150	0.300	8.70	−0.06
23	-H	-Cl	0.000	0.114	0.114	8.71	0.02
24[d]	-Cl	-H	0.114	0.000	0.114	8.76	0.07
25	-Cl	-Cl	0.114	0.114	0.228	8.77	0.04
26	-H	-CN	0.000	0.659	0.659	8.91	0.03
27	$-CF_3$	-Cl	0.612	0.114	0.726	8.97	0.06

[a] See ref. 1. [b] $d = \delta_{H\text{-}8}(\text{obsd.}) - \delta_{H\text{-}8}(\text{calcd.})$. [c] $\delta_{H\text{-}8} = 8.61$ p.p.m. [d] $\delta_{H\text{-}6} = 9.13$ p.p.m.

2-NH_2 and 2-Cl, are available, they seem to fit reasonably well.

However, the slight inequality of the two coefficients in eq. 5 may be real. That is the effect of a given substituent on the shielding of the 8-proton could well be expected to be different depending on whether the substituent was in the 2- or 6-position. This is borne out in two cases for which we have data, -Cl and $-NH_2$: in both cases the substituent exerts a greater effect on H-8 from the 2-position, the difference being in the same direction suggested by the coefficients of $\sigma_{p_2}{}^+$ and $\sigma_{p_6}{}^+$ in eq. 2.

Data for only ten compounds, shown in Table IV, are available in trifluoroacetic acid (TFAA). With the amino-containing compounds included, eq. 7 results,

$$\delta_{H\text{-}8} = (9.438 \pm 0.050) + (0.233 \pm 0.065)\sum_{2,6}\sigma_p{}^+ \qquad (7)$$

with $r = 0.785$ and $s_{\delta H\text{-}8} = \pm\ 0.142$. With compounds having this substituent excluded the fit is greatly improved, giving eq. 8 with $r = 0.995$ and $s_{\delta H\text{-}8} =$

$$\delta_{H\text{-}8} = (9.449 \pm 0.010) + (0.368 \pm 0.017)\sum_{2,6}\sigma_p{}^+ \qquad (8)$$

±0.022 (see Figure 4). Practically no improvement in this last correlation is obtained by separation of the substituent constants according to ring position, eq. 9.

$$\delta_{H\text{-}8} = (9.454 \pm 0.010) + (0.339 \pm 0.032)\sigma_{p_2}{}^+ + (0.397 \pm 0.032)\sigma_{p_6}{}^+ \qquad (9)$$

Here, $r = 0.996$ and $s_{\delta H\text{-}8} = \pm 0.020$. It is interesting to note that in TFAA the relative magnitudes of the coefficients have been reversed from those found in DMSO.

TABLE IV

CHEMICAL SHIFTS OF SUBSTITUTED PURINES IN TRIFLUOROACETIC ACID

(concentration = 5.0 g./dl.)

Compound	Substituents 2	Substituents 6	$\Sigma_{2,6}\sigma_p{}^+$	$\delta_{H\text{-}8}$	$\delta_{H\text{-}2}$	$\delta_{H\text{-}6}$
1	-H	$-NH_2$	−1.3	8.91	9.31	...
2	-SMe	-SMe	−1.208	9.01	...	...
3	-H	-OMe	−0.778	9.14	9.20	...
4	-Cl	$-NH_2$	−1.2	9.21	...	...
5	-SMe	$-NH_2$	−1.9	9.31	...	...
6	-D	-Me	−0.311	9.35	...	...
7	-Et	-Cl	−0.181	9.41	...	...
8	-H	-H	0.000	9.41	9.59	9.97
9	-Cl	-Cl	0.228	9.55	...	...
10	$-CF_3$	-Cl	0.726	9.71	...	...

Of the three aminopurines studied in TFAA, only one, adenine, would fit eq. 8 or 9, and only in this case does the p.m.r. spectrum definitely show absorption of the amino group distinct from the solvent absorption. Since the amino absorption of adenine is very broad and overlaps both the H-2 and H-8 bands, it was necessary to add a known concentration of another compound as standard to determine the number of protons represented by the overlapping absorption. This was done twice, using acetic acid as standard once, and hexamethyldisiloxane as standard the second time. In both cases, the overlapping absorption due to adenine is shown to represent four protons, indicating that the amino group has not been protonated.

In the cases of the other two purines having an amino substituent, some very broad absorption is also observed overlapping the absorption from H-8. However, it is difficult to evaluate the number of protons represented since the solvent peak has been shifted upfield sufficiently to interfere. This upfield shift of the solvent peak may, of course, be the result of exchange with the amino protons. We have not, therefore, been able to determine whether protonation has occurred on the amino group in these compounds.

It seems reasonable to assume that all of the purines studied in TFAA are protonated in that solvent, even though the position of protonation is not known. Part of the downfield shift for H-8 of these compounds in TFAA from their positions in DMSO may well be caused by such protonation. This solvent shift remains remarkably constant from one compound to another, except for 2-chloroadenine and 2-methylthioadenine (compounds 4 and 5 of Table IV), as can be seen from the fact that the slopes in Figures 3 and 4 are nearly equal (0.347 and 0.368 from eq. 6 and 8).

The failure of 2-chloroadenine and 2-methylthioadenine to fit eq. 8, H-8 appearing downfield from the predicted position, together with the fact that the same two compounds fit eq. 6 when studied in DMSO, raises the question whether they may be protonated differently, in position or extent, from the other purines studied in this solvent.

In summary, the excellent fit of the data for three different substitution types in DMSO to eq. 6 would allow one to predict $\delta_{H\text{-}8}$ for a 2-, 6-, or 2,6-disubstituted purine to within 5% of the total range of variation, 1.25 p.p.m., for the 27 compounds studied. The results for the purines substituted in the 6-position alone show, surprisingly, that the inductive effect of the 6-substituent on the shielding of the 2-proton is negligible, but its effect on the 8-proton is quite significant. This may be readily seen by comparing eq. 3 and 4 in terms of the relative chemical shifts from unsubstituted purine, as in eq. 10 and 11. These equations indicate

$$\Delta\delta_{H\text{-}8} = 0.4\sigma_I + 0.7\sigma_R \qquad (10)$$

$$\Delta\delta_{H\text{-}2} = 0.0\sigma_I + 0.9\sigma_R \qquad (11)$$

that no single substituent parameter can measure the effect of the 6-substituent in purines on both the 2- and 8-positions. Apparently the mechanism of transmission of substituent effects is different in the two cases, purely resonance from the 6- to the 2-position in the pyrimidine ring and a combination of induction and enhanced resonance from the 6- to the 8-position, across both rings.

Also, the magnitude of the range of chemical shifts of H-2, about 1 p.p.m. for the eight 6-substituted purines studied, may be compared with the corresponding range for the chemical shifts of the *meta* protons of the 2,4,6-trideuterated 1-substituted benzenes measured by Langenbucher, Schmid, and Mecke,[8] about 0.5 p.p.m. The greater relative shift for the purines indicates that electron charge–density changes on the nearest neighbor nitrogen atoms has a greater effect on the chemical shift of H-2 than do changes in charge–density on the nearest neighbor *ortho* and *para* carbon atoms in the substituted benzenes, presumably because of the greater electronegativity of nitrogen than carbon, causing a concentration of electron charge in purines at positions 1 and 3. The nitrogens at positions 7 and 9 are probably affected to about the same degree, since the range of $\Delta\delta_{H\text{-}8}$ is also almost 1 p.p.m. We hope next to determine whether the effects of the 2- and 6-substituents on $\delta_{H\text{-}8}$ remain equal, additive, and measurable by σ_p^+, when N-7 or N-9 are substituted, providing increased localization of the π electrons in the imidazole ring.

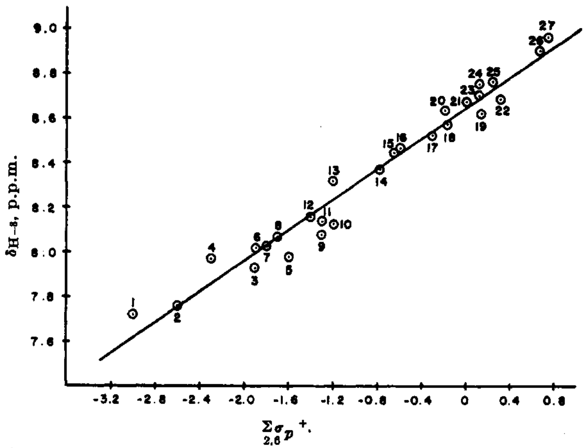

Figure 3.—$\delta_{H\,8}$ of 2-, 6-, and 2,6-disubstituted purines, in dimethyl sulfoxide, as a function of $\sum_{2,6}\sigma_p^+$. To identify points see compound numbers in Table III.

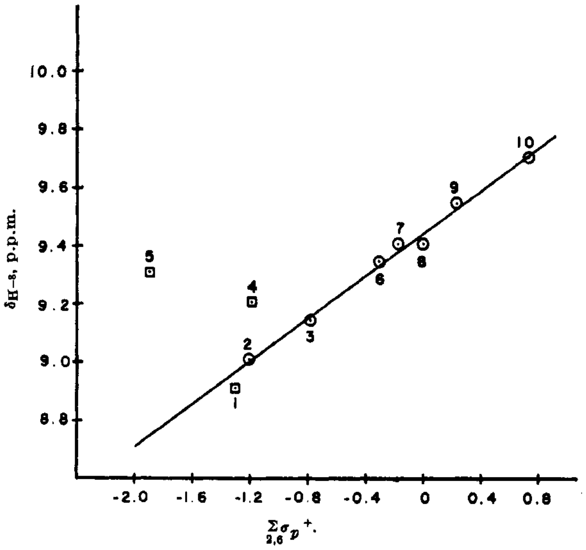

Figure 4.—$\delta_{H\text{-}8}$ of 6- and 2,6-disubstituted purines in trifluoroacetic acid as a function of $\sum_{2,6}\sigma_p^+$. To identify points see compound numbers in Table IV. ⊡ is amino-substituted purines.

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[8] F. Langenbucher, E. D. Schmid, and R. Mecke, *J. Chem. Phys.*, **39**, 1901 (1963).