Regioselective Radical Methylation of Carbon-2 and Carbon-8 of 6- and 3,6-Substituted Purines[1]

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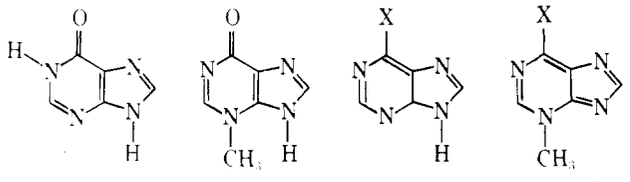
The pseudo-first-order rate constants for the reaction of the 2 and 8 positions of 6- and 3,6-substituted purines in acidic and neutral media with methyl radical produced by the photolysis of *tert*-butyl peracetate were determined. Under acid conditions, hypoxanthine (**1**), 6-methoxypurine (**3**), and 6-methylthiopurine (**5**) yielded the corresponding 8-methylpurine predominantly. Conversely, 3-methylhypoxanthine (**2**), 6-methoxy-3-methylpurine (**4**), and 3-methyl-6-methylthiopurine (**6**) were methylated mainly at the 2 position. This regioselectivity was correlated with the site of cation formation via ^1H NMR analysis of the aromatic protons in acidic and neutral media. Methylation was found to occur fastest on the carbon atom whose proton resonated at lowest field in the acid spectrum. This has led to the reassignments of the literature values for the H-8 resonance of the cations of **3** and **5**. These competitive 2- vs. 8-methylations are depicted in Scheme II as a substitution occurring on the major cationic forms. In neutral solution, the previous preference for the 2 position of 3,6-substituted purines was reversed, favoring 8-methylation instead. On the other hand, the methyl radical specificity for carbon-8 of the 6-substituted purines declined drastically, resulting in both the 2- and 8-methylation products although the latter was still the major isomer. Such regioselectivity displayed by the methylation reaction of two series of purine compounds in neutral media is compatible with an S_EAr mechanism involving a radical σ complex as shown in Scheme III.

The free-radical alkylation of purine compounds has continued to attract considerable interest. Our previous paper[2] presents the kinetics and mechanism of methylation of purine bases and nucleosides by methyl radical, providing a quantitative model to understand radical–nucleic acid reactions. The methylation occurs specifically at carbon-8 in an acidic medium although multiple reaction sites appear at higher pH's. This regioselectivity problem, an important issue for adenine, hypoxanthine, and the like which have both C-2 in the pyrimidine ring and C-8 in the imidazole ring available for radical attack, has not been treated in the literature. For example, Elad et al.[3] irradiated 6-ethoxypurine in the presence of 2-propanol and obtained both the 8-alkylated and the 2,8-dialkylated purine in a ratio of 1:0.6. Maeda et al. reported[4] the radical methylation of hypoxanthine in 1 N H_2SO_4 using the Fe(II) induced homolysis of *tert*-butyl hydroperoxide as a source of methyl radical which yielded 2-methyl-, 8-methyl-, and 2,8-dimethylhypoxanthine in a ratio of 0.1:1.0:0.2, respectively. Neither paper gives a detailed explanation of the product distributions. We have studied the regioselectivity



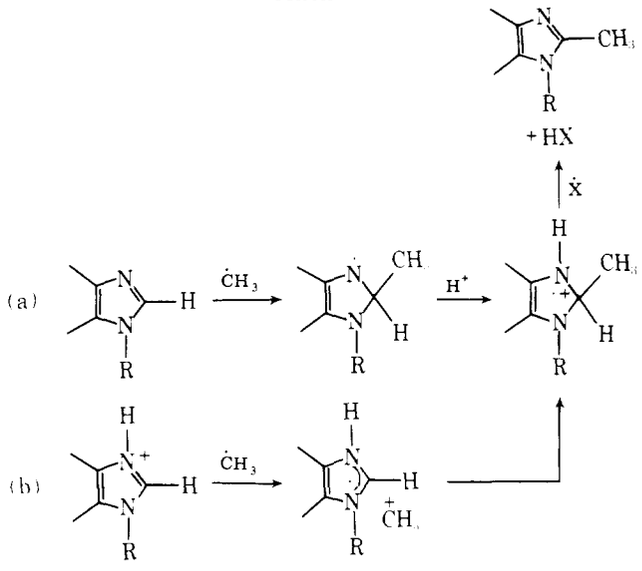
1 **2** **3**, X = OCH_3 **4**, X = OCH_3 **5**, X = SCH_3 **6**, X = SCH_3

of radical methylation of purines using photoinduced decomposition of *tert*-butyl peracetate (BPA) as the source of methyl radical. Comparison of the kinetics in the methylation of 6- and 3,6-substituted purines, two series of purine compounds **1–6** shown below, has revealed a dramatic trend in the selectivity of the methyl radical toward the C-2 and the C-8 position of the purine nucleus which varies with pH. This varying regioselectivity can be rationalized on the basis of the two previously reported[2] reaction mechanisms shown in Scheme I.

Results and Discussion

Methylation in Acid Media. The purines **1–6** were subjected to methylation in D_2O–CF_3COOD using the photoinduced homolysis (λ >300 nm) of BPA as the source of methyl radical.[2] There were no purine products other than the

Scheme I



methyl derivatives. The rate of methylation at the two unsubstituted carbons of the purine nucleus was determined by LC analysis of the C-2 methyl and C-8 methyl derivatives produced. The pseudo-first-order rate constants are compiled in Table I. Thus, the 6-substituted purines methylate faster at C-8 with large C-8/C-2 kinetic ratios although the reverse is true for the 3,6-substituted purines. It should be noted that methylation of 6-(methylthio)purine (**5**) and 3-methyl-6-(methylthio)purine (**6**) were complicated by the thiohydrolysis of both the starting purines and the products under the acidic conditions used. However, this also facilitated the identification of the products from the methylation of **5** and **6**, viz., 8-methyl-6-(methylthio)purine (**7**) from **5** via thiohydrolysis to 8-methylhypoxanthine (**8**),[4] and 2,3-dimethyl-6-(methylthio)purine (**9**) from **6** after thiohydrolysis to 2,3-dimethylhypoxanthine (**10**).[5] Their reaction kinetics were followed to less than one-half life whereas 1–2 half-lives were monitored for purines **1–4**. The other methylated purines are stable under the reaction conditions, and 2,8-dimethyl products are insignificant. Also, the methylation reaction of **1** and **2** could be affected by the thermally induced decomposition of BPA at 80 °C at rates 3.7- and 1.4-fold slower, respectively, than the photoreactions. The hydrolysis problem prevented the thermal reaction study of purines **3–6**.

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Table I. Rate Constants for the Free-Radical Methylation of Purine Derivatives[a]

purines	registry no.	$k_{C-2} \times 10^5$ s^{-1}	$k_{C-8} \times 10^5$ s^{-1}	k_{C-8}/k_{C-2}
hypoxanthine (1)	68-94-0	0.05 (±0.01)	0.88 (±0.01)	17.6
3-methylhypoxanthine (2)	1006-11-7	0.20 (±0.04)	0.06 (±0.01)	0.3
6-methoxypurine (3)	1074-89-1	0.07 (±0.01)	0.61 (±0.02)	8.7
3-methyl-6-methoxypurine (4)	3324-66-1	1.33 (±0.10)	0.27 (±0.06)	0.2
6-(methylthio)purine (5)	50-66-8	*b*	1.04 (±0.13)	
3-methyl-6-(methylthio)purine (6)	1008-08-8	1.94 (±0.19)	0.54 (±0.06)	0.28

[a] 1.7 M of purine solutions in 2:1 D_2O–CF_3COOD containing a ninefold excess of BPA. Irradiated with a 450 W Hanovia water cooled mercury lamp (Pyrex filter) at room temperature. *k* calculated via LC analysis of C-2 methyl and C-8 methyl derivatives using a computer-assisted least-squares curve-fitting routine. Standard deviations were determined from four to six individual runs. [b] Not observed.

Table II. Chemical Shifts of Aromatic Protons of Purine Compounds in Neutral and Acidic Solutions[a]

purines	δ H-2		δ H-8	
	neutral	cation	neutral	cation
1	8.01	8.61	8.15	9.44
2	8.31	9.32	8.21	8.60
3	8.59	8.69	8.48	9.37
4	8.81	9.29	8.13	8.91
5	8.87	9.13	8.62	9.36
6	8.64	9.24	8.00	8.98

[a] The neutral spectra were done in dimethyl-d_6 sulfoxide and the acid spectra in D_2O–CF_3COOD 2:1.

Table III. Comparison of Radical Methylation of 6- and 3,6-Substituted Purines at pH 1.1 and 7[a]

purines	pH	% yield C2	% yield C8	% ratio C-8/C-2
hypoxanthine (1)	1.1	<1	85.2	>85
	7.0	9.9	24.6	2.5 ± 0.3
3-methylhypoxanthine (2)	1.1	47.4	8.8	0.2 ± 0.1
	7.0	7.8	34.9	5.1 ± 0.3
6-methoxypurine (3)	1.1	2.3	67.4	29.2 ± 0.8
	7.0	11.6	22.8	2.0 ± 0.2
3-methyl-6-methoxypurine (4)	1.1	25.7	17.5	0.7 ± 0.1
	7.0	<1	24.2	>24
6-(methylthio)purine (5)	1.1	3.1	53.6	16.8 ± 1.6
	7.0	5.7	34.6	5.9 ± 0.7
3-methyl-6-(methylthio)-purine (6)	1.1	21.7	13.5	0.6 ± 0.0
	7.0	16.8	25.5	1.5 ± 0.2

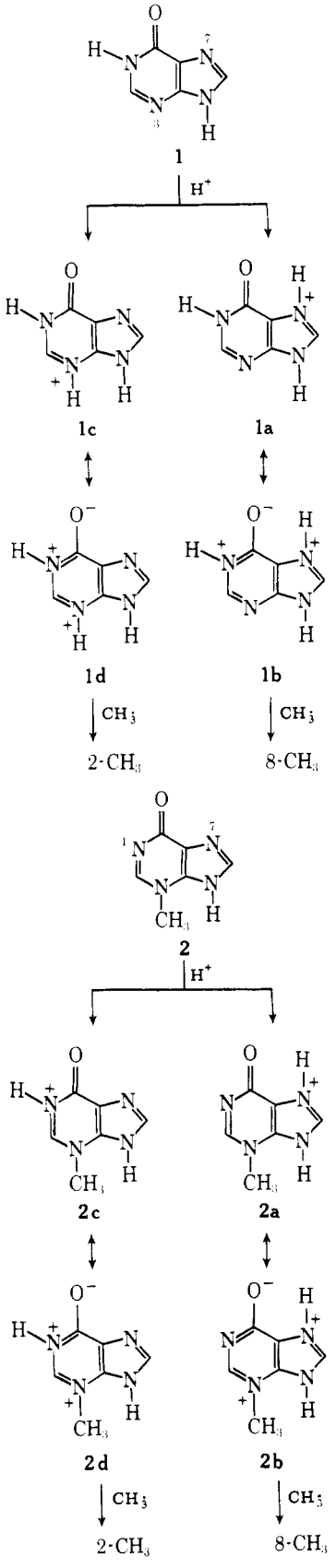
[a] 0.005 M solutions in 0.1 M buffer with fivefold excess of BPA. Irradiated for 15 h at 450 W, 32 °C. Product yields were determined via LC analysis.

Correlation of Regioselective C-2 and C-8 Methylation with the Site of Cation Formation as Indicated by δ H of the Aromatic Proton at the Reaction Site. The position of cation formation becomes important in discussing the mechanism of free-radical methylation of purines since it has been shown that the free-radical alkylations of quinolines and pyridines in acidic media always occur at the positions α and γ to the protonated heteroatom.[6] For the reaction of protonated 4-substituted pyridines with methyl radical, Minisci and co-workers[6b] found a linear correlation between the relative rates of reaction and the chemical shift of the proton at the reaction site. Thus, the relative rate increased with the amount of deshielding experienced by the aromatic hydrogen upon ring protonation. This sensitivity to the cationic effects is interpreted in terms of a nucleophilic $\dot{C}H_3$ attack yielding a purine radical $-CH_3^+$ complex as shown in Scheme Ib. In the present case of C-2 vs. C-8 reactivity of the 6- and 3,6-substituted purines, the methylation reaction appears to prefer the site of the more deshielded proton as revealed by the acid ^{1}H NMR spectra.

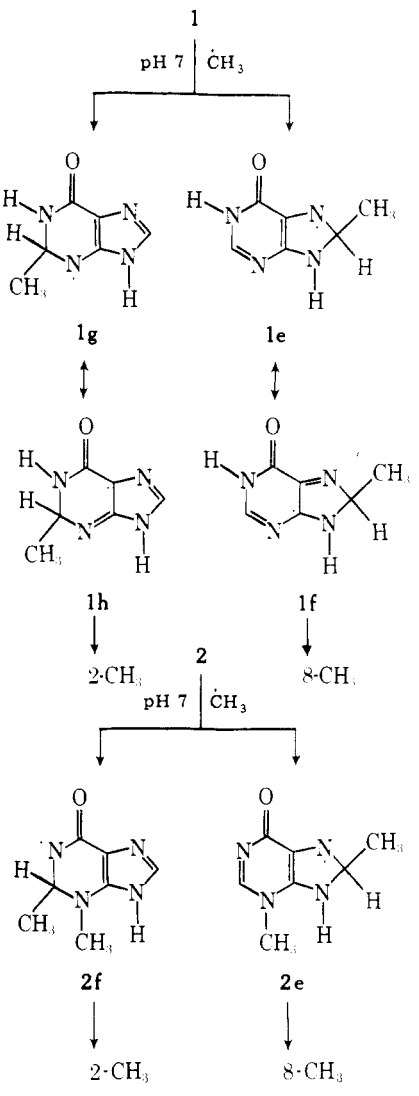
The protonated ^{1}H NMR spectra of purines **1, 2, 5,** and **6** were reported by Bergmann and co-workers.[5,7] We have determined the ^{1}H NMR spectra for the six purines used in this study and their chemical shifts and assignments are shown in Table II. The previous assignment[8] of H-8 of the cationic 6-methoxypurine at higher field than H-2 is now corrected. Thus, when 6-methoxypurine (**3**) was allowed to react with BPA in dimethyl sulfoxide under neutral conditions, H-8, the higher field proton, disappeared more rapidly. At the conclusion of the reaction when the medium was made acidic by adding trifluoroacetic acid and the spectrum retaken immediately, the proton yielding the least area (H-8, the site of reaction) was found at lower field at δ 9.10 whereas the less reactive proton was at δ 8.71. Upon acid hydrolysis of the isolated reaction product, 8-methylhypoxanthine (**8**) was obtained which was identified by co-chromatography with an authentic sample. Furthermore, the previous assignment[7] for the H-8 of compound **5** in the cationic form also appears to be in error. In this case, methylation reaction was again observed at the lower field resonance (i.e., H-8) of the acid spectrum, and the product isolated was identified as 8-methyl-6-(methylthio)purine (**7**). On the basis of these conjugate acid species, the regioselectivity for methylation of 6- and 3,6-substituted purines in acidic solution can be rationalized. Using the hypoxanthine (**1**) and 3-methylhypoxanthine (**2**) pair for comparison, Scheme II illustrates their protonation schemes preceding the methyl radical attack. Thus, N-7 or N-3 protonation of **1** leads to the respective cation for 8- and 2-methylation of **1** via the S_EAr mechanism as shown in Scheme I. Likewise, N-7 or N-1 protonation of **2** precedes the similar regiospecific reaction of **2.** Hypoxanthine is known to protonate at N-7,[9] making **1a** a much more probable conjugate acid than **1c**. However, formation of **2a** by N-7 protonation of **2** must be significantly depressed because of the direct attachment of the quaternized N-3 to the imidazolium ring in **2b.** On the other hand, the adverse charge effect of the quaternized N-1 in **1b** is one carbon atom further removed. Conversely, the N-1 protonated species **2c** should be more stable than **1c** as can be seen in comparing their respective resonance forms **1d** and **2d** where the quaternized N-3 in **2d** is stabilized by the methyl group. The combined effects of the above are that the k_{obsd} of 2-methylation is enhanced while that of 8-methylation is depressed for the 3-methyl derivative **2.** Similar mechanisms appear to prevail for the radical methylation of the other two pairs in their cationic forms.

Methylation in Neutral Media. Purines **1–6** were reacted with methyl radical in pH 7.0 aqueous solutions to determine the regioselectivity for the purines in the neutral form. The same reactions were also carried out at pH 1.1 for comparison purposes. The results given in Table III were obtained by

Scheme II



Scheme III



analysis of product distribution after 15 h of irradiation. No rate constants were obtained for the neutral reactions since methylation proceeded too slowly with side reactions quite noticeable at prolonged reaction times. Thus, in comparing the methylation reaction in neutral vs. acidic solutions, it was found that, for the 6-substituted purines, the preference for 8-methylation is retained in neutral medium although both the reaction yield and the C-8/C-2 ratio are much lower. For the 3,6-disubstituted purines, the selectivity has reversed, favoring 8-methylation in neutral solutions.

The product distribution appears to be compatible with the formation of a σ radical intermediate as shown in Scheme III, a mechanism derived previously[2] for methyl radical attack of the purine neutral species. Thus, radical intermediates **1e** and **1g** are responsible for 8- and 2-methylation of **1**, respectively. While they are both amino radicals, hence comparable in stability, their corresponding resonance forms **1f** and **1h** are not. Structure **1f** contains a carbon radical substituted by an amino N, an imino N, and an imine, while the carbon radical in **1h** is attached to a carbonyl, an imine N, and an imine. The net difference is that the aminoalkyl radical in **1f** is stabilized by a "three-electron bond" ($>\dot{C}-\ddot{N} \leftrightarrow >C^{-}-\dot{N}^{+}$)[10] whereas **1h** exhibits the α-carbonylalkyl radical conjugation. Since abstraction of an α-hydrogen of amines by the phenyl radical was 4.7 times faster than abstracting a ketone α-hydrogen,[11] **1f** should be more stable than **1h.** In the same vein, 8-methylation of **2** involves the amino radical **2e** which is reminiscent of a tertiary alkyl radical in the ease of formation.[12] The counterpart **2f** is an amidyl radical whose rate of formation lags behind even the α-carbonylalkyl radical.[13] Therefore, **1e** and **2e** are the preferred radical intermediates, leading to methylation at the 8 position of both **1** and **2**.

Experimental Section

Materials. Hypoxanthine (**1**), 6-methoxypurine (**3**), and 6-(methylthio)purine (**5**) were purchased from Aldrich Chemical Co.

Table IV. LC Conditions and Retention Times for the Analysis of the Methylation Reactions

purines	registry no.	solvent	flow rate, mL/min	T_R, min
hypoxanthine (1)		0.05 M NH_4OAc	3	3.2
2-methylhypoxanthine (13)	5167-18-0	0.05 M NH_4OAc	3	6.5
8-methylhypoxanthine (8)	30467-02-8	0.05 M NH_4OAc	3	7.0
3-methylhypoxanthine (2)		15% MeOH/0.05 M NH_4OAc	3	2.3
2,3-dimethylhypoxanthine (10)	69257-60-9	15% MeOH/0.05 M NH_4OAc	3	3.1
3,8-dimethylhypoxanthine (16)	25108-93-4	15% MeOH/0.05 M NH_4OAc	3	3.5
6-methoxypurine (3)		25% MeOH/0.01 M NH_4OAc	3	2.5
6-methoxy-2-methylpurine (14)	1198-45-4	25% MeOH/0.01 M NH_4OAc	3	3.7
6-methoxy-8-methylpurine (11)	69257-61-0	25% MeOH/0.01 M NH_4OAc	3	4.6
6-methoxy-3-methylpurine (4)		20% MeOH/0.05 M NH_4OAc	4	3.7
6-methoxy-2,3-dimethylpurine (12)	69257-62-1	20% MeOH/0.05 M NH_4OAc	4	4.5
6-methoxy-3,8-dimethylpurine (17)	69257-63-2	20% MeOH/0.05 M NH_4OAc	4	5.0
6-(methylthio)purine (5)		40% MeOH/0.05 M NH_4OAc	3	2.8
2-methyl-6-(methylthio)purine (15)	1008-47-5	40% MeOH/0.05 M NH_4OAc	3	3.6
8-methyl-6-(methylthio)purine (7)	1008-51-1	40% MeOH/0.05 M NH_4OAc	3	4.7
3-methyl-6-(methylthio)purine (6)		35% MeOH/0.2 M NH_4OAc	3	3.2
2,3-dimethyl-6-(methylthio)purine (9)	5759-57-9	35% MeOH/0.2 M NH_4OAc	3	4.3
3,8-dimethyl-6-(methylthio)purine (18)	5098-10-2	35% MeOH/0.2 M NH_4OAc	3	4.8

3-Methylhypoxanthine (2),[14] 6-methoxy-3-methylpurine (4),[15] and 3-methyl-6-(methylthio)purine (6)[14] were prepared according to published procedures. The *tert*-butyl peracetate (75% in benzene) was obtained from K&K division of ICN.

Reaction Mixture Analysis. ^{1}H-NMR spectra were run on a Perkin-Elmer R12A spectrometer in D_2O–CF_3COOD or Me_2SO-d_6 with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard. The high-pressure liquid chromatography (LC) system used was described previously.[2] The LC columns for analysis and preparative work were the Whatman Partisil 10 ODS columns, 4 mm i.d. × 25 cm and 9.4 mm i.d. × 50 cm. The solvent systems, flow rates, and retention times of the starting materials and the products in isocratic elution of the reaction mixtures are listed in Table IV.

Rate Studies of Purine–*tert*-Butyl Peracetate Reaction in Acidic Medium. Solutions of purines 1–6 (1.7 M in D_2O–CF_3CO_2D 2:1) containing a 9 M excess of BPA were placed in clear ^{1}H NMR tubes. These were irradiated at 25 °C at a distance of 1.2 cm from a 450 W UV lamp (Hanovia water-cooled immersion well, Pyrex filter). The tubes were removed periodically for ^{1}H NMR analysis of the extent of reaction via integration of the residual aromatic protons of the purines. Concurrent with obtaining the ^{1}H NMR spectra, samples were removed for LC analysis. The rate constants were derived from the pseudo-first-order plots of log [residual purine] vs. time, and the data were submitted to a computer-assisted least-squares curve fit routine.

Methylation Product Isolation and Identification. 8-Methylhypoxanthine (8). Irradiation of a hypoxanthine solution in aqueous trifluoroacetic acid was continued until no residual H-8 was observed. The solution was neutralized and the product which precipitated from solution was collected and identified by LC co-chromatography with an authentic sample:[4] λ_{max} (pH 1) 248 nm (log ϵ 3.34), (pH 12) 261 nm (log ϵ 3.40); ^{1}H NMR (D_2O–CF_3COOD 2:1) δ 8.39 (s, 1), 2.86 (s, 3).

2,3-Dimethylhypoxanthine (10). Irradiation of a 3-methylhypoxanthine solution in aqueous acid was continued until the residual H-2 was at a minimum as evidenced by ^{1}H NMR analysis. The solution was neutralized and the product which precipitated from solution was collected and recrystallized: λ_{max} (pH 1) 255 nm (log ϵ 3.90) [lit.[5] (pH 1) 254.5 nm (log ϵ 4.05)]; ^{1}H NMR (D_2O–CF_3COOD 2:1) δ 8.42 (s, 1), 4.13 (s, 3), 2.93 (s, 3).

6-Methoxy-8-methylpurine (11). Irradiation of a 6-methoxypurine solution in aqueous acid was continued until a minimum amount of H-8 was detected by ^{1}H NMR analysis. The product was isolated via preparative high pressure liquid chromatography using the solvent system listed in Table IV: mp 213–15 °C; λ_{max} (pH 7) 256 nm (log ϵ 3.86); ^{1}H NMR (D_2O–CF_3COOD 2:1) δ 8.88 (s, 1), 4.38 (s, 3), 3.04 (s, 3). Acid hydrolysis of **11** yielded **8** which was identified by co-chromatography with an authentic sample.[4]

6-Methoxy-2,3-dimethylpurine (12). Irradiation of 6-methoxy-3-methylpurine in aqueous acid was continued until a minimum amount of H-2 was detected by ^{1}H NMR analysis. The product was isolated by preparative LC using the solvent system listed in Table IV: ^{1}H NMR (D_2O–CF_3COOD 2:1) δ 8.67 (s, 1), 4.39 (s, 3), 4.30 (s, 3), 3.11 (s, 3). The product was found to undergo rapid hydrolysis to **10** which was identified by co-chromatography with an authentic sample.[5]

8-Methyl-6-(methylthio)purine (7). Irradiation of a 6-(methylthio)purine solution in aqueous acid was continued until a minimum amount of H-8 was detected by ^{1}H NMR analysis. The product was isolated by preparative LC using the solvent system listed in Table IV: mp 215–8 °C (lit.[16] mp 223–4 °C); λ_{max} (pH 7) 292 nm (log ϵ 3.72); ^{1}H NMR (D_2O–CF_3COOD 2:1) δ 8.93 (s, 1), 3.04 (s, 3), 2.87 (s, 3).

2,3-Dimethyl-6-(methylthio)purine (9). Irradiation of 3-methyl-6-(methylthio)purine solution in aqueous acid was continued until the H-2 proton was at a minimum as evidenced by ^{1}H NMR analysis. The product was isolated by preparative LC and was identified by UV spectroscopy (λ_{max} (H_2O) 312 and 237 nm) and by hydrolysis in acidic hydrogen peroxide to 2,3-dimethylhypoxanthine. The latter was identified by co-chromatography with an authentic sample.[5]

2-Methylhypoxanthine (13). The presence of 2-methylhypoxanthine (13), a minor product in the methylation of hypoxanthine (1), was confirmed by co-chromatography with an authentic sample purchased from Het-Chem-Co.

6-Methoxy-2-methylpurine (14). The reaction mixture of 6-methoxypurine (3) containing the minor product **14** was allowed to reflux in 1 N hydrochloric acid for 1 h. The 2-methylhypoxanthine (13), thus obtained, was identified by co-chromatography with the authentic sample mentioned above.

2-Methyl-6-(methylthio)purine (15). The reaction mixture of 6-(methylthio)purine (5) containing **15** was allowed to reflux in 30% hydrogen peroxide for 1 h. The 2-methylhypoxanthine (13), thus obtained, was identified by co-chromatography with the authentic sample.

3,8-Dimethylhypoxanthine (16). The reaction mixture of 3-methylhypoxanthine (2) was submitted to LC. The peak on the LC trace corresponding to 3,8-dimethylhypoxanthine (16) was trapped in the flow cell of the Tracor scanning variable wavelength detector. The UV spectrum of the trapped material was identical to that reported in the literature:[17] λ_{max} (H_2O) (pH 8) 266 nm.

6-Methoxy-3,8-dimethylpurine (17). The reaction mixture of 6-methoxy-3-methylpurine (4) was allowed to reflux in 1 N hydrochloric acid for 1 h. The 3,8-dimethylhypoxanthine (16), thus obtained, was identified by co-chromatography with the methylation product of 3-methylhypoxanthine (2).

3,8-Dimethyl-6-(methylthio)purine (18). The reaction mixture of 3-methyl-6-(methylthio)purine (6) was allowed to reflux in 30% hydrogen peroxide for 1 h. The 3,8-dimethylhypoxanthine (16), thus obtained, was identified by co-chromatography with the product isolated from the methylation mixture of 3-methylhypoxanthine (2).

Comparison of Reactions of Purines with *tert*-Butyl Peracetate in Acidic and Neutral Media. Solutions of purines 1–6 (0.005 M in 0.1 M HCl or 0.1 M pH 7 buffer prepared from 0.1 M KH_2PO_4

and 0.1 M NaOH) containing a 5 M excess of BPA were placed in clear Pyrex tubes. These were irradiated for 15 h at 32 °C at a distance of 1 cm from a 450 W UV lamp (Hanovia water-cooled immersion well, Pyrex filter). The product distributions were determined by LC analysis of the reaction mixtures and the results are listed in Table III.

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Registry No.—BPA, 107-71-1.

References and Notes

(1) This is part 8 of our continuation study of the Reactivities and Electronic Aspects of Nucleic Acid Heterocycles. Part 7: J. H. Keck, Jr., R. A. Simpson, and J. L. Wong, *J. Org. Chem.*, **43**, 2587 (1978).
(2) M. F. Zady and J. L. Wong, *J. Am. Chem. Soc.*, **99**, 5096 (1977).
(3) H. Steinmaus, I. Rosenthal, and D. Elad, *J. Org. Chem.*, **36**, 3594 (1971).
(4) M. Maeda, K. Nushi, and Y. Kawazoe, *Tetrahedron*, **30**, 2677 (1974).
(5) D. Lichtenberg, F. Bergmann, and I. Ringel, *J. Magn. Reson.*, **6**, 600 (1972).
(6) (a) A. Clerici, F. Minisci, and O. Porta, *Tetrahedron*, **30**, 4201 (1974); (b) F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *ibid.*, **28**, 2403 (1972).
(7) U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. Chem. Soc., Perkins Trans. 1*, 793 (1973).
(8) W. C. Coburn, M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, **30**, 1114 (1965).
(9) D. Lichtenberg and F. Bergmann, *J. Chem. Soc., Perkins Trans. 1*, 789 (1973).
(10) F. D. Greene, J. D. Burrington, and A. M. Karkowsky, "Organic Free Radicals", W. A. Pryor, Ed., American Chemical Society, Washington, D.C., 1978, pp 123 and 124.
(11) G. A. Russell, "Free Radicals", Vol. 1, J. K. Kochi, Ed., Wiley, New York, 1973, pp 229–304.
(12) B. G. Gowenlock, P. P. Jones, and D. R. Snelling, *Can. J. Chem.*, **41**, 1911 (1963).
(13) E. Hayon, T. Ibata, N. N. Lichtin, and M. Simic, *J. Am. Chem. Soc.*, **93**, 5388 (1971).
(14) J. J. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 1914 (1962).
(15) F. Bergmann, Z. Neiman, and M. Kleiner, *J. Chem. Soc. C*, 10 (1966).
(16) H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958).
(17) F. Bergmann and M. Tamari, *J. Chem. Soc.*, 4468 (1961).

Substituent Effect on the Electrochemical Oxidation of Trityl Anions

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The reversible one-electron oxidations of triaryl anions and the irreversible second oxidative processes were examined for a series of sequentially substituted *p*-methyl anions. The cycle voltammograms of the lithium salts prepared in dimethoxyethane reveal that each of the potentials depends upon the substituent in the para positions. The relative effect of substituent on the stability of the several species is compared with other known measurements. Additionally, the relationship between carbanion stability and reduction potential is discussed.

The use of electrochemical data to provide entries into the thermodynamic stabilities of cations and anions is based on the interrelationship with the corresponding radical as shown below:

$$ROH \rightleftarrows R^+ \overset{e}{\rightleftarrows} R\cdot \overset{e}{\rightleftarrows} R^- \rightleftarrows RH$$

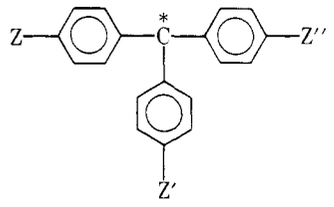
The important successes of the method are attested to by the recent contributions of Breslow and co-workers[1] and the extensive work by Henglein on the electrochemical properties of radical intermediates determined by pulse radiolysis polarography.[2]

In this study we utilize this approach to investigate the oxidation potentials of triaryl anions with two objectives: first, to provide information on the factors that govern carbanion and free-radical energy differences; second, to assess the relative substituent effect on the stability of anions, radicals, and carbonium ions. The first relates to the contributions of one and two electron transfer processes to nucleophilicity.[3] In a homologous series knowledge of anion stability and reduction potential can be used to probe relationships with nucleophilicities. The second relates to the types of contributions substituents can and do make on stability.

Accordingly, we have investigated the electrochemistry of a series of triaryl anions with a systematic substituent variation. Included in this work are the reversible and irreversible oxidation potentials of the series of para methyl substituted anions.

Results and Discussion

The lithium anions Ia → IVa were generated from the corresponding hydrocarbons and reaction with *n*-butyllithium



I, Z = H; Z′ = H; Z″ = H
II, Z = CH_3; Z′ = H; Z″ = H
III, Z = CH_3; Z′ = CH_3; Z″ = H
IV, Z = CH_3; Z′ = CH_3; Z″ = CH_3

a, * = 2 electrons
b, * = 1 electron
c, * = 0 electrons
d, * = H
e, * = OH
f, * = Cl

in dimethoxyethane (DME).[4] The triaryl methanes IId and IIId were obtained via Grignard syntheses. Compound IVd was prepared from the corresponding chloride following the method of Gomberg.[5] To minimize decomposition of the air-moisture sensitive anions the freshly prepared solutions were generated on a No-Air system directly in the electrochemical cell.

The voltammogram of Ia depicted in Figure 1 reveals the reversible one-electron oxidation at −1.20 V and the irreversible oxidation at +0.57 V. These results are in agreement with those obtained by others for this same anion.[1a,b] Additionally the degree of reversibility and reproducibility, ±0.007 mV, of the measurements are acceptable. Accordingly, we investigated the corresponding electrochemical behavior of the substituted anions IIa → IVa. These data are depicted in

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