($C_{34}H_{48}O_{11}$, mol wt 632.76). The intensity data were collected on a Picker FACS-1 diffractometer equipped with a graphite monochromator (Mo Kα radiation, λ = 0.71069) and with modified Nonius low-temperature device.[12] A crystal measuring approximately 0.15 × 0.35 × 0.5 mm was used for data collection at 96 K. Cooling was used in order to increase the number of observed reflections, which was very limited at room temperature. A total of 5827 independent reflections were measured (θ < 30°) of which 3889 were considered to be observed [$I > 2.0\sigma(I)$]. The data were not corrected for absorption (μ = 1.01 cm^{-1}).

The structure was solved by direct methods, using the program MULTAN[13] and refined by full-matrix least-squares methods, using the X-RAY system.[14] The 48 H atoms were located in difference maps. In the final refinement anisotropic thermal parameters were used for C and O atoms, and isotropic temperature factors (B = 2.0 Å^2) were used for H atoms, but only positional parameters for the H atoms were refined. The final discrepancy index is R = 0.080 for the 3889 reflections. Unit weights were used for all observed reflections. (See paragraph at the end of the paper about supplementary material.)

Acknowledgment. We are grateful to Professor F. Sandberg for supply of plant material, Dr. Elfinn Larsen for recording the mass spectra, and Dr. K. Schaumburg and Dr. H. Eggert for recording the FT NMR spectra with the Bruker HX-270S and the JEOL FX 90Q spectrometers of the Danish Natural Science Research Council. Dr. S. Larsen and Mr. F. Hansen are thanked for help in X-ray data collection.

Registry No. 1, 67526-95-8; 2, 77521-47-2; 3, 80063-00-9; 4, 80048-99-3; 5, 80063-01-0; 6, 77521-46-1; 7, 77521-45-0; 8, 80049-00-9; 9, 80049-01-0; 10, 77521-43-8; 11, 67526-94-7; 12, 80049-02-1; 13, 80049-03-2.

Supplementary Material Available: Figure 2 giving the notation of the atoms and tables III-VII listing torsion angles, final atomic coordinates and anisotropic thermal parameters, bond lengths, and bond angles (6 pages). Ordering information is given on any current masthead page.

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Competitive Reactivity of Nitrenium and Carbenium Ion Contributors of Purinium Cations with "Soft" Bases[1]

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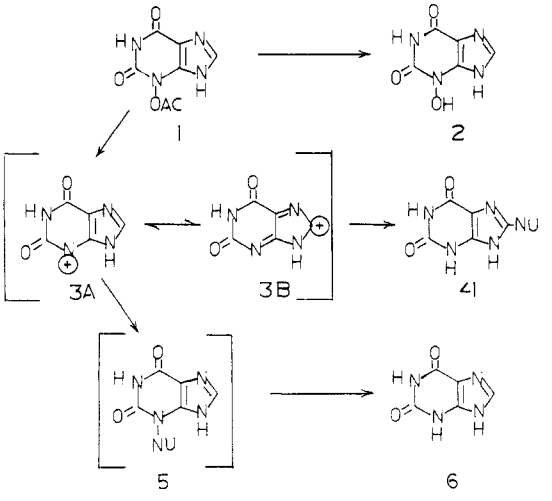
Received September 15, 1981

Delocalized cations formed by ionization of "activated" esters of carcinogenic purine N-oxides react with many nucleophiles to yield C-substitution products but afford oxidation-reduction products with others. The present study provides experimental support for the proposals (1) that these two reactivities result from nucleophilic substitutions at different sites of the delocalized cations and (2) that HSAB "hard" bases react only at carbenium ion sites to form C-substitution products, while "soft" bases react preferentially at nitrenium ion contributors to afford adducts that ultimately yield redox products. "Soft" bases showed the following order of reactivity at a purine nitrenium ion: iodide ≈ selenourea ≫ thio amides ≈ thio acids ≈ biselenide > bisulfide ≈ thiols ≈ disulfides > thiosulfate. This order differs significantly from that observed for the double S_N2 displacement reaction of nucleophiles with compounds of the type NH_2-X. This appears to be the first report of differing orders of nucleophilicities of bases involved in S_N1 and S_N2 reactions at electron-deficient nitrogen centers. No evidence was found for radical intermediates formed by electron transfer.

3-Hydroxyxanthine and several related N-oxidized purines are potent carcinogens in rats.[2-7] Studies on the mechanism of tumor induction demonstrated that while the N-oxides undergo few reactions, their O-esters are extremely reactive under mild conditions. Metabolic esterification in vivo is an essential step for tumor development.[8-10] In vitro N-(acyloxy)purines undergo a variety of reactions including hydrolysis, spontaneous reduction, nucleophilic substitution, and an oxidation-reduction reaction with certain nucleophiles.[11-15] Nucleophilic sub-

Scheme I



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0022-3263/82/1947-0652$01.25/0

Table I. Product Compositions from Reactions of 3-Acetoxyxanthine with Selected Nucleophiles at pH 7

name	structure	yield[a,d] 4 (Nu = OH)	2	6 (±)	8-NuXan, 4 [Nu=][b]	total[c]
control		40 (2)	4 (1)	20 (2)		64
	(A) "Soft" Bases					
iodide	I^-			70 (6)		70
selenourea	$H_2NCSeNH_2$		4 (1)	80 (6)		84
thio amides						
thiourea	H_2NCSNH_2			50 (4)	28 (3) [SH]	78
6-mercaptopurine	$C_5H_4N_4S$	7 (1)	5 (2)	50 (4)		62
thioacetamide	CH_3CSNH_2			40 (3)	26 (1) [SH]	66
thio acids						
ethyl xanthate	$EtOCS_2^-$			42 (3)	52 (1) [SH]	94
thioacetate	CH_3COS^-			43 (1)	52 (3) [SH]	95
thiocarbonate	CS_3^{2-}		14 (1)	43 (1)	38 (1) [SH]	95
biselenide	HSe^-	3 (1)	5 (1)	40 (3)		48
thiols						
bisulfide	HS^-		13 (4)	32 (5)	29 (2) [SH]	74
N-acetyl-L-cysteine	$HSCH_2CHNHAcCO_2^-$	38 (1)	7 (1)	37 (2)		82
thiophenol	C_6H_5SH	14 (9)	3 (1)	30 (2)	13 (2) [SC_6H_5]	60
tert-butylmercaptan	$(CH_3)_3CSH$	38	8	28		74
dimethyl disulfide	$(CH_3S)_2$	15 (1)		27 (2)		42
thiosulfate	$S_2O_2^{2-}$		6 (2)	24 (2)	48 (3) [SH]	78
cyanide	CN^-	45 (2)	6 (2)	18 (3)		69
	(B) "Borderline" Bases					
bisulfite	HSO_3^-	12 (6)	16 (5)	18 (1)		46
nitrite	NO_2^-		3 (1)	10 (3)	30 (1) [NO_2]	43
	(C) Reducing Agents					
borohydride	BH_4^-	17 (1)		34 (3)		51
dithionite	$S_2O_4^{2-}$	14	26	14		54
dithionate	$S_2O_6^{2-}$	39	9	20		68

[a] Yields are expressed as mole percent of starting material. [b] Substituent at the 8-position of 4 (Scheme I). [c] Percent recovery of starting material. [d] Values in parentheses are standard deviations.

stitution of purine *N*-oxide esters resembles that of esters of arylhydroxylamines, the "activated" form of arylamine oncogens.[16,17] Similar types of delocalized aromatic cations appear to be involved as intermediates in these S_N1' substitution reactions.[15-18] The formation of covalent adducts between arylamine cations and nucleophilic sites in DNA is generally considered to be the initiating factor in the induction of tumors.[19,20] Nucleophilic addition products at both the electron-deficient nitrogen and carbon sites in arylhydroxylamine esters have been identified.[16,19] Only C-substitution products have been isolated from reactions of *N*-(acyloxy)purines with nucleophiles in vitro[11-13,15] or in vivo.[6,8,21,22] This alkylating reactivity may account for the oncogenic properties of some purine *N*-oxides.

In contrast to most nucleophiles, iodide ion does not react with *N*-(acyloxy)purines to afford 8-iodopurines. Instead, it produces a redox reaction that yields the parent purine and iodine.[13] Studies on the mechanism of this unexpected redox activity[15,23-25] implicated the delocalized cations involved in nucleophilic C-substitution as intermediates in the redox reaction. It was proposed[15] that the electron-deficient nitrogens of such aromatic cations, e.g., **3A** (Scheme I), are exceptionally "soft" acids by the criteria of the Pearson hard and soft acid and base (HSAB) classification.[26,27] Accordingly, they should exhibit a strong preference for reacting selectively with "soft" base nucleophiles such as iodide ion. However, the formation of a nitrenium ion–nucleophile adduct, e.g., the iodoamide **5** (Nu = I), from a purine cation and a "soft" base does not lead to a stable product but produces an intermediate that reacts further to yield the observed redox products, xanthine (**6**) and iodine.

The present studies were undertaken to test the validity of the earlier proposals,[15,25] which were based on studies with only two nucleophiles, that the nucleophilic substitution and redox reactions are dual reactivities of a single ambident electrophile and that the type of reaction that will occur with this intermediate is determined by the character of the nucleophile. This represents the first investigation into the relative reactivity of two electron-deficient sites within a single aromatic cation that differ substantially in their nucleophilic properties.

Results

Reactions were performed under standarized conditions with 5 equiv of nucleophile at pH 7.0 in 0.1 M phosphate buffer. This was previously shown not to affect the

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product composition from 1.[15] At pH 7 the major product formed spontaneously from 1 is uric acid [4 (Nu = OH), Scheme I], arising by nucleophilic substitution at the 8-position of the cation **3B** with the solvent (Table I). A significant portion (20%) of 1 undergoes spontaneous reduction to xanthine (**6**), while a small amount (4%) is hydrolyzed to 3-hydroxyxanthine (**2**). The remaining 36% of starting material is not detectable by UV absorption and probably consists of a mixture of oxidation products of uric acid; oxidation of uric acid to non-UV-absorbing products by 1 has been demonstrated.[14]

The addition of most nucleophiles to a reaction of 1 diminishes or eliminates reactions of 1 with the solvent, including hydrolysis to 3-hydroxyxanthine, reduction to xanthine, and 8-substitution with the solvent, and produces an 8-substituted xanthine derivative of the nucleophile, **4**.[12,13] The presence of a redox reaction between a nucleophile and **3A** was indicated primarily by an enhancement, rather than a decrease, in the yield of the reduction product, xanthine (**6**), compared to that formed via the spontaneous reduction of 1 in buffer only (Table I, control). With iodide ion, formation of the oxidation product, triiodide ion, could be monitored as well. The yield of triiodide correlated well with that of **6**. Thus, at least with iodide ion, the evidence indicates that the redox reaction with **3A** consumes all of 1, and there is little or no spontaneous reduction of 1 to xanthine. With the other nucleophiles the yield of oxidation product was not determined independently, hence it must be assumed that some, perhaps as much as the usual 20%, of **6** may be produced by the spontaneous reduction of 1. For this reason only the enhancements in the yield of **6** over the control value are considered.

Table I lists the product compositions from the reactions of 1 in the presence of a series of "soft" and "borderline" base nucleophiles and two reducing agents. Compounds have been arranged in decreasing order of their ability to act as a reducing agent of 1. With some "soft" nucleophiles there was no C-substitution via **3B** while others formed a C-substitution product, e.g., 8-thiouric acid (**4**, Nu = SH). The yields of uric acid and 3-hydroxyxanthine were greatly decreased or eliminated in the presence of most nucleophiles. Iodide was the only "soft" base to yield **6** exclusively. It was closely followed by selenourea, which afforded a small amount of 3-hydroxyxanthine (**2**). Thio amides and thio acids produced elevated yields of **6** and also reacted to a significant, often larger, extent at the carbenium ion of **3B** to yield 8-thiouric acid. The extent of reduction of 1 was relatively constant for all of the thiocarbonyl derivatives (40–50% yields of **6**), while reactivity at the carbenium ion of **3B** varied. C-Substitution was greater for thio acids than for thio amides. 6-Mercaptopurine behaved somewhat anomalously; it enhanced the yield of **6** but gave no C-substitution product. Thiocarbonate reacted well at both electron-deficient sites of **3**. It was also apparently reactive with 1 prior to the formation of **3**, as shown by the increase in formation of 3-hydroxyxanthine (**2**). Since the very "soft" nitrenium ion of **3** would be unlikely to react with any "hard" oxygen nucleophile, **2** must arise from the "soft–soft" interaction between thiocarbonate and the "soft" carbonyl carbon of 1. This interaction occurred completely at the expense of nucleophilic addition to the carbenium ion.

Thiols were less effective reducing agents than thiocarbonyl compounds and reacted significantly less at the carbenium ion; only bisulfide and thiophenol afforded 8-substitution products. Bisulfide, like thiocarbonate, also increased the yield of **2**. The absence of formation of 8-substitution products with the two aliphatic thiols was surprising, in view of their known high nucleophilic properties and the report that *N*-acetyl-L-cysteine affords an *S*-(8-xanthyl)cysteine adduct at pH 6 in low yield (14%).[14] That amount or even less would have been readily detectable in the present studies but was not observed. The enhanced yield of **6** observed with *N*-acetyl-L-cysteine does complement the observation[14] that *N*-acetyl-L-cysteine is oxidized in part to cysteic acid in the presence of 1 and suggests that the two products are formed as part of a redox reaction.

The behavior of dimethyl disulfide was qualitatively similar to that of the alkyl thiols; it enhanced the yield of xanthine slightly but did not react at C(8) of **3B**. Thiosulfate reacted appreciably at C(8) of **3B** to yield 8-thiouric acid, but in contrast to the thiocarbonyl acids, it demonstrated little reducing activity toward **3**. The "soft" base cyanide, the "borderline" base bisulfite, and dithionate showed no indication of reacting at either electron-deficient site of **3**, while the "borderline" base nitrite reacted only at the carbenium ion of **3B**. The fully oxidized dithionate would not be expected to react with **3** and served as an internal control.

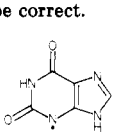
Discussion

Previous studies[18] on the spontaneous reactions of 3-acetoxyxanthine (1, Scheme I) in aqueous solution demonstrated that the ester could undergo C-substitution at the 8-position by two possible reaction paths. The extent of each was determined by the pH (path a < pH 3 > path b). Both pathways involved the delocalized cation, **3A,B**, as the electrophilic intermediate in the C-substitution reaction. A second type of reactivity, spontaneous reduction of a portion of 1 to xanthine (**6**), was observed only in conjunction with C-substitution via the pathway operative at pH's above 3. The mechanism of this spontaneous reduction reaction has not been established.[28]

A third type of reactivity of 1 was indicated by the exclusive formation of the reduction product, xanthine, in the presence of iodide ion. The concomitant formation of 1 equiv of iodine demonstrated the redox nature of the process.[13] This reactivity was subsequently shown to be a general property of all *N*-(acyloxy)purines that could undergo nucleophilic substitution.[21,23,25] In each instance iodide ion could completely eliminate 8-substitution in favor of a redox reaction, affording iodine and the parent purine.

Certain other nucleophiles exhibited similar, although less dramatic, abilities to participate in redox reactions with *N*-(acyloxy)purines. Bromide ion affords C-substitution products with most *N*-(acyloxy)purines,[13] but with 3-acetoxy-1,7-dimethylguanine it behaved as a redox agent and produced 1,7-dimethylguanine and tribromide ion.[23] No 8-substitution occurred with bromide ion. Bromide was a less efficient reducing agent than iodide ion, and high concentrations (3 M) were required to effect complete reduction. The extent of reduction of the ester was a direct function of the bromide ion concentration and both were

(28) It was originally suggested[18] that the spontaneous reduction of 1 might be a radical process involving the amidyl radical, 7. It was then assumed that 7 was also associated with the redox reaction observed in the presence of iodide. However, data from recent studies[15,23-25] indicate that the hypothesis cannot be correct.



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inversely correlated with the extent of 8-substitution that took place with the solvent. Thiourea decreased the yields of uric acid and 3-hydroxyxanthine, elevated the yield of xanthine, and formed 8-thiouric acid.[15] Similarly, very high concentrations of thiourea enhanced the reduction of 3-acetoxy-9-methylxanthine and 3-acetoxy-9-methylguanine to the parent purines.[25] This was accompanied by a corresponding decrease in 8-substitution with the solvent and the formation of small amounts of 8-thio derivatives.

The data from those studies[15,23,25] consistently indicate that the redox reaction of *N*-(acyloxy)purines observed with a few nucleophiles and the 8-substitution reaction seen with the majority of nucleophiles are competitive reactions involving a common intermediate. An obvious candidate for this intermediate from **1** is the delocalized cation, **3A,B**. It was proposed[15] that these dual reactivities of **3A,B** result from different reactions at each of its electron-deficient sites, i.e., the nitrenium ion of **3A** and the carbenium ion of **3B**. The reactions at each site occur with different groups of nucleophiles, which could be categorized as either "hard" or "soft" bases, as defined by the hard and soft acid and base concept (HSAB) of Pearson.[26] Thus the dual reactivities of **3A,B** could be atrributed to "hard" bases reacting exclusively at the carbenium ion of **3B** to produce 8-substituted xanthines and "soft" bases reacting preferentially at the nitrenium ion of **3A** to afford intermediates that reacted further in an oxidation–reduction process.

To test the validity of these proposals, we have examined the effect of a series of "soft" and "borderline" bases on the product composition from **1** under a standardized set of conditions (Table I) and find that the data accord with the proposals. Substitution reactions of **1** were performed previously mainly with "hard" or "borderline" bases, e.g., Cl^-, N_3^-, NO_2^-, amines, and alcohols.[12,13] The only "soft" bases reacted with **1** were a thioether (methionine)[12,13] and a thiol (*N*-acetyl-L-cysteine),[21] both of which were reported to afford 8-substitution products. We find that at pH 7, 5 equiv of cysteine enhances the yield of xanthine but does not produce the *S*-(8-xanthyl)cysteine adduct reported[21] previously. Thiolate nucleophiles, in general, increased the formation of xanthine by 7–17%, but only the most reactive, bisulfide and thiophenol, afforded C-substitution products under the present conditions. The yields of those were not high. Aliphatic thiols, dimethyl disulfide, and thiosulfate proved to be the boundary between "soft" bases that could enhance the yield of xanthine and those with no effect.

Biselenide, thio acids, and thio amides showed a greater effect on the formation of xanthine, increasing its yield by 20–30% over the control value. The thiocarbonyl compounds also reacted to a significant extent at C-8 of **3B** to afford 8-thiouric acid. C-Substitution was larger for thio acids (40–50%) than for thio amides (0–28%). The greatest enhancements in the formation of xanthine from **1** were shown by selenourea, which increased the yield of **6** by 60%, and the very "soft" base iodide. As with iodide, no 8-substitution product could be detected with either selenium nucleophile, selenourea or biselenide.

The "soft" bases in Table I show the following order or reducing ability toward **3**: iodide ≈ selenourea ≫ thio amides ≈ thio acids > thiols ≈ disulfides > thiosulfate. This order is consistent with a reaction that is frontier orbital controlled,[29] i.e., one involving "soft–soft" interactions. The relative reactivities of two pairs of bases, thio-, and selenourea and bisulfide and biselenide, with **3** are strongly indicative of frontier orbital control for the redox reaction. Selenium nucleophiles are "softer" bases than the corresponding sulfur analogues.[26,27] Accordingly, seleno derivatives should exhibit greater selectivity than sulfur analogues toward reaction at the "softer" of two acid sites.[26] In the aromatic cation **3** that would be the nitrenium ion **3A**. If reaction at N-3 of **3A** initiates a redox reaction, selectivity would be manifested by greater enhancements in the yield of xanthine by seleno nucleophiles than by the sulfur counterparts. That was indeed observed: selenourea (60% enhancement) > thiourea (30%); biselenide (20%) > bisulfide (12%). The greater selectivity of the selenium nucleophiles was also shown by their lack of reaction at the "harder" acid site of **3**, the carbenium ion **3B**. This behavior was also observed with the very "soft" base iodide ion. In contrast, the sulfur nucleophiles reacted significantly at both electrophilic sites of **3**. These data are thus strongly supportive of the proposal that reactivity at the nitrenium ion of **3A**, leading to a redox reaction, is determined by the "softness" of a nucleophile.

The redox reaction between **1** and "soft" bases is very reminiscent of the double-displacement redox reaction (eq 1 and 2) observed with certain nucleophiles and O-esters

$$\underset{}{I^-} + \underset{\mathbf{8}}{NH_2OSO_3^-} \rightarrow \underset{\mathbf{9}}{NH_2I} + SO_4^{-2} \quad (1)$$

$$\underset{}{I^-} + \underset{\mathbf{9}}{NH_2I} \rightarrow NH_2^- + I_2 \quad (2)$$

$$I^- + \underset{\mathbf{3A}}{>N^+} \rightarrow \underset{\mathbf{5}}{>N\text{–}I} \quad (3)$$

$$I^- + \underset{\mathbf{5}}{>N\text{–}I} \rightarrow \underset{\mathbf{6}}{>N^-} + I_2 \quad (4)$$

of hydroxylamines, e.g., hydroxylamine-*O*-sulfonate (**8**, eq 1).[30–34] The intermediate formed initially in those reactions, e.g., iodoamine (**9**, eq 1), with iodide ion rapidly undergoes a second S_N2 reaction with a second mole of nucleophile to afford ammonia and the oxidized nucleophile, iodine (eq 2). However, it was established earlier that this is not the mechanism of the redox reaction between the *O*-acyl hydroxamate **1** and "soft" bases.[15] There was no dependency on the concentration of iodide ion beyond the required 2 equiv. Instead, at pH's below 3 (path a) iodide ion produced xanthine (**6**) only to the extent that C-substitution occurred in the absence of iodide (5%). These data indicate that the redox reaction cannot be initiated until after the cation, **3A,B**, has been formed. We propose that the redox reaction of *N*-(acyloxy)purines is a two-step process somewhat similar to that observed with O-esters of hydroxylamine, **8** (eq 1 and 2), but differing in its requirement for an initial ionization of **1** to **3A,B**. Frontier orbital controlled nucleophilic addition of "soft" bases at the electron-deficient nitrogen of **3A** produces the adduct **5** (eq 3). This product subsequently reacts at the substituted nitrogen with a second mole of nucleophile to yield the observed redox products (eq 4). The first step of the redox reaction of **1** (**1** → **3** and eq 3) can be considered the S_N1 equivalent of the initial S_N2 reaction between O-esters of hydroxylamine and nucleophiles (eq 1).

The second step for both reactions (eq 2 and 4) involves displacement at the nitrogen by a second mole of nucleo-

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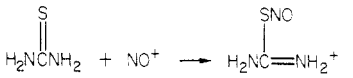
phile. There are several known examples of comparable displacements involving many of the nucleophiles that are most reactive with **3A**. These include the oxidation of iodide ion by *N*-iodo amides;[35] oxidation of thiourea to the disulfide by *S*-nitrosoisothiouronium salts (**10**, eq 6), which



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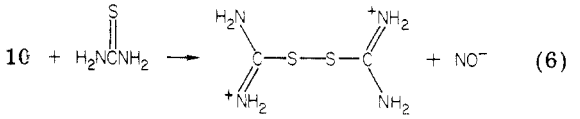
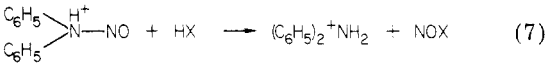


(6)

are formed, in turn, by nitrosation of thiourea (eq 5);[36] denitrosation of aromatic *N*-nitroso amines by thiourea and halide ions (eq 7);[37-40] formation of disulfides from



(7)

$$RSH + N_2O_4 \rightarrow RSNO \quad (8)$$

$$RSNO + R'SH \rightarrow RSSR' + HNO \quad (9)$$

$$RSH + R'SN< \rightarrow RSSR' + HN< \quad (10)$$

thiols and thionitrites (eq 9)[41,42] or thioimides (eq 10);[43-46] and the oxidation of thiols to disulfides by *N*-bromoacetamide.[47,48] The two reaction sequences involving nitrosation of thiourea or thiols to *S*-nitroso intermediates (eq 5 and 8) which subsequently react to yield the disulfides (eq 6 and 9) are almost identical with the proposed mechanism for the redox reaction of **1**. All three reactions involve nucleophilic addition to an electron-deficient nitrogen to form an activated intermediate that reacts readily with "soft" bases. Intermediates have been isolated from reactions with nitrite only with great care[41] but are usually not obtainable.[36,48] All attempts to trap intermediates from **1** with "soft" bases have been unsuccessful.

Many of the nucleophiles that reacted with **3A** have also been studied with hydroxylamine-*O*-sulfonate.[31-34] It is noteworthy that the nitrenium ion of **3A** does not exhibit the same order of reactivity toward nucleophiles as does the "soft" trivalent nitrogen of hydroxylamine-*O*-sulfonate. For S_N2 displacement in compounds of the type NH_2–X the order of nucleophilicity was thiolate > thiourea > thiosulfate > iodide,[34] while that toward the electron-deficient nitrogen center in **3A** was iodide > thiourea > thiol > thiosulfate (Table I). This difference is a reflection of the differing mechanisms for the two reactions. Although it has been shown that the order of nucleophilicities of bases participating in S_N2 reactions differs substantially from that observed in S_N1 processes at carbon centers,[49-51] this appears to be the first report of differing orders of nucleophilicities of bases involved in S_N1 and S_N2 reactions at nitrogen centers.

A plausible alternative mechanism to that proposed involving a covalent intermediate (**5**, eq 3) would be electron transfer from "soft" bases to the nitrenium ion of **3A** to produce an amidyl radical, **7**.[28] This would readily abstract a hydrogen atom to produce the reduction product, **6**. For examination of that hypothesis, reactions of **1** with iodide and thiourea at pH 7 containing the spin-trapping agent 5,5′-dimethylpyrroline *N*-oxide were monitored by ESR.[52] No signals could be detected to the limit of detection in the presence or absence of the spin trap.

The reactions of two reducing agents, borohydride and dithionite, are also indicative of an ionic, rather than a radical, mechanism for the initial reaction at the nitrenium ion **3A** (eq 3). Dithionite reduces by electron transfer from a radical intermediate.[53,54] It did not react at either electron-deficient site of **3A,B** but instead reduced the acyl group of **1** to afford an enhanced yield of 3-hydroxyxanthine (**2**). Borohydride, however, which has been used previously to trap carbenium ion intermediates,[55-58] did enhance the yield of xanthine. Since hydride ion is a "soft" base, but approaching the "borderline" category, reduction might be expected to occur by addition to the carbenium ion of **3B**, rather than to the nitrenium ion of **3A**. The formation of nearly half the usual amount of uric acid indicates that borohydride competes poorly with water for **3B** and is a poorer reducing agent of **3B** than many of the "soft" bases are of **3A**. These results do not indicate a role for electron transfer in the redox reaction of *N*-(acyloxy)purines but are consistent with the formation of a covalent intermediate.

In summary, the present studies provide experimental support for the proposals that the C-substitution and oxidation–reduction reactions of *N*-(acyloxy)purines are dual reactivities of delocalized aromatic cations released from the esters. The two reactivities arise from nucleophilic substitutions at different electron-deficient sites of the cations. The type of reaction is determined by the reaction site, and this is defined, in turn, by the nucleophilic properties of the approaching nucleophile. HSAB "hard" bases react only at carbenium ion sites and yield stable C-substitution products. Extremely "soft" bases, such as iodide ion and selenourea, react exclusively at the nitrenium ion and produce redox products in high yield. Thio acids, thio amides, bisulfide ion, aromatic thiols, and

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thiosulfate react at both electron-deficient sites to varying degrees and afford mixtures of redox and C-substitution products. Aliphatic thiols and disulfides react slightly at the nitrenium ion. There was no evidence for electron transfer to form a radical intermediate.

Experimental Section

Weighed samples of 10 μmol (2.5 mg) of analytically pure 3-acetoxyxanthine hydrochloride[15] were dissolved in 5 mL of 0.1 M NaH_2PO_4 buffer containing 0.01 M (5 equiv) of the desired nucleophile. Reactions were allowed to proceed in the dark at ambient temperature for 24 h, most of the solvent was removed under reduced pressure, and the solutions were chromatographed over 9 × 150 mm columns containing Dowex 50 (H^+) resin. H_2O eluted uric acid, 8-thiouric acid, 8-nitroxanthine, 8-(phenylthio)xanthine, and **2** while 0.1 or 1 N HCl eluted **6**. Products were identifiable both by their position of elution from the column and by comparison of UV spectral values in acid and base to those of authentic samples or to reported values. Yields were determined from the optical density of measured elution volumes and known ε values: 8-nitroxanthine (pH 1), λ_{max} 360 nm (ε 10600);[59] 3-hydroxyxanthine (**2**; (pH 2-4), λ_{max} 272 nm (ε 10000);[60] 8-thiouric acid (pH 2), λ_{max} 303 nm (ε 18200);[61] xanthine (**6**; pH 0), λ_{max} 260 nm (ε 9200).[15] OD values were determined with a Unicam SP800A recording spectrophotometer. Values in Table I are the average of two or more determinations when standard deviations are indicated. Assignment of structure of 8-(phenylthio)xanthine is based on the similarity of the UV spectra of the product in acid (λ_{max} 288 nm and, in base, 297 nm) to those of 8-(methylthio)-xanthine: λ_{max} (pH 1) 218 nm (ε 12400), 289 (15800); λ_{max} (pH 12) 252 (7000), 292 (12800). Since the λ_{max} and ε values of 8-ethoxy-[62] and 8-phenoxyxanthine[62] are reasonably close, the extinction of 8-(methylthio)xanthine was used to estimate the yield of 8-(thiophenoxy)xanthine in Table I. The yield of triiodide (70%) was determined spectrophotometrically at 352 nm (ε 26500).[14]

Acknowledgment. We are very much indebted to Dr. Roger Sealy of the National Biochemical ESR Center for his time and effort in performing the ESR experiments and thank Dr. George Bosworth Brown for his support and interest in this work.

Registry No. **1**·HCl, 64761-25-7; **2**, 13479-29-3; **4** (Nu = OH), 69-93-2; **4** (Nu = SH), 2476-54-2; **4** (Nu = SC_6H_5), 80106-08-7; **4** (Nu = NO_2), 80106-09-8; **6**, 69-89-6; I^-, 20461-54-5; $H_2NCSeNH_2$, 630-10-4; H_2NCSNH_2, 62-56-6; $C_5H_4N_4S$, 50-44-2; CH_3CSNH_2, 62-55-5; $EtOCS_2^-$, 28563-38-4; CH_3COS^-, 29632-72-2; CS_3^{2-}, 15644-49-2; HSe^-, 16661-43-1; HS^-, 15035-72-0; $HSCH_2CHNHAcCO_2^-$, 41079-67-8; C_6H_5SH, 108-98-5; $(CH_3)_3CSH$, 75-66-1; $(CH_3S)_2$, 624-92-0; $S_2O_3^{2-}$, 14383-50-7; CN^-, 57-12-5; HSO_3^-, 15181-46-1; NO_2^-, 14797-65-0; BH_4^-, 16971-29-2; $S_2O_4^{2-}$, 14844-07-6; $S_2O_6^{2-}$, 14781-81-8.

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Transmission of Substituent Effects via Molecular Lines of Force: Defense of the DSP Method and an Illustration of Its Use in Explaining π Polarization

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Received July 3, 1981

This paper disputes the conclusions of a recent report by Laszlo and co-workers[33] regarding the applicability of the dual substituent parameter (DSP) method to studies of substituent effects on ^{13}C chemical shifts. We show that the ρ_I and ρ_R transmission coefficients obtained from DSP analyses of ^{13}C shifts in side chains of styrene derivatives provide useful mechanistic information. Trends in chemical shifts for a number of C=O or C≡N probe groups are discussed and interpreted in terms of the π-polarization mechanism. The concept that π-polarization effects may be partially transmitted via "molecular lines of force" is introduced and compared with the classical through-space transmission mode of polarization effects. The interrelationship between this concept and that of extended polarization is discussed.

^{13}C NMR chemical shifts have been used extensively as monitors of molecular structure and electron distribution. In particular, the use of substituent chemical shifts (SCS) to monitor the transmission of electronic effects in rigid molecular frameworks has been a fruitful area of research for many years.[1-10] Studies have been made of the transmission of substituent effects both within aromatic rings[1,3,5,9,11-14] and in (often unsaturated) side chains attached to those substituted aromatic systems.[15-29]

The most successful analyses of substituent effects on chemical shifts have used Hammett-type[30] treatments. The dual substituent parameter (DSP)[31] extension of the Hammett approach has proven particularly useful. In this method, the observed ^{13}C SCS (δ^c) values are correlated

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