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Supplementary Material Available: Proton NMR spectra and, in some instances, analyses and Kugelrohr boiling points of ethyl 3-(benzylthio)pentanoate, ethyl 3-(benzylthio)-4-methylpentanoate, ethyl 3-(benzylthio)-4,4-dimethylpentanoate, 3-(benzylthio)-1-pentanol, 3-(benzylthio)-4-methyl-1-pentanol, 3-(benzylthio)-4,4-dimethyl-1-pentanol, 3-(benzylthio)-1-pentyl *p*-toluenesulfonate, 3-(benzylthio)-4-methyl-1-pentyl *p*-toluenesulfonate, 3-(benzylthio)-4,4-dimethyl-1-pentyl *p*-toluenesulfonate, ethyl-3-methyl-3-(phenylthio)butanoate, ethyl 3-methyl-3-(*p*-tolythio)butanoate, ethyl 3-[(*p*-methoxyphenyl)thio]-3-methylbutanoate, ethyl 3-[(*p*-fluorophenyl)thio]-3-methylbutanoate, ethyl 3-[(*p*-chlorophenyl)thio]-3-methylbutanoate, ethyl 3-(*n*-butylthio)-3-methylbutanoate, ethyl 3-(*sec*-butylthio)-3-methylbutanoate, ethyl 3-(*tert*-butylthio)-3-methylbutanoate, 3-methyl-3-(phenylthio)-1-butanol, 3-methyl-3-(*p*-tolylthio)-1-butanol, 3-methyl-3-[(*p*-methoxyphenyl)thio]-3-methyl-1-butanol, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butanol, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butanol, 3-(*p*-butylthio)-3-methyl-1-butanol, 3-(*sec*-butylthio)-3-methyl-1-butanol, 3-(*tert*-butylthio)-3-methyl-1-butanol, 3-methyl-3-(phenylthio)-1-butyl *p*-toluenesulfonate, 3-methyl-3-(*p*-tolylthio)-1-butyl *p*-toluenesulfonate, 3-(*p*-methoxyphenyl)-3-methyl-1-butyl *p*-toluenesulfonate, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butyl *p*-toluenesulfonate, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*n*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*sec*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*tert*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(benzylthio)pentyl methyl ether, 3-(benzylthio)-4-methylpentyl methyl ether, 3-(benzylthio)-4,4-dimethylpentyl methyl ether, 1-(benzylthio)-3-pentyl methyl ether, 1-(benzylthio)-4-methyl-3-pentyl methyl ether, 3-methyl-3-(phenylthio)-1-butyl methyl ether, 3-methyl-3-(*p*-tolylthio)-1-butyl methyl ether, 3-[(*p*-methoxyphenyl)thio]-3-methyl-1-butyl methyl ether, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butyl methyl ether, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butyl methyl ether, 3-(*n*-butylthio)-3-methyl-1-butyl methyl ether, 3-(*sec*-butylthio)-2-methyl-1-butyl methyl ether, 3-(*t*-butylthio)-3-methyl-1-butyl methyl ether, 4-[(*p*-methylphenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-methoxyphenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-fluorophenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-chlorophenyl)thio]-2-methyl-2-butyl methyl ether (10 pages). Ordering information is given on any current masthead page.

Theoretical Investigation of Acidity and Isotope Exchange in Purine Nucleotide Cations

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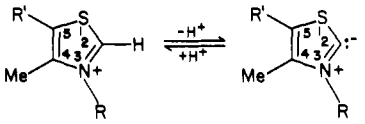
Abstract: The protonation of purine nucleotide models at N(7) and the C(8)H acidity of the purine cations have been explored by semiempirical (INDO) and ab initio (STO-3G) molecular orbital calculations performed on neutral, N(7)-protonated, and C(8)-deprotonated purine species. Factors associated with relative rates of C(8)H isotope exchange among different nucleotides were investigated. Substituent effects for natural nucleotides, such as electron-donation or -withdrawal, stabilization or destabilization, etc., were analyzed in the context of effects from the other common electron-withdrawing and -releasing groups at C(2) and C(6). The calculated N(7) basicity of neutral purines shows guanine, adenine, and hypoxanthine to be among the strongest bases along with methyl- and methoxypurines. Xanthine and fluoro- or nitropurine are computed to be among the weakest bases of the group. Ionization of C(8)H was predicted to be the most facile for xanthine and fluoro- and nitropurines and least facile for adenine, guanine, hypoxanthine, dimethyladenine, and dimethylguanine. The predicted thermodynamic ordering (xanthine > purine > hypoxanthine > adenine) is consistent with the observed exchange rate constants for the nucleosides and nucleotides, but guanine is predicted to be thermodynamically the least susceptible to exchange. Analysis of charge distributions in the N(7) protonated species reveals that approximately 35% of the positive charge appears at C(8)H. The magnitude of the charge appears to be a good indicator of the effect of substituents on C(8)H lability. The C(8)-deprotonated purines appear to be ylides, stabilized by π polarization, with little zwitterionic character. Both calculated proton affinities and C(8)H charges for the various C(2)- and C(6)-substituted purines show remarkably good correlations with standard Hammett σ values.

Relatively facile hydrogen isotope exchange in heterocyclic cations is a widespread, well-documented phenomenon with important biochemical implications. The earliest attention, motivated by Breslow's observations,[1] was focused on the ionization at C(2)H of the thiazolium ring due to its importance in the mechanism of thiamine-dependent enzyme processes.[2]



Subsequently this ionization/exchange has been observed in many other heterocyclic systems, such as thiazoles,[3] isothiazoles,[4] oxazoles,[3b] tetrazoles,[5] pyrazoles,[5] imidazoles,[3b,6] pyridines,[7] and purines.[6b,8-14]

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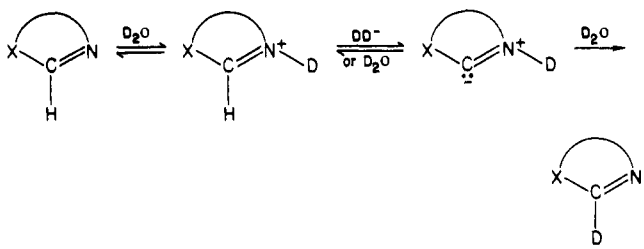
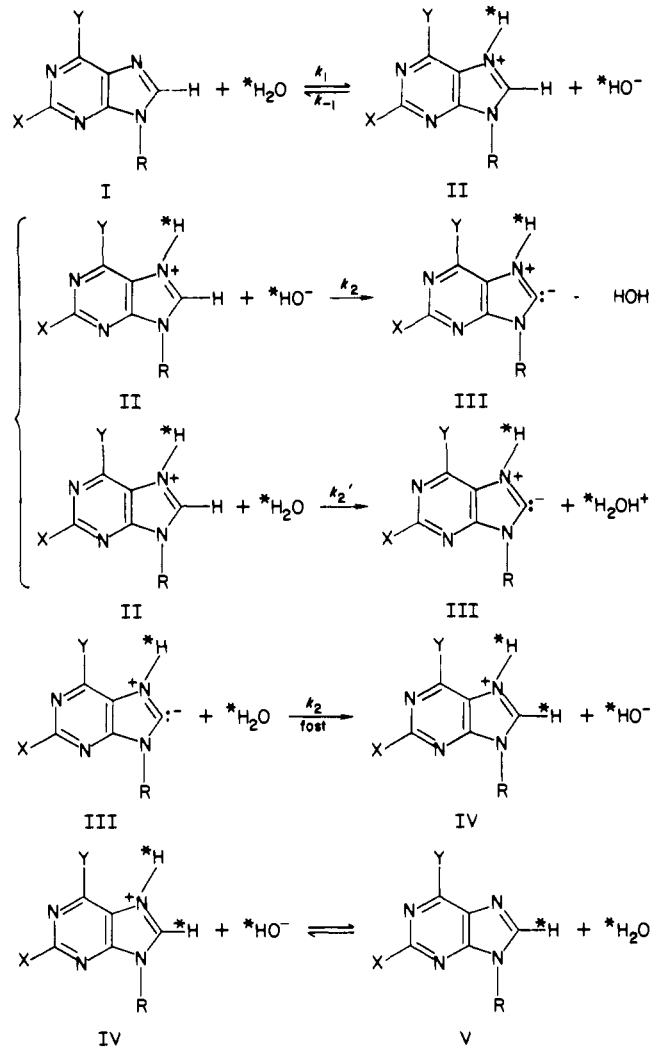


X = C, N, O, S

Since the initial detection of C(8)H isotope exchange in purine by proton magnetic resonance by Ts'o and co-workers[8a] and by Bullock and Jardetzky,[8b] C(8)H lability has been demonstrated in purine derivatives, including nucleosides, nucleotides, and nucleic acids. The kinetics and mechanism of the exchange process has also received considerable attention.[9-13] Tomasz et al.[9] have studied detritiation from [8-^{3}H]adenosine and [8-^{3}H]guanosine derivatives and have postulated a mechanism for the exchange process. Strong evidence for the zwitterionic (ylide) intermediate III (below) was presented. Jones and co-workers[12] have systematically measured rate constants for detritiation of numerous purines and purine nucleosides and have recently demonstrated a linear free energy relationship with pK_a's for the conjugate acid of the purine.[12a] A mechanism, resembling that of Tomasz,[9] was elaborated and expanded to take into account the pH dependence of the reaction. In more recent work, Thomas and co-workers[13] have measured pseudo-first-order rate constants and Arrhenius parameters by Raman spectroscopy for C(8)H and C(8)D nucleotides of adenine (A), hypoxanthine (I), and guanine (G) in D_2O and H_2O solutions. Relative rates for incorporation of deuterium (k_ψ^H) were found to be in the order 5'-rGMP ~ cGMP > 5'-rIMP ~ cIMP > 5'-rAMP ~ cAMP.[13a-d] C(8)H exchange in purines continues to receive intense experimental scrutiny as a probe of conformation and environment in DNA and RNA.[14]

From the foregoing experimental work, exchange shows extreme sensitivity to molecular structure, substituents, and environment of the purine base. The relative rates for isotope exchange demonstrate that substituents at C(6) and C(2) markedly affect the lability of the 8-proton. The sugar–phosphate moiety of nucleotides has a small but noticeable effect on the rate of exchange due to intramolecular electronic effects and intermolecular interactions involving solvent. Base stacking and pairing in single- and double-stranded polynucleotides substantially retards the exchange rates from those of the mononucleotides.[14]

Scheme I



Aside from the biochemical significance of this exchange phenomenon, the process involves proton-transfer chemistry which is uniquely different from that of other carbon acids. The proton at C(8) in neutral purines is only very weakly acidic. Proton abstraction from neutral purines only becomes important at high pH. (See ref 9 and 12 for inclusion of this exchange pathway into the mechanism.) However, after equilibration with water and protonation at N(7), these protons become considerably more acidic. The proposed mechanism[9,12] (Scheme I) for the exchange reaction in aqueous solution (pH ~7) involves reversible protonation at N(7) to produce a protonated purine II which is both a nitrogen acid and a carbon acid. Dissociation at N(7)H regenerates the purine base, a process defined by the associated pK_a which has been measured for numerous derivatives. Although protonation also takes place at other sites in the purine systems (namely N(1) and N(3), as well as on substituent groups), only the N(7)-protonated species is kinetically active in producing appreciable C(8)H exchange.[12a] Besides the acidity at N(7), considerable acidity is conferred to C(8)H. In a rate-determining step, proton abstraction at C(8) by the base generates the zwitterion species III, a nitrogen ylide. Finally III is reprotonated by water in a diffusion-controlled step (with replacement by an isotope of hydrogen). The reaction sequence and intermediates pose fundamental questions regarding (a) the mechanism of stabilization of nitrogen ylides, (b) the degree of stabilization of aromatic ylides through a σ and/or π system, and (c) the effect of electron-withdrawing and -releasing substituents on ylide stability, basicity at N(7) and acidity at C(8).

Although isotope exchange in purines has been extensively studied experimentally, relatively little is known of the mechanism and intermediates from a theoretical point of view. An almost

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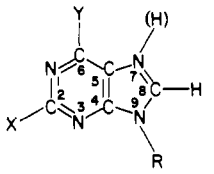
endless array of molecular orbital calculations have been reported on simple, neutral purine systems, involving both ground[15-17] and excited states.[18] There are, however, only few investigations of protonation and acidity in purines.[19] Sites of protonation in adenine and guanine have been mapped by Pullman and coworkers[19e] by the method of electrostatic potentials. Jordan and Sostman[19c,d] have reported CNDO/2 and MINDO computations on neutral and protonated 9-methyladenines and 9-methylguanines. Protonation sites were predicted based upon percent 2s character, σ-electron density, and net charges. Effects of protonation on charge distributions on stacking interactions in polynucleotides, on base-pairing, and on syn vs. anti conformational populations (defined by glycosidic bond rotations) were considered.[19f] Neiman[19g] has also used the CNDO/2 method to compare total energies, molecular binding numbers, and charge density in protonated tautomers of purine. In addition to these semiempirical computations, ab inito molecular orbital theory using STO-3G and 4-31G wave functions has been applied by Mezey et al[19a] and Del Bene.[19b] Energies and optimized structures for neutral and protonated species and proton affinities were systematically computed for a series of tautomeric forms of adenine and guanine protonated at several sites.

Table I. Bond Lengths and Angles in Standard Purine Ring



	bond lengths, Å		angles, deg
N_1C_2	1.39	$N_1C_2N_3$	121.5
C_2N_3	1.33	$C_2N_3C_4$	115.5
N_3C_4	1.37	$N_3C_4C_5$	125.7
C_4C_5	1.36	$C_4H_5C_6$	119.5
C_5C_6	1.43	$C_5H_6N_1$	113.2
N_1C_6	1.38		
C_5H_7	1.37	$C_6N_1C_2$	124.6
C_7H_8	1.32	$C_4H_5N_7$	108.3
C_8N_9	1.34	$C_5N_7C_8$	105.4
C_4N_9	1.36	$N_7C_8N_9$	112.7
		$C_8N_9C_4$	105.5
		$N_9C_4C_5$	108.1

In the present work, we have explored the exchange mechanism of purine nucleotide models in the framework of both semiempirical and ab initio theory. Specific emphasis has been placed on energy differences (proton affinities) and charge distributions among the principal intermediates II and III, as well as the neutral purine I. Purine species considered here include those of the common nucleotide purines adenine and guanine, as well as those of the less common purines, hypoxanthine, xanthine, and dimethylguanine, and dimethyladenine. To further elucidate the role of substituents at C(2) and C(6) in C(8)H lability and in the stabilization or destabilization of intermediates II and III, we have treated the substituents present in natural purine nucleotides (X or Y ≡ =O or NH_2) in the context of effects from other common electron-donating and -withdrawing groups at C(2) and C(6) (i.e., X or Y ≡ H, $N(CH_3)_2$, OH, OCH_3, CH_3, F, $COOCH_3$, OCF_3, CF_3, CN, and NO_2).

Computational Methods

In order to elaborate the mechanism, the relative exchange rates of model nucleotides, and the stability of the proposed intermediates, we have applied semiempirical molecular orbital theory by using the INDO formalism.[20] Ab initio MO theory was also employed at the STO-3G[21] level wherever feasible. Computations were performed on several series of neutral purines I, protonated purines II, and deprotonated purines III. In order to make the calculations tractable, the mononucleotides were modeled by simple substituted purine rings with R ≡ H and R ≡ CH_2OH. The hydroxymethyl group at N(9) was utilized to more accurately simulate the electronic effects of the ribofuranosyl ring. One basic assumption made here is that the major differences in C(8)H lability

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Table II. N(7) Proton Affinity PA(1) of Neutral Purine Derivatives

	PA(1) INDO, au				PA(1) STO-3G, au	
substituent	X ≡ variable, Y ≡ H, R ≡ H	X ≡ H Y ≡ variable, R ≡ H	X ≡ variable, Y ≡ H, R ≡CH_2OH	X ≡ H, Y ≡ variable, R ≡CH_2OH	X ≡ variable, Y ≡ H, R ≡ H	X ≡ H, Y ≡ variable, R ≡ H
H	0.5792	0.5792	0.5868	0.5868	0.4325	0.4325
CH_3	0.5847	0.5826	0.5919	0.5900	0.4372	0.4355
NH_2	0.5936	0.5871	0.6003	0.5942	0.4457	0.4347
OCH_3	0.5824	0.5829	0.5897	0.5903	0.4363	0.4396
OH	0.5811	0.5750	0.5885	0.5827	0.4347	0.4197
$COOCH_3$	0.5734	0.5785	0.5812	0.5862		
OCF_3	0.5713	0.5696	0.5794	0.5776		
F	0.5696	0.5699	0.5778	0.5780	0.4285	0.4275
CF_3	0.5633	0.5633	0.5716	0.5716	0.4253	0.4257
CN	0.5740	0.5729	0.5817	0.5808	0.4193	0.4205
NO_2	0.5550	0.5610	0.5638	0.5695	0.4134	0.4243
=O	0.5625	0.5828	0.5708	0.5904	0.4264	0.4431
$N(CH_3)_2$	0.5947	0.5883	0.6012	0.5952	0.4491	0.4359

among different purines arises from within the purine ring. To a good approximation, the sugar and phosphate groups of the model nucleotides provide only a small, constant perturbative effect.

Geometries, used for the varius species I, II, and III, were obtained from X-ray crystallographic data on the neutral parent. Structural information is available on a limited number of the protonated species II.[22] Geometries of adenine and guanine mononucleotide models were taken from the work of Arnott[23] on poly(dAT) and poly(dGC).[24] Bond lengths and angles in the rare nucleotides hypoxanthine (IMP), xanthine (XMP), dimethylguanine (DMGMP), and dimethyladenine (DMAMP) were obtained from X-ray structures of inosine,[25] xanthosine dihydrate,[26] N^2,N^2-dimethylguanosine,[27] and N^6,N^9-dimethyladenine,[28] respectively. In addition, the molecular structure of unsubstituted purine was taken from the X-ray diffraction data of Watson, Sweet, and Marsh.[29] Because bond lengths and angles involving hydrogens are inaccurately estimated in X-ray diffraction, standard bond lengths and angles were used for bonds to hydrogens. A summary of these standard internal coordinates is as follows: $r(C_{purine}–H)$ = 1.08 Å, $r(C_{methyl}–H)$ = 1.09 Å, r(N–H) = 0.995 Å, θ(H–N(6)–C(6)) = 120.5°,[30a] with hydrogens placed on the bisectors of ring angles. Bond lengths used for the hydroxymethyl group were r(C–H) = 1.096 Å, r(O–H) = 0.956 Å, r(C–O) = 1.427 Å, θ(C–O–H) = 108.9°.[30b] Strict C_s symmetry and tetrahedral geometry (at methyl and hydroxymethyl carbons) were assumed in all structures. In *N*,*N*-dimethylpurines, methyl hydrogens were oriented to minimize methyl–methyl repulsions.

In calculations, in which systematic variations in X substituents at C(2) and Y substituents at C(6) were evaluated, standard bond lengths and angles were employed. Standard purine ring coordinates (Table I) were derived from the weighted average of known crystallographic geometries. External bond lengths to pendent atoms were taken from the values of Pople and Beveridge.[20b]

In addition to the SCF calculations described above, computer graphics, along with Mulliken population analysis,[31] was utilized to represent electron density distributions. The electron distribution throughout a given molecule was projected onto the x–z plane and was represented as a three-dimensional figure in perspective format. The techniques employed here were those developed by Boerth and Yang[32] for NDO-type wave functions and by Streitwieser and co-workers[33] for ab initio wave functions. Electron distributions were mapped by evaluating the electron projection function, $P(x,z)$, as defined by Streitwieser,[33]

$$P(x,z) = \int_{-\infty}^{+\infty} \rho(x,y,z)\, dy \quad (1)$$

and the integrated electron population, N_e

$$N_e = P(x,z)\, dx\, dz \quad (2)$$

where $\rho(x,y,z)$ is the electron density at (x,y,z)

$$\rho(x,y,z) = \sum_{i}^{occ} n_i \phi_i^*(x,y,z)\phi_i(x,y,z) = \sum_{i}^{occ} n_i \sum_{p}\sum_{q} c^*_{pi} c_{qi} \chi_p^*(x,y,z)\chi_q(x,y,z) \quad (3)$$

where n_i is the occupation number of molecular orbital ϕ_i and c_{pi} and c_{qi} are MO coefficients for atomic orbitals χ_p and χ_q, respectively.

Results and Discussions

Proton Affinities. The acidity of a species is commonly interpreted in terms of the stability of the conjugate base or its proton affinity, i.e., the energy difference between acid and conjugate base. Two conjugate base species, I and III, were considered in this work. The corresponding proton affinities, PA(1) and PA(2), reflect the basicity at N(7) in the neutral species I and the basicity at C(8) in the deprotonated species III, respectively.

$$PA(1) = E_{tot}(I) - E_{tot}(II) \quad (4)$$

$$PA(2) = E_{tot}(III) - E_{tot}(II) \quad (5)$$

N(7)H and C(8)H acidity in protonated species II are inversely related to the corresponding proton affinities.

Before examination of the specific results and conclusions, it is important to note some limitations in the calculations. It is apparent that the results presented here pertain to the gas phase. We assume that these results will parallel those in solution since many linear free energy correlations have been established between solution and gas phases. Although solvation will doubtless be significantly different among the neutral, protonated, and deprotonated species of a given purine derivative, variations in solvation around the imidazole ring, the site of protonation–deprotonation, are likely to be small among all purine derivatives of a particular form. Hence, the relative trends introduced by different substitution at C(2) and C(6) will be of greater significance than the absolute values for the proton affinities.

An additional word of caution must be interjected here regarding the calculated proton affinities. Whereas the calculated proton affinities are related to *thermodynamic* or *equilibrium acidities* (with entropy effects neglected), the observed isotope-exchange rates correspond to *kinetic acidities*. It is well-known

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Table III. Proton Affinities of Neutral[a] and Deprotonated[b] Purine Species

	INDO				STO-3G	
purine deriv	PA(1) R ≡ H, au	PA(2) R ≡ H, au	PA(1) R ≡CH_2OH, au	PA(2) R ≡CH_2OH, au	PA(1) R ≡ H, au	PA(2) R ≡ H, au
adenine	0.5827	0.6947	0.5891	0.7008	0.4276	0.5011
guanine	0.6055	0.7023	0.6117	0.7083	0.4658	0.5156
hypoxanthine	0.5730	0.6903	0.5801	0.6972	0.4327	0.5110
xanthine	0.5587	0.6723	0.5653	0.6785	0.4268	0.4991
purine	0.5839 (0.5572)[c]	0.6863	0.5920	0.6942	0.4356 (0.4320)[c]	0.4955
N^6,N^6-dimethyladenine	0.5792	0.6991	0.5851	0.7045	0.4241	0.5101
N^2,N^2-dimethylguanine	0.5910	0.7082	0.5964	0.7131		

[a] Proton affinity at N(7) in neutral purine species. [b] Proton affinity at C(8) in deprotonated purine species. [c] Proton affinity at N(9) in neutral unsubstituted purine.

that kinetic and thermodynamic acidities may differ when the transition state does not resemble the equilibrium species.[34] Attempts to correctly predict the kinetic acidities by the energy difference method may require a refined model for the transition state.

The N(7) proton affinity in protonated species II, PA(1), is a measure of the preequilibrium step (I ⇄ II) in the isotope-exchange reaction and a measure of the N(7) basicity of neutral purine species I. PA(1) values show (Tables II and III) guanine (X ≡ NH_2, Y ≡ =O), adenine (Y ≡ NH_2), and the rare nucleotide purines hypoxanthine (Y ≡ =O), dimethyladenine (Y ≡ $N(CH_3)_2$), and dimethylguanine (X ≡ $N(CH_3)_2$, Y ≡ =O) along with 2- or 6-methyl- or methoxypurine to be among the strongest bases of the substituted purines. Xanthine (X and Y ≡ =O) and 2- or 6-fluoro- or nitropurine are among the weakest bases of the group. Results for the nucleoside models (R ≡ CH_2OH) parallel those found for the purines (R ≡ H). In addition, the ab initio calculations (STO-3G) follow a gratifyingly similar pattern with few exceptions. Data obtained by using crystallographic geometries (Table III) rather than standard geometries for the purines reflect the same trends although differences between standard and crystallographic values are apparent.

Limited comparisons with experimental values are possible. The observed order, based upon pK_a[35] values for I ⇄ II, is xanthine (1.3) and xanthosine (1.8) < hypoxanthine (1.9, 1.79) and inosine (1.5) < guanine (2.95, 3.3) and guanosine (2.231, 2.174, 1.6).[12a,36] The theoretical order, based upon proton affinities PA(1), is in agreement with the observed order, i.e., xanthine < hypoxanthine < adenine < guanine, although STO-3G calculations reverse the order of hypoxanthine and adenine. Adenine cannot be placed in the experimental sequence since the observed pK_a values (4.2 for adenine and 3.5 for adenosine) relate to protonation at N(1) rather than N(7). The calculated proton affinity suggests the basicity at N(7) to be somewhat less than in guanine. Apart from the apparent consistency of theory and experiment, it must be pointed out that whereas the observed pK_a's were obtained in solution, the theoretical results pertain to the gas phase.

Reaction rate constants and other properties are often correlated with standard Hammett σ values,[37] quantifying electron-withdrawing and -releasing effects of typical substituents. Correlation between theoretical proton affinities PA(1) and Hammett σ_{para} values[37] for the various substituents (X or Y ≡ H, CH_3, CN, F, NO_2, OCH_3, CF_3, $COOCH_3$, =O, OCF_3, OH, NH_2, or $N(CH_3)_2$) has been successfully attempted and is displayed in Figure 1. Our

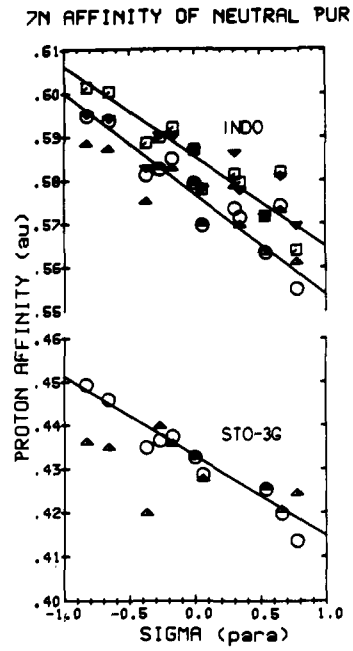

Figure 1. N(7) proton affinity of neutral purines [(○) X ≡ variable, Y ≡ H, R ≡ H; (△) X ≡ H, Y ≡ variable, R ≡ H; (□) X ≡ variable, Y ≡ H, R ≡ CH_2OH; (▽) X ≡ H, Y ≡ variable, R ≡ CH_2OH].

work here is analogous to the ab initio modeling of substituent effects in Hammett correlations involving benzene[38] and carbonyl[39] derivatives by Streitwieser and co-workers. Considering the fact that σ_{para} values are experimentally derived from benzenoid compounds, the reasonably good correlation ($|r|$ = 0.88 [INDO], 0.80 [STO-3G]) for N(7) protonation–deprotonation in purines is remarkable. In addition, correlation of PA(1) and σ_{para} for R ≡ CH_2OH species produces a line which is essentially parallel to that for R ≡ H species.

Points for a particular group at C(2) and C(6) fall near one another for the majority of substituents, suggesting that apparently substitution at C(2) is similar to that at C(6) in terms of stabilization of the protonated form. Notable exceptions include NH_2, NO_2, OH, and $COOCH_3$. Hydroxyl and amino substitution at C(6) shows greatly reduced N(7) proton affinity. In contrast, the electron-withdrawing substituents nitro and carbomethoxy show greater N(7) proton affinity when substituted at C(6). PA(1) values for oxo substitution cannot be correlated directly with σ_{para}. However, the computed proton affinity for 6-oxopurine falls near the correlation line if one uses the σ_{para} value for OH, the tautomeric partner of the oxo group. In contrast, the PA(1) value for 2-oxopurine would appear below the line, indicating greatly reduced N(7) proton affinity (and basicity).

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(35) pK_a = −log [BH][H⁺]/[BH_2^+].

(36) Izatt, R. M.; Christensen, J. J.; Rytting, J. H. *Chem. Rev.* **1971**, *71*, 439.

(37) Hammett σ_{para} values [$N(CH_3)_2$, −0.83; NH_2, −0.66; OH, −0.37; OCH_3, −0.268; CH_3, 0.170; H, 0.00; F, +0.062; $COOCH_3$, +0.31; OCF_3, +0.35; $-CF_3$, +0.54; CN, +0.660; NO_2, +0.778] were taken from the following sources: (a) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323. (b) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", Harper & Row: New York, 1981; pp 130–142. (c) Hammett, L. P., "Physical Organic Chemsitry"; McGraw-Hill: New York, 1970; pp 355–385.

(38) (a) Vorpagel, E. R.; Streitwieser, A., Jr.; Alexandratos, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 3777. (b) McKelvey, J. M.; Alexandratos, S.; Streitwieser, A., Jr.; Abboud, J. L. M.; Hehre, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 244.

(39) Grier, D. L.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 3556.

The proton affinity PA(2) (Table IV) reflects the thermodynamic acidity of the protonated species II at C(8)H and the stability of the carbanionic intermediate III (smaller PA(2) representing greater acidity). Ionization at C(8)H is predicted to be most facile for xanthine and 2- or 6-fluoro, trifluoromethyl, and nitropurine and least facile for adenine, guanine, hypoxanthine, dimethyladenine, and dimethylguanine. The common and rare nucleotide purines (except xanthine) along with 2- or 6-methyl- or methoxypurine are calculated to be less susceptible to C(8)H dissociation than is unsubstituted purine. Again trends in the proton affinities for the nucleoside models (R ≡ CH_2OH) follow those found for the purines (R ≡ H). Relative proton affinities computed from crystallographic geometries (Table III) follow the trend established by using the standard geometries (dimethylguanine > guanine > dimethyladenine > adenine > hypoxanthine > purine > xanthine). The ab initio results (STO-3G) display similar patterns with some exceptions. The order for adenine and hypoxanthine is reversed, and purine is predicted to be more labile than xanthine.

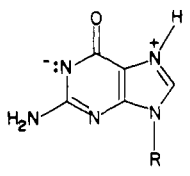
Unfortunately there is no experimental measurement of the thermodynamic C(8)H acidity (II ⇄ III). The nitrogen ylide intermediate III appears only as a transient species which either is rapidly reprotonated by solvent in a diffusion-controlled step or undergoes rapid rearrangement by hydride shift from N(7) to C(8) (III ⇄ V). The kinetic acidity, however, is measurable and is embodied in the observed hydrogen isotope-exchange rates.[9-13] The stability of intermediates A(III), I(III), and G(III) relative to unsubstituted purine, represented by their total molecular energies, parallels the observed exchange rates in nucleotides.[13] Stability of the vinyl ylide [G(III) > I(III) > A(III)] could be interpreted as facilitating the formation of III species and would be reflected in increased lability of H(8). However, this may be more fortuitous than meaningful if the transition state of the reaction does not closely resemble III.

The variation in relative C(8)H acidity, given by PA(2), is predicted to be small among the nucleotide model compounds as are the differences in experimental kinetic acidites. Nevertheless, the calculated acidities are only partially in agreement with experiment. The predicted (INDO) thermodynamic ordering (hypoxanthine > adenine) is consistent with the observed exchange rate constants for nucleotides,[13] but guanine is predicted to be thermodynamically least susceptible to exchange. When compared with the exchange rate constants for nucleosides and purine derivatives without ribose,[12] the theoretical proton affinities PA(2) are again in partial agreement, i.e., xanthine < purine < adenine.

There are several possible explanations for the apparent discrepancy between the greater experimental exchange rate for GMP and the large proton affinity (low C(8)H acidity) for guanine. First, the exchange rate constant is affected by the preequilibrium protonation step whereas PA(2) is not. The observed rate constant incorporates both the preequilibrium step (I ⇄ II), as well as the deprotonation step (II → III), i.e.

$$k_{expt} = \frac{K_w k_2}{K_A} \qquad (6)$$

When N(7) protonation becomes more facile (larger pK_a), the observed rate constant increases. It is noteworthy that N(7) protonation is significantly more favorable for guanine than for either adenine or hypoxanthine. The implication is that the larger observed rate for GMP may derive, in part, from a more favorable preequilibrium step than is present for AMP and IMP. Second, as was pointed out by Tomasz,[9] the exchange in guanine derivatives is affected by an important contribution from the zwitterionic species VI, which also places a proton and positive charge at N(7).



VI

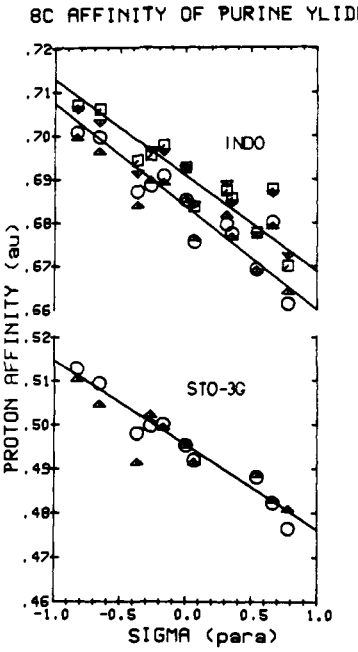


Figure 2. C(8) proton affinity of deprotonated purines [(○) X ≡ variable, Y ≡ H, R ≡ H; (△) X ≡ H, Y ≡ variable, R ≡ H; (□) X ≡ variable, Y ≡ H, R ≡ CH_2OH; (▽) X ≡ H, Y ≡ variable, R ≡ CH_2OH].

Third, a variety of factors, such as solvent and conformational effects and intramolecular hydrogen bonding, as well as presence or absence of phosphate, may also be responsible for the discrepancies between experimental and computed C(8)H acidities. In addition, it is to be noted that guanine derivatives are known to have anomalous properties of their own due to freedom of rotation about the glycosidic bond and differences in electronic structure.[40]

The computed proton affinities PA(2) show a pronounced correlation ($|r|$ = 0.91 [INDO], 0.95 [STO-3G]) with Hammett σ_{para} values[37] for X and Y substituents at C(2) and C(6) from both semiempirical and ab initio calculations (Figure 2). From the location of the points for a given substituent, the position of the substituent C(2) or C(6) has little effect on the proton affinity, except in the case of the amino, hydroxy, carbomethoxy, and nitro groups. Placement of an amino or hydroxy substituent at C(6) decreases PA(2) (increases C(8)H acidity) compared with C(2) substitution. In contrast, placement of a carbomethoxy or nitro group at C(2) produces a smaller PA(2) value (greater C(8)H acidity) compared with C(6) substitution. Again, oxo substitution at C(6) and C(2) has widely divergent effects on PA(2). Proton affinity PA(2) values for 2-oxopurines are consistently markedly lower than those for 6-oxopurines; i.e., 2-oxopurines are predicted to have greater C(8)H lability. As in the case of PA(1) values, the results for R ≡ CH_2OH species are strikingly parallel to those exhibited with R ≡ H.

Charge Distribution in Protonated Species II. Both semiempirical (INDO) and ab initio (STO-3G) calculations correctly represent the enhanced acidity of H(8) upon protonation of the purine ring at N(7) (Table V). The tendency of INDO to underestimate charge is clearly seen in these results. Nevertheless, the qualitative effects, including the influence of substituents, appear to be adequately represented. Although the positive charge is distributed throughout the protonated purine system II, 35% ± 5% of the positive charge appears in the C(8)H region. Only about 17% remains near N(7)H. The calculated net charges at C(8) and H(8) in II species, $Q_{C(8)H}$, reveals a pattern consistent with the acidity order established by the proton affinity PA(2), including a remarkably good Hammett correlation with σ_{para}[37]

(40) Guschlbauer, W. In "Proceedings of the 1971 Jerusalem Symposium on Quantum Chemistry and Biochemistry"; Pullman, B., Bergmann, E.D., Eds.; Academic Press: New York, 1972; Vol. IV, pp 297–310 and references cited therein.

Table IV. C(8) Proton Affinity PA(2) of Deprotonated Purine Species

substituent	PA(2) INDO, au				PA(2) STO-3G, au	
	X ≡ variable, Y ≡ H, R ≡ H	X ≡ H, Y ≡ variable, R ≡ H	X ≡ variable, Y ≡ H, R ≡ CH_2OH	X ≡ H, Y ≡ variable, R ≡ CH_2OH	X ≡ variable, Y ≡ H, R ≡ H	X ≡ H, Y ≡ variable, R ≡ H
H	0.6851	0.6851	0.6925	0.6925	0.4951	0.4951
CH_3	0.6907	0.6890	0.6976	0.6962	0.4999	0.4991
NH_2	0.6996	0.6961	0.7060	0.7030	0.5092	0.5044
OCH_3	0.6884	0.6895	0.6954	0.6967	0.4996	0.5019
OH	0.6870	0.6837	0.6942	0.6912	0.4979	0.4912
$COOCH_3$	0.6795	0.6815	0.6873	0.6890		
OCF_3	0.6774	0.6765	0.6854	0.6844		
F	0.6755	0.6762	0.6836	0.6842	0.4917	0.4912
CF_3	0.6693	0.6690	0.6776	0.6772	0.4880	0.4885
CN	0.6800	0.6789	0.6876	0.6866	0.4821	0.4828
NO_2	0.6612	0.6640	0.6700	0.6724	0.4764	0.4807
=O	0.6710	0.6901	0.6790	0.6975	0.4961	0.5099
$N(CH_3)_2$	0.7006	0.6994	0.7069	0.7060	0.5126	0.5102

Table V. Mulliken Net Charges in Protonated Purine Species

atom	X or Y												
	H	$N(CH_3)_2$	NH_2	OH	OCH_3	CH_3	F	$COOCH_3$	OCF_3	CF_3	CN	NO_2	=O
						A. INDO (X ≡ variable)[a]							
N(1)	−0.1868	−0.2660	−0.2640	−0.2326	−0.2360	−0.2102	−0.2289	−0.1772	−0.2261	−0.1609	−0.1923	−0.1650	−0.2353
	(0.1896)	(−0.2680)	(−0.2662)	(−0.2350)	(−0.2384)	(−0.2124)	(−0.2316)	(−0.1795)	(−0.2286)	(−0.1635)	(−0.1946)	(−0.1675)	(−0.2391)
C(2)	0.2872	−0.4247	0.4416	0.4820	0.4803	0.3049	0.5411	0.2154	0.4851	0.1837	0.3095	0.2797	0.5095
	(0.2855)	(0.4235)	(0.4400)	(0.4800)	(0.4785)	(0.3026)	(0.5386)	(0.2128)	(0.4828)	(0.1813)	(0.3067)	(0.2770)	(0.5098)
N(3)	−0.2037	−0.3166	−0.3139	−0.2917	−0.2917	−0.2343	−0.2584	−0.1804	−0.2774	−0.1717	−0.2105	−0.1753	−0.1746[b]
	(−0.2104)	(−0.3219)	(−0.3200)	(−0.2979)	(−0.2975)	(−0.2405)	(−0.2655)	(−0.1861)	(−0.2833)	(−0.1781)	(−0.2166)	(−0.1814)	(−0.1764)[b]
C(4)	0.2367	0.2620	0.2639	0.2602	0.2575	0.2390	0.2601	0.2299	0.2631	0.2348	0.2367	0.2395	0.2511
	(0.2269)	(0.2525)	(0.2543)	(0.2503)	(0.2477)	(0.2292)	(0.2495)	(0.2199)	(0.2529)	(0.2247)	(0.2267)	(0.2289)	(0.2386)
C(5)	0.0159	−0.0320	−0.0311	−0.0138	−0.0142	0.0049	−0.0043	0.0245	−0.0077	0.0290	0.0149	0.0288	−0.0173
	(0.0167)	(−0.0305)	(−0.0297)	(−0.0126)	(−0.0129)	(0.0063)	(−0.0032)	(0.0259)	(−0.0065)	(0.0301)	(0.0162)	(0.0300)	(−0.0166)
C(6)	0.1698	0.1945	0.1965	0.1933	0.1917	0.1723	0.1966	0.1631	0.1962	0.1699	0.1713	0.1755	0.1890
	(0.1682)	(0.1933)	(0.1953)	(0.1919)	(0.1904)	(0.1709)	(0.1951)	(0.1615)	(0.1946)	(0.1682)	(0.1698)	(0.1737)	(0.1891)
H(C^6)	0.0223	0.0116	0.0136	0.0219	0.0205	0.0178	0.0282	0.0231	0.0265	0.0303	0.0237	0.0347	0.0246
	(0.0201)	(0.0099)	(0.0117)	(0.0199)	(0.0185)	(0.0159)	(0.0259)	(0.0211)	(0.0245)	(0.0281)	(0.0217)	(0.0325)	(0.0224)
N(7)	−0.0129	−0.0051	−0.0051	−0.0069	−0.0072	−0.0119	−0.0075	−0.0140	−0.0073	−0.0136	−0.0123	−0.0123	0.0102
	(−0.0210)	(−0.0129)	(−0.0128)	(−0.0149)	(−0.0152)	(−0.0196)	(−0.0156)	(−0.0221)	(−0.0158)	(−0.0217)	(−0.0203)	(−0.0207)	(0.0019)
H(N^7)	0.1813	0.1735	0.1746	0.1795	0.1788	0.1785	0.1836	0.1822	0.1823	0.1857	0.1819	0.1880	0.1874
	(0.1770)	(0.1698)	(0.1707)	(0.1753)	(0.1747)	(0.1744)	(0.1791)	(0.1779)	(0.1779)	(0.1812)	(0.1776)	(0.1834)	(0.1829)
C(8)	0.2992	0.2877	0.2889	0.2952	0.2942	0.2958	0.3004	0.3004	0.2991	0.3046	0.2996	0.3067	0.2754
	(0.2890)	(0.2797)	(0.2806)	(0.2859)	(0.2851)	(0.2864)	(0.2901)	(0.2901)	(0.2890)	(0.2937)	(0.2896)	(0.2953)	(0.2668)
H(C^8)	0.0467	0.0398	0.0410	0.0456	0.0448	0.0439	0.0501	0.0475	0.0489	0.0513	0.0474	0.0539	0.0520
	(0.0496)	(0.0434)	(0.0444)	(0.0486)	(0.0479)	(0.0471)	(0.0528)	(0.0504)	(0.0517)	(0.0539)	(0.0503)	(0.0563)	(0.0544)
N(9)	−0.0568	−0.0646	−0.0639	−0.0610	−0.0607	−0.0588	−0.0574	−0.0552	−0.0585	−0.0544	−0.0565	−0.0533	−0.0552
	(−0.0388)	(−0.0476)	(−0.0469)	(−.0433)	(−0.0430)	(−0.0415)	(−0.0391)	(−0.0371)	(0.0397)	(−0.0358)	(−0.0385)	(−0.0340)	(−0.0371)
H(N^9)/ CH_2OH(N^9)	0.1869	0.1800	0.1814	0.1858	0.1847	0.1840	0.1913	0.1882	0.1907	0.1915	0.1875	0.1947	0.1886
	(0.2159)	(0.2050)	(0.2068)	(0.2136)	(0.2122)	(0.2114)	(0.2219)	(0.2183)	(0.2211)	(0.2231)	(0.2169)	(0.2279)	(0.2202)
X(C^2)	0.0143	0.1105	0.0766	−0.0576	−0.0427	0.0741	−0.1948	0.0526	−0.1149	0.0198	−0.0008	−0.0956	−0.3746
	(0.0110)	(0.1040)	(0.0717)	(−0.0619)	(−0.0480)	(0.0696)	(−0.1980)	(0.0470)	(−0.1205)	(0.0148)	(−0.0053)	(−0.1013)	(−0.3799)
						B. INDO (Y ≡ variable)[c]							
N(1)	−0.1868	−0.3051	−0.3001	−0.2556	−0.2812	−0.2171	−0.2450	−0.1704	−0.2637	−0.1498	−0.1932	−0.1568	−0.1690[d]
	(−0.1896)	(−0.3068)	(−0.3022)	(−0.2581)	(−0.2831)	(−0.2193)	(−0.2477)	(−0.1727)	(−0.2658)	(−0.1524)	(−0.1954)	(−0.1592)	(−0.1697)[d]
C(2)	0.2872	0.3188	0.3203	0.3129	0.3131	0.2917	0.3120	0.2781	0.3156	0.2810	0.2875	0.2849	0.3255
	(0.2855)	(0.3173)	(0.3186)	(0.3112)	(0.3114)	(0.2900)	(0.3103)	(0.2763)	(0.3139)	(0.2791)	(0.2857)	(0.2830)	(0.3232)

H(C^2)	0.0143	0.0000	0.0026	0.0128	0.0077	0.0095	0.0193	0.0159	0.0166	0.0237	0.0161	0.0279	0.0193
	(0.0110)	(−0.0029)	(−0.0005)	(0.0095)	(0.0046)	(0.0063)	(0.0159)	(0.0128)	(0.0134)	(0.0203)	(0.0129)	(0.0245)	(0.0162)
N(3)	−0.2037	−0.2656	−0.2634	−0.2370	−0.2406	−0.2180	−0.2223	−0.1912	−0.2283	−0.1832	−0.2035	−0.1796	−0.2612
	(−0.2104)	(−0.2719)	(−0.2698)	(−0.2439)	(−0.2472)	(−0.2246)	(−0.2292)	(−0.1977)	(−0.2351)	(−0.1901)	(−0.2104)	(−0.1864)	(−0.2667)
C(4)	0.2367	0.2620	0.2632	0.2606	0.2570	0.2404	0.2587	0.2290	0.2583	0.2337	0.2379	0.2365	0.2654
	(0.2269)	(0.2521)	(0.2532)	(0.2505)	(0.2469)	(0.2304)	(0.2484)	(0.2190)	(0.2480)	(0.2235)	(0.2277)	(0.2260)	(0.2530)
C(5)	0.0159	−0.0622	−0.0630	−0.0569	−0.0435	−0.0057	−0.0387	0.0385	−0.0325	0.0448	0.0113	0.0354	−0.0807
	(0.0167)	(−0.0608)	(−0.0618)	(−0.0557)	(−0.0422)	(−0.0044)	(−0.0376)	(0.0398)	(−0.0312)	(0.0460)	(0.0129)	(0.0367)	(−0.0793)
C(6)	0.1698	0.3183	0.3356	0.3753	0.3747	0.1933	0.4338	0.0970	0.3763	0.0652	0.1968	0.1617	0.4345
	(0.1682)	(0.3167)	(0.3337)	(0.3735)	(0.3729)	(0.1913)	(0.4317)	(0.0950)	(0.3743)	(0.0632)	(0.1947)	(0.1596)	(0.4331)
N(7)	−0.0129	−0.0087	−0.0015	−0.0029	−0.0001	−0.0110	0.0006	−0.0151	−0.0016	−0.0170	−0.0119	−0.0119	0.0296
	(−0.0210)	(−0.0165)	(−0.0096)	(−0.0109)	(−0.0080)	(−0.0188)	(−0.0075)	(−0.0230)	(−0.0098)	(−0.0251)	(−0.0198)	(−0.0199)	(0.0219)
H(N^7)	0.1813	0.1755	0.1691	0.1738	0.1808	0.1764	0.1876	0.1943	0.1847	0.1903	0.1827	0.2039	0.1855
	(0.1770)	(0.1715)	(0.1650)	(0.1695)	(0.1766)	(0.1723)	(0.1813)	(0.1901)	(0.1803)	(0.1859)	(0.1784)	(0.1994)	(0.1813)
C(8)	0.2992	0.2856	0.2885	0.2970	0.2929	0.2958	0.3002	0.2992	0.2983	0.3058	0.2997	0.3055	0.2687
	(0.2890)	(0.2768)	(0.2793)	(0.2869)	(0.2834)	(0.2861)	(0.2897)	(0.2893)	(0.2881)	(0.2949)	(0.2894)	(0.2945)	(0.2596)
H(C^8)	0.0467	0.0399	0.0420	0.0465	0.0449	0.0444	0.0504	0.0480	0.0491	0.0525	0.0482	0.0547	0.0480
	(0.0496)	(0.0433)	(0.0452)	(0.0494)	(0.0480)	(0.0475)	(0.0530)	(0.0509)	(0.0519)	(0.0551)	(0.0510)	(0.0571)	(0.0508)
N(9)	−0.0568	−0.0606	−0.0598	−0.0580	−0.0590	−0.0575	−0.0575	−0.0563	−0.0576	−0.0547	−0.0560	−0.0549	−0.0494
	(−0.0388)	(−0.0432)	(−0.0420)	(−0.0398)	(−0.0411)	(−0.0401)	(−0.0389)	(−0.0385)	(−0.0390)	(−0.0361)	(−0.0383)	(−0.0362)	(−0.0317)
H(N^9)/	0.1869	0.1818	0.1838	0.1880	0.1861	0.1846	0.1914	0.1867	0.1903	0.1912	0.1877	0.1931	0.1853
$CH_2OH(N^9)$	(0.2159)	(0.2082)	(0.2108)	(0.2170)	(0.2140)	(0.2130)	(0.2215)	(0.2158)	(0.2201)	(0.2226)	(0.2176)	(0.2250)	(0.2146)
Y(C^6)	0.0223	0.1203	0.0829	−0.0565	−0.0329	0.0731	−0.1906	0.0464	−0.1056	0.0165	−0.0034	−0.1005	−0.3650
	(0.0201)	(0.1163)	(0.0799)	(−0.0590)	(−0.0362)	(0.0703)	(−0.1927)	(0.0426)	(−0.1092)	(0.0131)	(−0.0065)	(−0.1043)	(−0.2677)
					C. STO-3G (X or Y ≡ variable)[e]								
N(1)	−0.1986	−0.2419	−0.2373	−0.2151	−0.2152	−0.2119	−0.2169			−0.1954	−0.1868	−0.1788	−0.2004
	(−0.1986)	(−0.2799)	(−0.2679)	(−0.2322)	(−0.2624)	(−0.2190)	(−0.2271)			(−0.1911)	(−0.1804)	(−0.1706)	(0.3425)[f]
C(2)	0.1654	0.3479	0.3647	0.3690	0.3632	0.2398	0.3878			0.1933	0.2392	0.3178	0.3833
	(0.1654)	(0.1740)	(0.1756)	(0.1777)	(0.1730)	(0.1649)	(0.1759)			(0.1677)	(0.1693)	(0.1724)	(0.2291)
H(C^2)	(0.1475)	(0.1358)	(0.1398)	(0.1485)	(0.1424)	(0.1434)	(0.1509)			(0.1516)	(0.1550)	(0.1597)	(0.1514)
N(3)	−0.2128	−0.2904	−0.2796	−0.2737	−0.2723	−0.2322	−0.2400			−0.2084	−0.1975	−0.1861	−0.3492[g]
	(−0.2128)	(−0.2618)	(−0.2543)	(−0.2338)	(−0.2387)	(−0.2235)	(−0.2222)			(−0.2063)	(−0.2014)	(−0.1935)	(−0.2698)
C(4)	0.2142	0.2243	0.2247	0.2241	0.2219	0.2141	0.2248			0.2171	0.2185	0.2222	0.2673
	(0.2142)	(0.2247)	(0.2254)	(0.2246)	(0.2222)	(0.2142)	(0.2230)			(0.2162)	(0.2180)	(0.2198)	(0.2328)
C(5)	0.1000	0.0679	0.0728	0.0844	0.0838	0.0925	0.0924			0.1030	0.1054	0.1096	0.0770
	(0.1000)	(0.0659)	(0.0702)	(0.0662)	(0.0828)	(0.0883)	(0.0822)			(0.1029)	(0.1119)	(0.1178)	(0.0741)
C(6)	0.0755	0.0823	0.0847	0.0886	0.0859	0.0741	0.0889			0.0800	0.0825	0.0885	0.0729
	(0.0755)	(0.2660)	(0.2804)	(0.2798)	(0.2712)	(0.1530)	(0.2941)			(0.1013)	(0.1465)	(0.2215)	(0.3172)
H(C^6)	0.1347	0.1270	0.1303	0.1373	0.1355	0.1313	0.1400			0.1387	0.1422	0.1471	0.1325
N(7)	−0.2799	−0.2784	−0.2777	−0.2778	−0.2776	−0.2800	−0.2781			−0.2791	−0.2787	−0.2779	−0.2677
	(−0.2799)	(−0.2806)	(−0.2796)	(−0.2827)	(−0.2742)	(−0.2803)	(−0.2760)			(−0.2793)	(−0.2779)	(−0.2751)	(−0.2650)
H(N^7)	0.3254	0.3178	0.3195	0.3240	0.3232	0.3233	0.3263			0.3274	0.3290	0.3312	0.3295
	(0.3254)	(0.3170)	(0.3139)	(0.3148)	(0.3284)	(0.3221)	(0.3292)			(0.3293)	(0.3323)	(0.3475)	(0.3319)
C(8)	0.2898	0.2781	0.2808	0.2861	0.2848	0.2870	0.2902			0.2924	0.2942	0.2969	0.2700
	(0.2898)	(0.2782)	(0.2842)	(0.2907)	(0.2861)	(0.2874)	(0.2916)			(0.2930)	(0.2945)	(0.2954)	(0.2720)
H(C^8)	0.1865	0.1765	0.1790	0.1840	0.1829	0.1838	0.1875			0.1890	0.1909	0.1937	0.1811
	(0.1865)	(0.1775)	(0.1813)	(0.1869)	(0.1837)	(0.1840)	(0.1885)			(0.1895)	(0.1916)	(0.1936)	(0.1798)
N(9)	−0.2785	−0.2860	−0.2849	−0.2818	−0.2826	−0.2803	−0.2791			−0.2778	−0.2769	−0.2755	−0.2849
	(−0.2785)	(−0.2826)	(−0.2808)	(−0.2787)	(−0.2813)	(−0.2800)	(−0.2792)			(−0.2781)	(−0.2769)	(−0.2772)	(−0.2779)
H(N^9)	0.3308	0.3216	0.3245	0.3279	0.3268	0.3283	0.3323			0.3331	0.3348	0.3380	0.3226
	(0.3308)	(0.3255)	(0.3282)	(0.3326)	(0.3293)	(0.3292)	(0.3331)			(0.3331)	(0.3347)	(0.3358)	(0.3282)
X(C^2)/	0.1475	0.1532	0.0986	0.0230	0.0398	0.1303	−0.0562			0.0865	0.0031	−0.1267	−0.2147
Y(C^6)	(0.1347)	(0.1403)	(0.0837)	(0.0054)	(0.0376)	(0.1161)	(−0.0641)			(0.0703)	(−0.0171)	(−0.1471)	(−0.2343)

[a] Net charges are for X ≡ variable, Y ≡ H, R ≡ H; charges for R ≡ CH_2OH species appear in parentheses. Standard geometries used throughout. [b] Charges for $H_{N(3)}$ are 0.1694 ≡ R ≡ H and 0.1628 for R ≡ CH_2OH species. [c] Net charges are for Y ≡ variable, X ≡ H, R ≡ H; charges for R ≡ CH_2OH species appear in parentheses. Standard geometries used throughout. [d] Net charges for $H_{N(1)}$ are 0.1636 for R ≡ H and 0.1614 for R ≡ CH_2OH species. [e] Net charges are for R ≡ H, X ≡ variable, Y ≡ H species; charges for R ≡ H, Y ≡ variable, X ≡ H species appear in parentheses. Standard geometries used throughout. [f] Net charge for $H_{N(1)}$ is 0.2730 for X ≡ H, Y ≡ =O. [g] Net charges for $H_{N(3)}$ is 0.2807 for Y ≡ H, X ≡ =O.

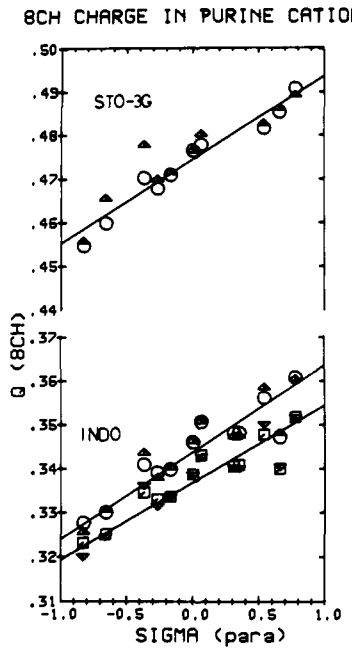
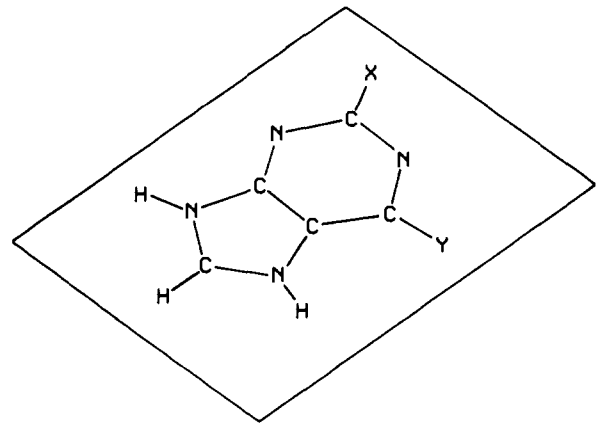


Figure 3. C(8)H net charge in purine cations [(○) X ≡ variable, Y ≡ H, R ≡ H; (△) X ≡ H, Y ≡ variable, R ≡ H; (□) X ≡ variable, Y ≡ H, R ≡ CH_2OH (▽) X ≡ H, Y ≡ variable, R ≡ CH_2OH].

(Figure 3). Hence, the additional correlation between PA(2) and $Q_{C(8)H}$ is not surprising (Figure 4). In the context of common substituent groups, the oxo and amino groups in guanine, adenine, dimethylguanine, dimethyladenine, xanthine, and hypoxanthine place the least positive change in the C(8)H vicinity. In this respect, oxo and amino groups manifest effects similar to methyl and methoxy substituents. In contrast, acidity based upon net charges is predicted to be greater in unsubstituted purine and is significantly enhanced in nitro-, fluoro-, and trifluoromethylpurines. Substitution of a particular group at C(2) or C(6) results in markedly similar net charges at C(8)H. Replacement of R ≡ H by R ≡ CH_2OH at N(9) leads to increased positive charge at H(8) but to decreased C(8)H net charge. Nevertheless, the charge pattern for the nucleoside models (R ≡ CH_2OH) follow the same trends established for the purines (R ≡ H). In general, the relative STO-3G net charges from the ab initio computations are consistent with the INDO net charges. Again the calculations based upon X-ray crystallographic structures (Table VI) produce data which follow trends established by computations with standard geometries. However, absolute values differ depending upon the structure chosen.

Although the C(8)H net charge is adequate for predictions regarding gross relative acidities, care must be taken in making distinctions among purines where acidity differences are small. Because of σ–π polarization effects (vide infra), π-electron density tends to accumulate in regions depleted of density in the σ system. The total net charge reflects the compensation, which often masks the positive charge accretion in the region. Jordan[19c] has suggested the use of σ-electron charge to measure acidity effects. We have found that both the relative net charge on H(8) as well as the C(8)H σ charge are appropriate measures of acidity. Our calculated relative acidities (X > G > I > A) based upon $Q_{H(8)}$ (INDO) and $Q_{\sigma C(8)H}$ (STO-3G) are completely consistent with experimental labilities.[12,13] $Q_{H(8)}$ (STO-3G) and $Q_{\sigma C(8)H}$ (INDO) also agree favorably with two exceptions: (1) $Q_{H(8)}$ (STO-3G) predicts A > G, and (2) $Q_{\sigma C(8)H}$ (INDO) predicts I > G. Our predictions for adenine are consistent with the experimental rates for the nucleotides which place AMP at the low end of the reactivity series.[13] These theoretical results with nucleotide models will doubtless require further refinement accounting for both solvent and conformational effects.

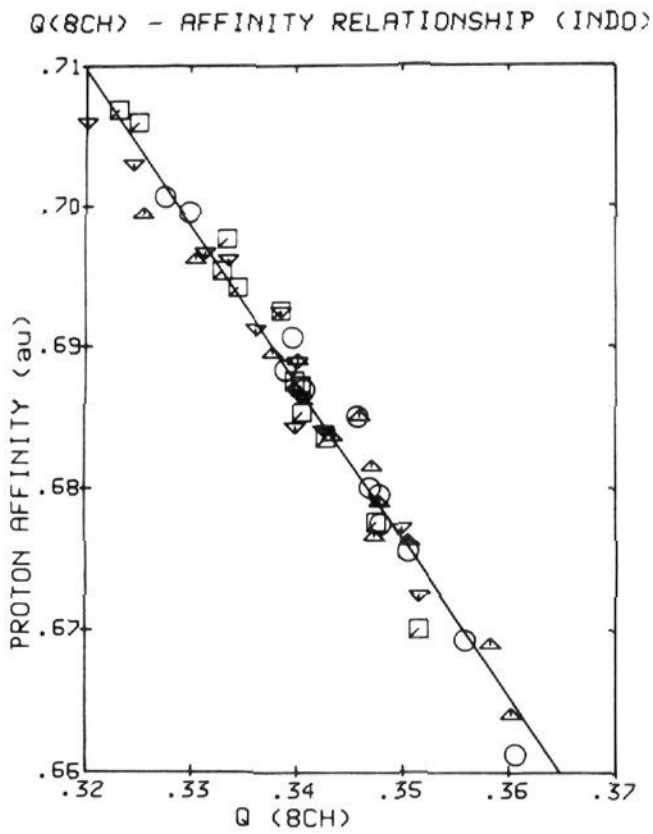
Significant perturbation at N(7), H(8), and C(8) upon protonation at N(7) is accompanied by electron reorganization in other parts of the purine ring system. Results are presented in



tabular form as net charges from Mulliken population analysis[31] in Tables V and VI and graphically in Figures 5 and 6. It is well-known that Mulliken population analysis, a vehicle for expressing electron probability distributions in common chemical terms, gives only a partial (and sometimes incorrect) picture of electron distribution in molecules.[33] Computer graphics enhances the analysis of electron distribution by providing a three-dimensional, perspective view of electron density with all of the spatial implications.

In addition to positive charge buildup at N(7)H (~17%) and C(8)H (~35%) upon protonation, smaller changes are evident elsewhere in the purine ring. Approximately 13% of the positive charge is centered at N(9)R while the remainder appears in the pyrimidine ring, which serves as an electron reservoir Since one-third or more of the positive charge is transferred to the pyrimidine ring, the substituents X and Y at C(2) and C(6) have a substantial influence. The ability of the pyrimidine ring to accommodate the positive charge is clearly dependent upon the nature of the substituent and to a lesser extent its location on the ring. In this respect, substituents X ≡ CH_3, OCH_3, NH_2, $N(CH_3)_2$, and OH and Y ≡ CH_3, NH_2, and $N(CH_3)_2$ are effective in charge accommodation, whereas the groups X or Y ≡ NO_2, F, and CF_3 are ineffective. It is important to note that the rare and common nucleotide bases containing the amino function, i.e., adenine, guanine, dimethyladenine, and dimethylguanine, appear in this effective group. In addition, the groups X or Y ≡ CN, $COOCH_3$, =O, and OCF_3 and Y ≡ OCH_3 and OH are of intermediate effectiveness, i.e., similar to unsubstituted purine (X or Y ≡ H). The oxo functions in xanthine (and to a lesser extent hypoxanthine) are ineffective in charge accommodation in the pyrimidine ring. In general, substitution at C(2) leads to greater positive charge accommodated in the pyrimidine ring than is present with substitution at C(6). The most striking example of this is found with the methoxy group at C(6), which actually permits less charge accumulation in the pyrimidine ring than in unsubstituted purine. In contrast, placement of the methoxy group at C(2) leads to substantially greater positive charge in the six-membered ring. In view of this substituent location effect, it is surprising that it is not reflected in pronounced differences in C(8)H net charge among protonated purines with OCH_3, NO_2, or F at C(2) and those at C(6). It is also interesting that in spite of the limited accommodation of positive charge in pyrimidine rings in oxopurines, such as hypoxanthine, there is considerably less acidity at C(8)H than in nitro- or fluoropurines. Apparently other atoms in the system, principally nitrogen atoms and pendent groups in the imidazole ring, take on additional charge and attenuate these differences.

The spatial maps of electron density reveal additional interesting features of the effects of protonation and substitution at C(2) or C(6). Figure 5 presents the total integrated electron density of protonated guanine, adenine, hypoxanthine, xanthine, and purine projected onto the molecular plane. The plot "landscape" appears as a series of peaks of high electron density near nuclei separated by ridges of intermediate density in covalent bond regions. Not surprisingly, electron density in the vicinity of the electronegative



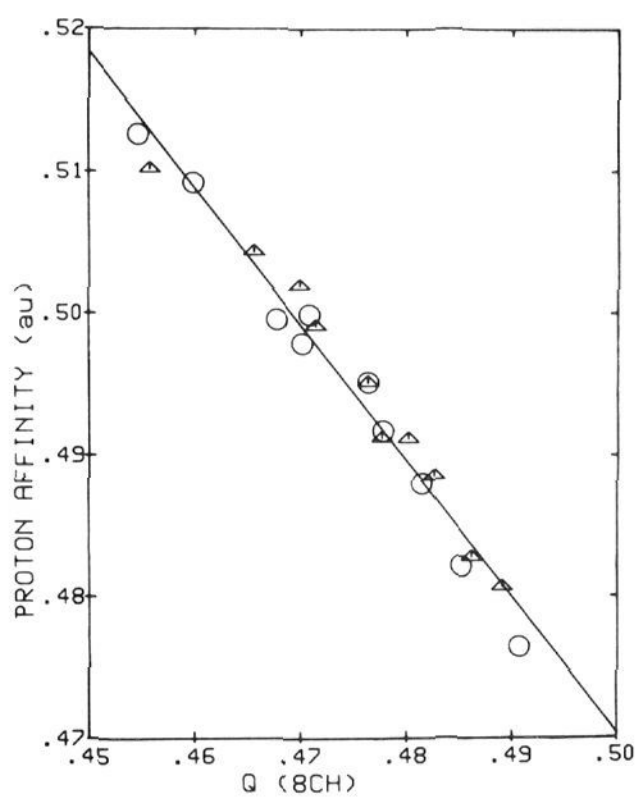


Figure 4. (a). Correlation of C(8)H net charge and C(8) proton affinity (INDO) [(○) X ≡ variable, Y ≡ H, R ≡ H; (△) X ≡ H, Y ≡ variable, R ≡ H; (□) X ≡ variable, Y ≡ H, R ≡ CH_2OH; (▽) X ≡ H, Y ≡ variable, R ≡ CH_2OH]. (B). Correlation of C(8)H net charge and C(8) proton affinity (STO-3G) [(○) X ≡ variable, Y ≡ H, R ≡ H; (△) X ≡ H, Y ≡ variable, R ≡ H].

nitrogen and oxygen atoms is considerably greater than that near carbon atoms. However, plots of projected density from σ electrons only (Figure 6) demonstrate that, except for N(3) in purine, adenine, guanine, and hypoxanthine, N(1) in adenine and purine, and O(2) and/or O(6) in all oxopurines, all carbon and nitrogen atoms share approximately equally in the pool of σ electrons. The differences in the total density arise principally from variations in π-electron density.

Density difference plots disclose features of electron reorganization in protonated species II which are not apparent in the integrated electron density plots of the individual species. The difference in integrated electron density between neutral (I) and protonated (II) species, $\delta P(x,z)$ where

$$\delta P(x,z) = P(x,z)_{II} - P(x,z)_{I} \qquad (7)$$

were mapped for several nucleotide purines and appear in Figure 7. Regions of increased or decreased electron density appear as peaks or depressions, respectively. In all of the nucleotide purines, a massive accumulation of electron density occurs in the N(7)H

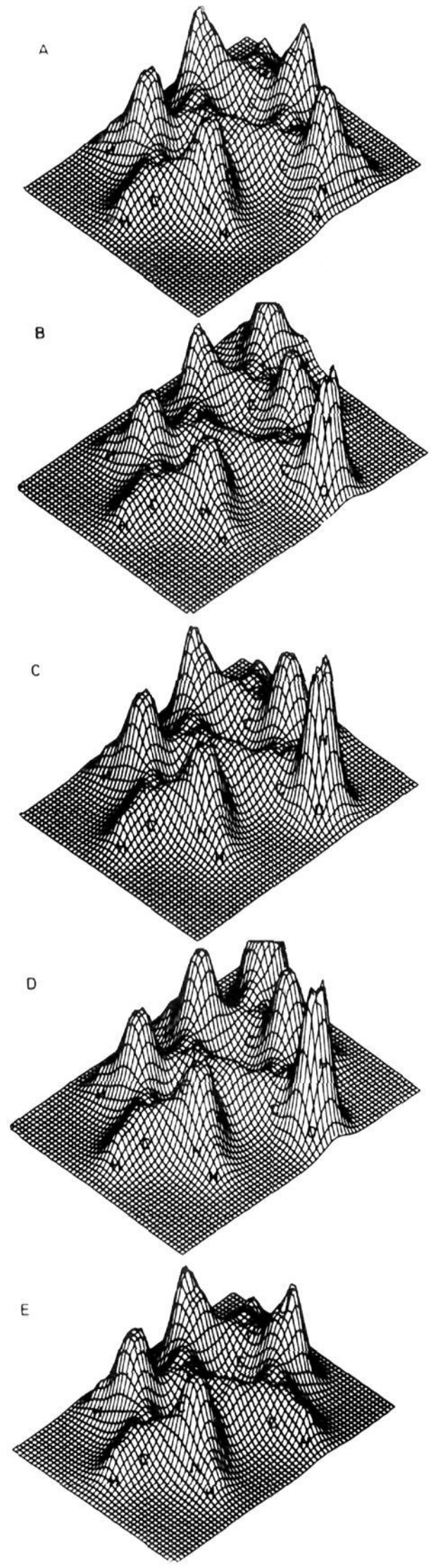


Figure 5. Integrated total electron density maps, $P(x,z)$, of protonated purine derivatives: (A) adenine, (B) guanine, (C) hypoxanthine, (D) xanthine, (E) purine.

bonding region and in the N(7) back-bonding region. Also evident in the N(7) back-bonding region is a deep depression, suggesting some positive charge at N(7). Smaller depressions at C(8), H(8), N(9), and H(9) are visible in the imidazole ring. Small changes are polarized elsewhere in the pyrimidine ring. Almost all atoms in the pyrimidine ring experience small indentations in the plot

Table VI. Mulliken Net Charges in Protonated (II) and Deprotonated (III) Nucleotide Purines[a,b]

	purine[c]		adenine[d]		guanine[d]		hypoxanthine[e]		xanthine[f]		dimethyladenine[g]		dimethylguanine[h]	
atom	II	III	II	III	II	III	II	III	II	III	II	III	II	III
						A. INDO								
N(1)	−0.1724	−0.2378	−0.2958	−0.3483	−0.2189	−0.2232	−0.1651	−0.1780	−0.2553	−0.2636	−0.2874	−0.3349	−0.2363	−0.2415
	(−0.1751)	(−0.2364)	(−0.2977)	(−0.3465)	(−0.2189)	(−0.2229)	(−0.1658)	(−0.1776)	(−0.2554)	(−0.2633)	(−0.2891)	(−0.3334)	(−0.2364)	(−0.2412)
C(2)	0.2920	0.2637	0.3316	0.3068	0.4750	0.4342	0.3432	0.3027	0.5228	0.5186	0.3311	0.3068	0.4558	0.4221
	(0.2902)	(0.2638)	(0.3307)	0.3072	(0.4736)	(0.4352)	(0.3416)	(0.3033)	(0.5228)	(0.5190)	(0.3302)	(0.3071)	(0.4549)	(0.4230)
H(C^2)	−0.0020	−0.0576	−0.0171	−0.0707			0.0065	−0.0422			−0.0209	−0.0726		
	(−0.0055)	(−0.0573)	(−0.0201)	−0.0699			(0.0034)	(−0.0418)			(−0.0239)	(−0.0719)		
N(3)	−0.2020	−0.2614	−0.2515	−0.2973	−0.3585	−0.3795	−0.2618	−0.2883	−0.1998	−0.2169	−0.2564	−0.3016	−0.3656	−0.3862
	(−0.2089)	(−0.2622)	(−0.2578)	−0.2977	(−0.3642)	(−0.3808)	(−0.2677)	(−0.2893)	(−0.2009)	(−0.2166)	(−0.2624)	(−0.3017)	(−0.3700)	(−0.3864)
C(4)	0.2385	0.2310	0.2696	0.2489	0.2961	0.2535	0.2784	0.2397	0.2827	0.2385	0.2753	0.2578	0.3099	0.2747
	(0.2287)	(0.2261)	(0.2591)	(0.2443)	(0.2851)	(0.2496)	(0.2662)	(0.2349)	(0.2680)	(0.2321)	(0.2652)	(0.2532)	(0.2986)	(0.2703)
C(5)	0.0048	−0.0118	−0.0709	−0.0797	−0.1200	−0.1412	−0.0929	−0.1111	−0.0982	−0.1292	−0.0776	−0.0837	−0.1429	−0.1592
	(0.0056)	(−0.0103)	(−0.0694)	−0.0777	(−0.1181)	(−0.1387)	(−0.0915)	(−0.1087)	(−0.0963)	(−0.1260)	(−0.0765)	(−0.0821)	(−0.1416)	(−0.1570)
C(6)	0.1921	0.1557	0.3405	0.3024	0.4392	0.4204	0.4243	0.4039	0.4378	0.4247	0.3243	0.2884	0.4397	0.4197
	(0.1902)	(0.1557)	(0.3389)	0.3028	(0.4381)	(0.4204)	(0.4230)	(0.4035)	(0.4365)	(0.4243)	(0.3229)	(0.2885)	(0.4385)	(0.4196)
H(C^6)	0.0027	−0.0445												
	(0.0003)	(−0.0441)												
N(7)	−0.0233	−0.0207	−0.0030	−0.0122	0.0208	0.0150	0.0413	0.0350	0.0500	0.0410	−0.0064	−0.0090	0.0505	0.0452
	(−0.0311)	(−0.0240)	(−0.0107)	−0.0150	(0.0130)	(0.0117)	(0.0340)	(0.0317)	(0.0429)	(0.0377)	(−0.0137)	(−0.0120)	(0.0438)	(0.0418)
H(N^7)	0.1784	0.0947	0.1753	0.0938	0.1728	0.0916	0.1923	0.1099	0.1975	0.1147	0.1865	0.1044	0.1840	0.1024
	(0.1739)	(0.0958)	(0.1715)	0.0954	(0.1690)	(0.0930)	(0.1883)	(0.1113)	(0.1935)	(0.1160)	(0.1827)	(0.1060)	(0.1807)	(0.1043)
C(8)	0.3155	−0.1764	0.2943	−0.1762	0.2673	−0.1992	0.2731	−0.1890	0.2681	−0.1820	0.3004	−0.1796	0.2641	−0.2012
	(0.3040)	(−0.1660)	(0.2840)	−0.1647	(0.2603)	(−0.1868)	(0.2642)	(−0.1780)	(0.2596)	(−0.1706)	(0.2912)	(−0.1675)	(0.2580)	(−0.1875)
H(C^8)	0.0390		0.0434		0.0495		0.0464		0.0552		0.0348		0.0379	
	(0.0420)		(0.0468)		(0.0528)		(0.0490)		(0.0588)		(0.0390)		(0.0420)	
N(9)	−0.0574	−0.0457	−0.0752	−0.0729	−0.0697	−0.0487	−0.0723	−0.0689	−0.0771	−0.0739	−0.0786	−0.0731	−0.0866	−0.0787
	(−0.0378)	(−0.0382)	(−0.0546)	(−0.0648)	(−0.0536)	(−0.0448)	(−0.0543)	(−0.0616)	(−0.0551)	(−0.0641)	(−0.0595)	(−0.0657)	(−0.0690)	(−0.0713)
H(N^9)/	0.1942	0.1107	0.1839	0.1023	0.1753	0.0937	0.1842	0.1029	0.1856	0.1074	0.1816	0.1018	0.1745	0.0980
$CH_2OH(N^9)$	(0.2236)	(0.0971)	(0.2069)	(0.0823)	(0.1999)	(0.0776)	(0.2118)	(0.0868)	(0.2084)	(0.0894)	(0.2043)	(0.0827)	(0.1938)	(0.0765)
$NH_2(C^6)$			0.0750	0.0032										
			(0.0723)	(0.0043)										
$O(C^6)$					−0.3751	−0.4474	−0.3625	−0.4379	−0.3483	−0.4169			−0.3824	−0.4521
					(−0.3374)	(−0.4458)	(−0.3652)	(−0.4364)	(−0.3505)	(−0.4154)			(−0.3844)	(−0.4504)
$NH_2(C^2)$					0.0902	0.0141								
					(0.0858)	(0.0151)								
$O(C^2)$									−0.3693	−0.4376				
									(−0.3731)	(−0.4371)				
$N(CH_3)_2(C^6)$											0.0932	−0.0047		
											(0.0655)	(−0.0031)		
$N(CH_3)_2(C^2)$													0.1435	0.0397
													(0.1380)	(0.0412)
H(N^1)					0.1560	0.1167	0.1650	0.1214	0.1772	0.1393			0.1538	0.1169
					(0.1544)	(0.1172)	(0.1629)	(0.1218)	(0.1756)	(0.1397)			(0.1524)	(0.1174)
H(N^3)									0.1711	0.1360				
									(0.1654)	(0.1351)				

	purine[c]		adenine[d]		guanine[d]		hypoxanthine[e]		xanthine[f]		dimethyladenine[g]	
atom	II	III	II	III	II	III	II	III	II	III	II	III
						B. STO-3G						
N(1)	−0.1983	−0.2520	−0.2592	−0.3054	−0.3543	−0.3623	−0.3415	−0.3537	−0.3781	−0.3854	−0.2679	−0.3097
C(2)	0.1654	0.1258	0.1739	0.1399	0.4279	0.3933	0.2340	0.1924	0.4305	0.4209	0.1743	0.1417
H(C^2)	0.1384	0.0884	0.1302	0.0835			0.1485	0.1032			0.1261	0.0811
N(3)	−0.2145	−0.2571	−0.2568	−0.2902	−0.3340	−0.3493	−0.2719	−0.2878	−0.3526	−0.3687	−0.2607	−0.2926

C(4)	0.2227	0.1962	0.2346	0.1993	0.2485	0.1991	0.2391	0.1880	0.2798	0.2287	0.2371	0.2042
C(5)	0.0988	0.0747	0.0618	0.0368	0.0439	0.0064	0.0639	0.0292	0.0573	0.0085	0.0542	0.0306
C(6)	0.0763	0.0358	0.2768	0.2439	0.3133	0.2942	0.3102	0.2907	0.3162	0.3013	0.2639	0.2327
$H(C^6)$	0.1298	0.0864										
N(7)	−0.2804	−0.3528	−0.2767	−0.3584	−0.2656	−0.3479	−0.2655	−0.3480	−0.2573	−0.3460	−0.2778	−0.3593
$H(N^7)$	0.3230	0.2486	0.3174	0.2420	0.3176	0.2419	0.3384	0.2615	0.3416	0.2616	0.3261	0.2532
C(8)	0.2978	0.0994	0.2865	0.0970	0.2642	0.0812	0.2725	0.0865	0.2697	0.0909	0.2847	0.0890
$H(C^8)$	0.1858		0.1819		0.1787		0.1779		0.1811		0.1762	
N(9)	−0.2827	−0.3561	−0.2789	−0.3549	−0.2829	−0.3516	−0.2759	−0.3492	−0.2825	−0.3523	−0.2842	−0.3562
$H(N^9)$	0.3376	0.2627	0.3247	0.2497	0.3138	0.2409	0.3222	0.2468	0.3147	0.2425	0.3230	0.2505
$NH_2(C^6)$			0.0838	0.0168								
$O(C^6)$					−0.2364	−0.3053	−0.2281	−0.2984	−0.2240	−0.2853		
$NH_2(C^2)$					0.1045	0.0316						
$O(C^2)$									−0.2401	−0.2981		
$N(CH_3)_2(C^6)$											0.1250	0.0349
$H(N^1)$					0.2608	0.2278	0.2762	0.2387	0.2669	0.2359		
$H(N^8)$									0.2767	0.2454		

[a] Geometries for purines from crystallographic data. [b] Net charges are for R ≡ H; charges for R ≡ CH_2OH species appear in parentheses. [c] Geometry: ref 29, structure W. [d] Geometry: ref 23. [e] Geometry: ref 25. [f] Geometry: ref 26. [g] Geometry: ref 28, structure A. [h] Geometry: ref 27.

Figure 6. Integrated σ electron density maps, $P(x,z)_\sigma$, of protonated purine derivatives: (A) (A) adenine, (B) guanine, (C) hypoxanthine, (D) xanthine, (E) purine.

surface underscoring the importance of the pyrimidine ring in accepting positive charge. The most notable exception is a rather pronounced peak of electron density at C(5). Electron density builds up slightly in the N(9)H bond in all protonated purines, as well as the N(1)H and N(3)H bonds in protonated guanine, hypoxanthine, and xanthine.

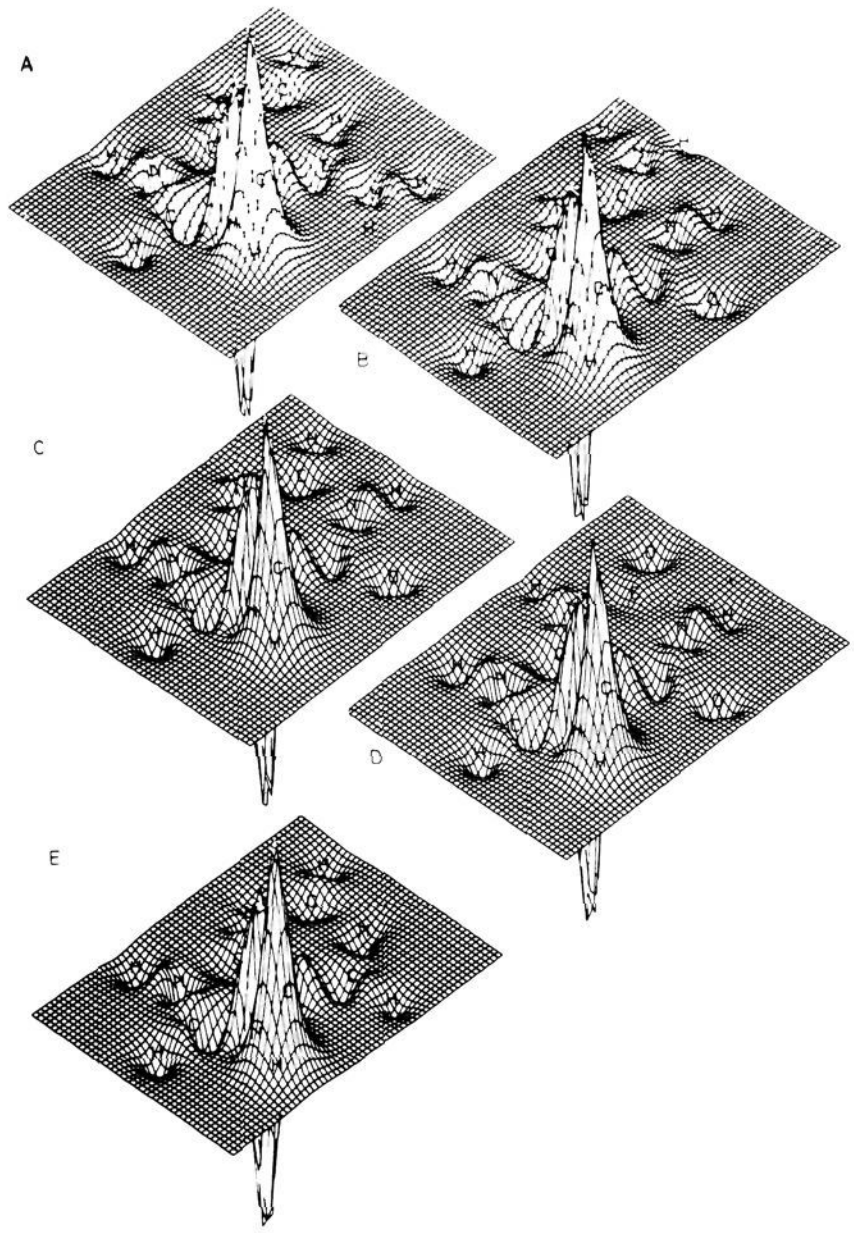


Figure 7. Difference maps of integrated total electron density between protonated and neutral purines: (a) Adenine, (B) guanine, (C) hypoxanthine, (D) xanthine, (E) purine.

Electronic Structure and Charge Distribution in the Ylide III. The deprotonated species III is a nitrogen ylide with characteristics quite unlike other common ylides. These purine ylides involve s-type carbanion lone pairs. As such, they are neither similar to the stabilized π-bonding ylides of sulfur[41,42] or phosphorus[42,43] nor similar to the destabilized π^*-antibonding ylides of oxygen[41a,42] or nitrogen.[42] The carbanion portion of these deprotonated purine species does bear some similarity to phenyl,[44] vinyl,[45,46] and ethynyl[45,47] carbanions with the carbanion lone pair orbital perpendicular to a polarizable pπ system. However, the purine species

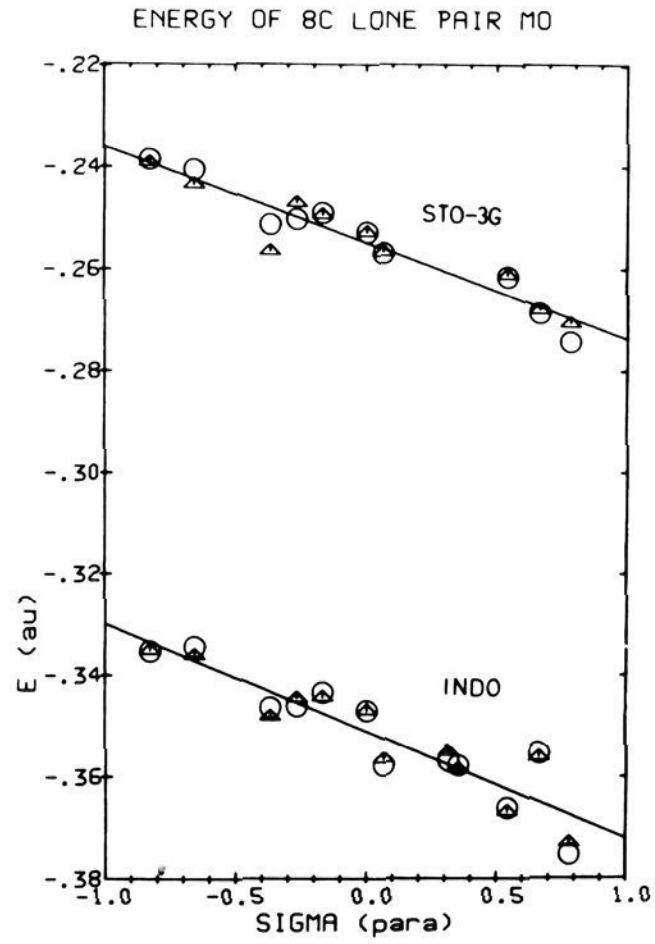


Figure 8. Correlation of C(8) lone pair MO energy with σ_{para} [(O) X ≡ variable, Y ≡ H, R ≡ H; (Δ) X ≡ H, Y ≡ variable, R ≡ H].

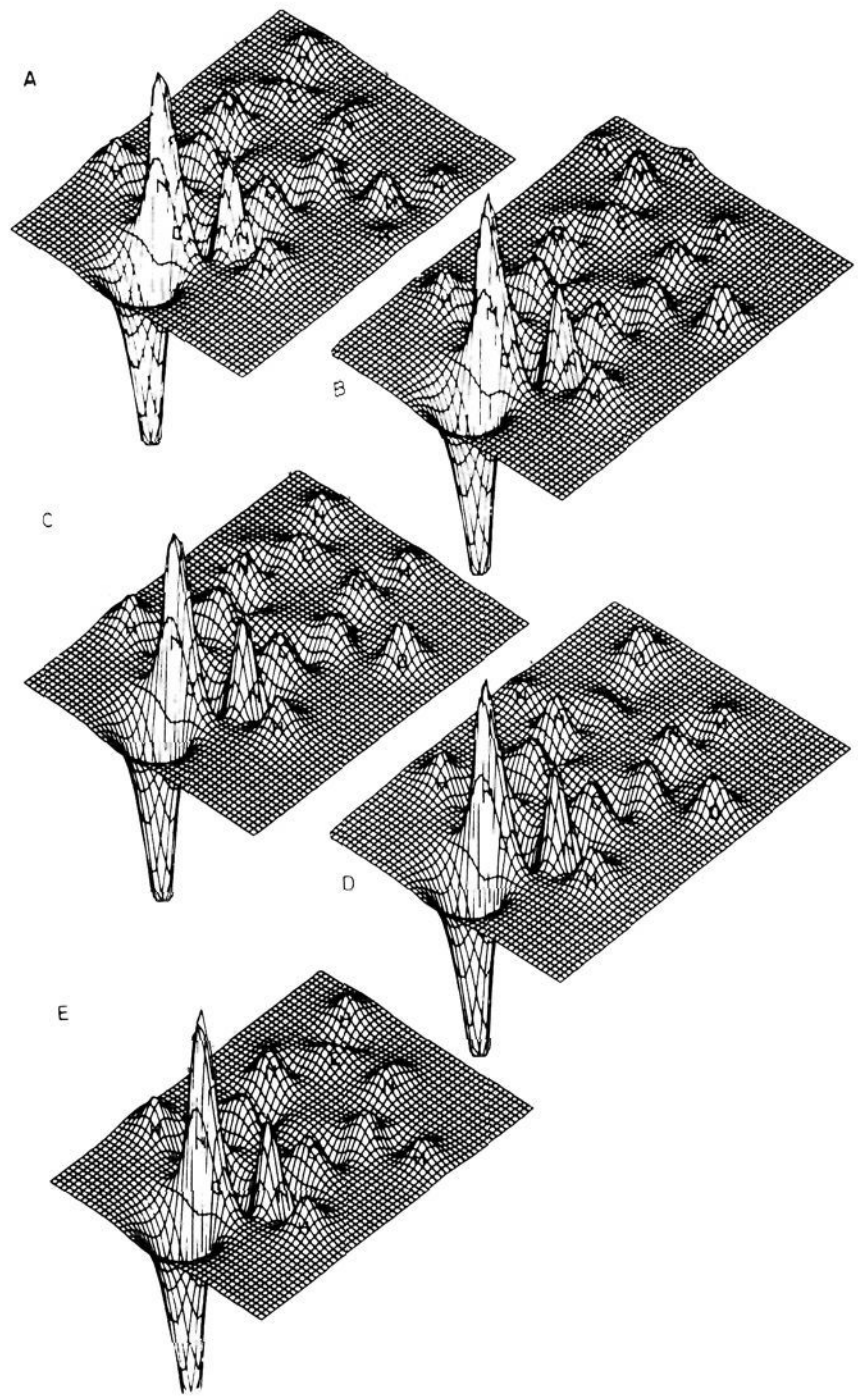


Figure 9. Difference maps of integrated total electron density between protonated and deprotonated purines: (A) adenine, (B) guanine, (C) hypoxanthine, (D) xanthine, (E) purine.

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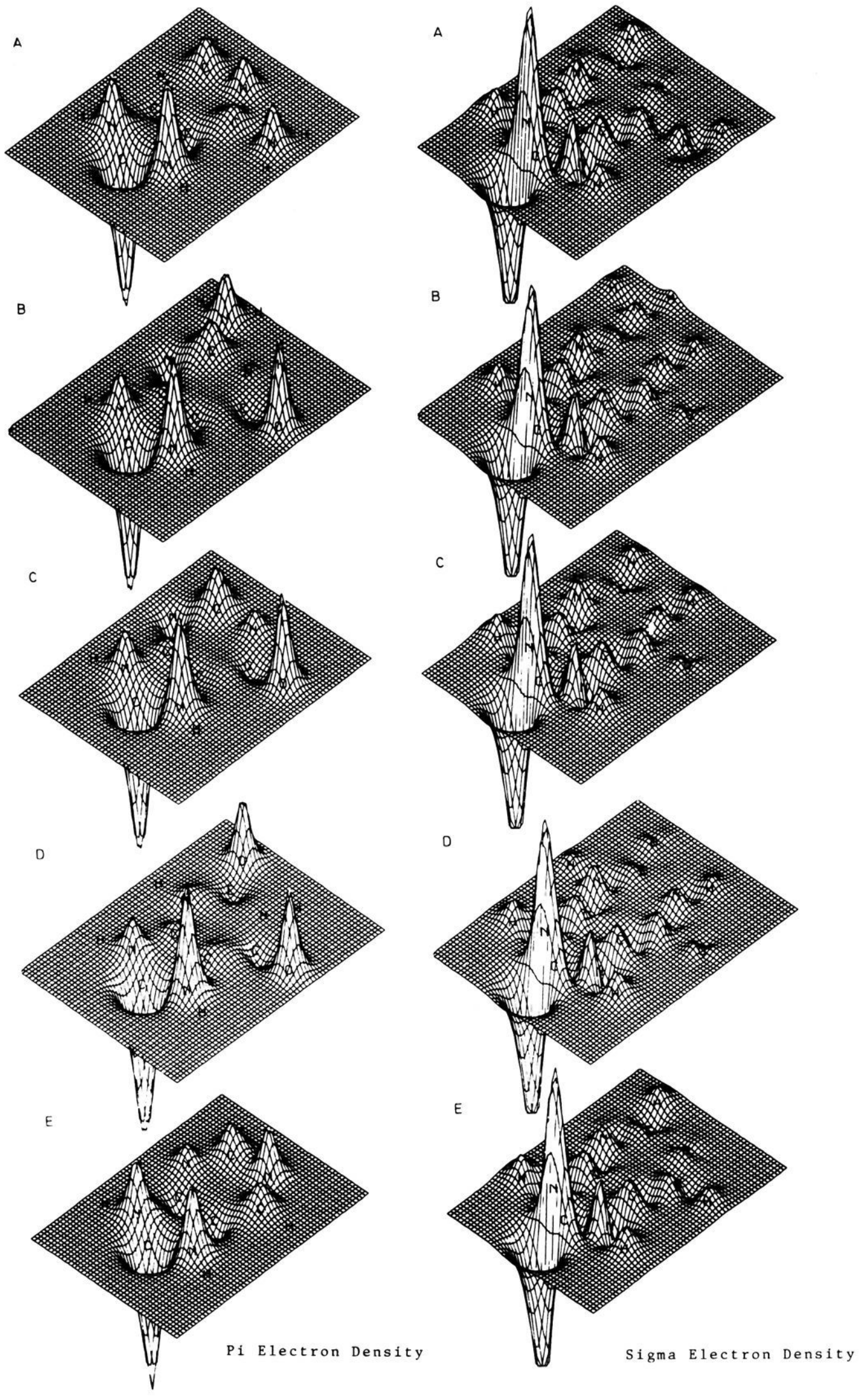

Figure 10. Difference maps of integrated σ- and π-electron density between protonated and deprotonated purines: (A) adenine, (B) guanine, (C) hypoxanthine, (D) xanthine, (E) purine.

III are considerably more stable than the corresponding phenyl, vinyl, and ethynyl carbanion species.

The orbital describing the carbanion lone pair is clearly discernible near the Fermi level. It appears as the highest occupied molecular orbital (HOMO) in all of the INDO calculations. In the STO-3G results, it is the HOMO but may appear below the HOMO in stabilized cases. Interestingly, the carbanion lone-pair MO is energetically below the HOMO in the guanine, hypoxanthine, and xanthine ylides III, but in adenine, dimethyladenine, and purine ylides, the carbanion MO is the highest occupied molecular orbital. The energy of the lone-pair MO is affected by the nature of the substituent at C(2) or C(6) as evidenced by a correlation with σ_{para} values (see Figure 8). It is noteworthy that the energy of the lone-pair molecular orbital appears to be

Table VII. Mulliken Net Charges in Deprotonated Purine Species

atom	X or Y												
	H	$N(CH_3)_2$	NH_2	OH	OCH_3	CH_3	F	$COOCH_3$	OCF_3	CF_3	CN	NO_2	=O
						A. INDO (X ≡ variable)[a]							
N(1)	−0.2537	−0.3249	−0.3269	−0.2976	−0.2994	−0.2692	−0.2937	−0.2320	−0.2873	−0.2181	−0.2485	−0.2172	−0.3239
	(−0.2521)	(−0.3237)	(−0.3255)	(−0.2961)	(−0.2981)	(−0.2676)	(−0.2926)	(−0.2311)	(−0.2864)	(−0.2173)	(−0.2473)	(−0.2165)	(−0.3231)
C(2)	0.2547	0.3911	0.4044	0.4429	0.4423	0.2616	0.4962	0.1717	0.4426	0.1444	0.2588	0.2355	0.5108
	(0.2550)	(0.3916)	(0.4050)	(0.4433)	(0.4427)	(0.2620)	(0.4965)	(0.1718)	(0.4428)	(0.1445)	(0.2591)	(0.2355)	(0.5110)
N(3)	−0.2575	−0.3505	−0.3531	−0.3346	−0.3321	−0.2770	−0.3067	−0.2192	−0.3172	−0.2172	−0.2512	−0.2162	−0.1917[b]
	(−0.2585)	(−0.3509)	(−0.3537)	(−0.3355)	(−0.3327)	(−0.2778)	(−0.3078)	(−0.2201)	(−0.3183)	(−0.2183)	(−0.2525)	(−0.2177)	(−0.1920)[b]
C(4)	0.2254	0.2486	0.2503	0.2469	0.2448	0.2270	0.2463	0.2170	0.2501	0.2229	0.2238	0.2253	0.2300
	(0.2208)	(0.2445)	(0.2461)	(0.2423)	(0.2403)	(0.2225)	(0.2414)	(0.2123)	(0.2451)	(0.2180)	(0.2190)	(0.2200)	(0.2239)
C(5)	0.0012	−0.0373	−0.0396	−0.0251	−0.0243	−0.0045	−0.0169	0.0182	−0.0175	0.0193	0.0072	0.0221	−0.0514
	(0.0030)	(−0.0356)	(−0.0380)	(−0.0234)	(−0.0226)	(−0.0027)	(−0.0153)	(0.0199)	(−0.0159)	(0.0208)	(0.0090)	(0.0236)	(−0.0491)
C(6)	0.1354	0.1614	0.1627	0.1588	0.1583	0.1373	0.1610	0.1276	0.1609	0.1341	0.1353	0.1382	0.1888
	(0.1355)	(0.1615)	(0.1629)	(0.1589)	(0.1582)	(0.1374)	(0.1609)	(0.1275)	(0.1608)	(0.1338)	(0.1354)	(0.1379)	(0.1885)
$H(C^6)$	−0.0227	−0.0290	−0.0293	−0.0219	−0.0223	−0.0247	−0.0165	−0.0177	−0.0160	−0.0116	−0.0182	−0.0065	−0.0195
	(−0.0222)	(−0.0284)	(−0.0287)	(−0.0214)	(−0.0218)	(−0.0242)	(−0.0161)	(−0.0174)	(−0.0157)	(−0.0114)	(−0.0178)	(−0.0064)	(−0.0192)
N(7)	−0.0141	−0.0115	−0.0113	−0.0113	−0.0113	−0.0140	−0.0106	−0.0140	−0.0110	−0.0135	−0.0135	−0.0119	−0.0020
	(−0.0174)	(−0.0148)	(−0.0146)	(−0.0146)	(−0.0148)	(−0.0173)	(−0.0142)	(−0.0176)	(−0.0145)	(−0.0171)	(−0.0169)	(−0.0155)	(−0.0016)
$H(N^7)$	0.0978	0.0923	0.0919	0.0966	0.0965	0.0963	0.1006	0.1018	0.1006	0.1047	0.1007	0.1079	0.1040
	(0.0990)	(0.0937)	(0.0934)	(.0978)	(0.0977)	(0.0976)	(0.1016)	(0.1027)	(0.1014)	(0.1055)	(0.1017)	(0.1085)	(0.1047)
C(8)	−0.1774	−0.1848	−0.1854	−0.1787	−0.1789	−0.1794	−0.1720	−0.1711	−0.1715	−0.1661	−0.1726	−0.1610	−0.1815
	(−0.1660)	(−0.1728)	(−0.1734)	(−0.1673)	(−0.1675)	(−0.1678)	(−0.1615)	(−0.1604)	(−0.1611)	(−0.1560)	(−0.1618)	(−0.1516)	(−0.1716)
N(9)	−0.0547	−0.0581	−0.0582	−0.0564	−0.0561	−0.0555	−0.0536	−0.0524	−0.0537	−0.0518	−0.0534	−0.0503	−0.0472
	(−0.0483)	(−0.0518)	(−0.0520)	(−0.0498)	(−0.0494)	(−0.0492)	(−0.0464)	(−0.0454)	(−0.0463)	(−0.0445)	(−0.0467)	(−0.0428)	(−0.0404)
$H(N^9)$/ $CH_2OH(N^9)$	0.1047	0.1009	0.1007	0.1048	0.1046	0.1033	0.1101	0.1091	0.1112	0.1118	0.1076	0.1159	0.1095
	(0.0901)	(0.0841)	(0.0838)	(0.0900)	(0.0898)	(0.0880)	(0.0979)	(0.0967)	(0.0993)	(0.1009)	(0.0944)	(0.1069)	(0.0999)
$X(C^2)$	−0.0392	0.0017	−0.0062	−0.1246	0.1487	−0.0014	−0.2441	−0.0390	−0.1911	−0.0587	−0.0760	−0.1818	−0.4627
	(−0.0388)	(0.0027)	(−0.0053)	(−0.1241)	(0.1489)	(−0.0009)	(−0.2440)	(−0.0388)	(−0.1912)	(−0.0588)	(−0.0756)	(−0.1821)	(−0.4625)
						B. INDO (Y ≡ variable)[c]							
N(1)	−0.2537	−0.3483	−0.3493	−0.3137	−0.3308	−0.2724	−0.3061	−0.2270	−0.3136	−0.2106	−0.2483	−0.2136	−0.1809[d]
	(−0.2521)	(−0.3471)	(−0.3479)	(−0.3127)	(−0.3295)	(−0.2712)	(−0.3051)	(−0.2259)	(−0.3127)	(−0.2098)	(−0.2472)	(−0.2128)	(−0.1805)[d]
C(2)	0.2547	0.2841	0.2856	0.2796	0.2791	0.2575	0.2790	0.2445	0.2822	0.2486	0.2535	0.2518	0.2764
	(0.2550)	(0.2845)	(0.2861)	(0.2799)	(0.2794)	(0.2578)	(0.2792)	(0.2448)	(0.2825)	(0.2488)	(0.2537)	(0.2520)	(0.2771)
$H(C^2)$	−0.0392	−0.0482	−0.0480	−0.0395	−0.0422	−0.0414	−0.0336	−0.0336	−0.0331	−0.0270	−0.0341	−0.0222	−0.0275
	(−0.0388)	(−0.0478)	(−0.0476)	(−0.0391)	(−0.0418)	(−0.0410)	(−0.0334)	(−0.0334)	(−0.0329)	(−0.0270)	(−0.0339)	(−0.0222)	(−0.0273)
N(3)	−0.2575	−0.3034	−0.3055	−0.2852	−0.2848	−0.2651	−0.2725	−0.2378	−0.2736	−0.2338	−0.2502	−0.2276	−0.2827
	(−0.2585)	(−0.3043)	(−0.3066)	(−0.2860)	(−0.2858)	(−0.2658)	(−0.2736)	(−0.2389)	(−0.2747)	(−0.2349)	(−0.2513)	(−0.2291)	(−0.2841)
C(4)	0.2254	0.2440	0.2450	0.2449	0.2414	0.2268	0.2440	0.2166	0.2437	0.2227	0.2246	0.2239	0.2279
	(0.2208)	(0.2397)	(0.2406)	(0.2404)	(0.2367)	(0.2224)	(0.2391)	(0.2119)	(0.2388)	(0.2179)	(0.2199)	(0.2188)	(0.2228)
C(5)	0.0012	−0.0712	−0.0740	−0.0686	−0.0535	−0.0133	−0.0515	0.0355	−0.0413	0.0379	0.0073	0.0314	−0.1042
	(0.0030)	(−0.0694)	(−0.0721)	(−0.0669)	(−0.0516)	(−0.0116)	(−0.0498)	(0.0372)	(−0.0397)	(0.0394)	(0.0090)	(0.0328)	(−0.1016)
C(6)	0.1354	0.2802	0.2945	0.3348	0.3341	0.1492	0.3881	0.0539	0.3316	0.0259	0.1456	0.1174	0.4145
	(0.1355)	(0.2803)	(0.2948)	(0.3349)	(0.3344)	(0.1492)	(0.3882)	(0.0540)	(0.3316)	(0.0257)	(0.1457)	(0.1173)	(0.4142)
N(7)	−0.0141	−0.0116	−0.0053	−0.0049	−0.0035	−0.0128	−0.0021	−0.0163	−0.0049	−0.0176	−0.0138	−0.0126	0.0260
	(−0.0174)	(−0.0150)	(−0.0085)	(−0.0084)	(−0.0068)	(−0.0164)	(−0.0055)	(−0.0198)	(−0.0084)	(−0.0213)	(−0.0173)	(−0.0162)	(0.0224)
$H(N^7)$	0.0978	0.0936	0.0867	0.0913	0.0989	0.0952	0.1049	0.1161	0.1036	0.1110	0.1029	0.1261	0.1029
	(0.0990)	(0.0949)	(0.0880)	(0.0924)	(0.1001)	(0.0964)	(0.1058)	(0.1171)	(0.1044)	(0.1118)	(0.1039)	(0.1267)	(0.1041)
C(8)	−0.1774	−0.1891	−0.1887	−0.1793	−0.1817	−0.1794	−0.1740	−0.1699	−0.1733	−0.1623	−0.1713	−0.1595	−0.1979
	(−0.1660)	(−0.1773)	(−0.1769)	(−0.1682)	(−0.1704)	(−0.1679)	(−0.1634)	(−0.1590)	(−0.1628)	(−0.1521)	(−0.1605)	(−0.1497)	(−0.1866)
N(9)	−0.0547	−0.0542	−0.0541	−0.0539	−0.0537	−0.0546	−0.0529	−0.0542	−0.0527	−0.0532	−0.0537	−0.0526	−0.0398
	(−0.0483)	(−0.0481)	(−0.0480)	(−0.0472)	(−0.0472)	(−0.0482)	(−0.0457)	(−0.0475)	(−0.0454)	(−0.0459)	(−0.0470)	(−0.0451)	(−0.0343)
$H(N^9)$/ $CH_2OH(N^9)$	0.1047	0.1013	0.1018	0.1060	0.1053	0.1035	0.1097	0.1073	0.1103	0.1115	0.1076	0.1141	0.1027
	(0.0901)	(0.0851)	(0.0860)	(0.0918)	(0.0905)	(0.0885)	(0.0969)	(0.0941)	(0.0978)	(0.1001)	(0.0945)	(0.1037)	(0.0898)
$Y(C^6)$	−0.0227	0.0228	0.0113	−0.1115	−0.1085	0.0069	−0.2330	−0.0353	−0.1789	−0.0531	−0.0702	−0.1766	−0.4370
	(−0.0222)	(0.0242)	(0.0122)	(−0.1109)	(−0.1079)	(0.0076)	(−0.2327)	(−0.0343)	(−0.1787)	(−0.0527)	(−0.0696)	(−0.1764)	(−0.4358)

	C. STO-3G (X or Y ≡ variable)[a]										
N(1)	−0.2522	−0.2951	−0.2925	−0.2698	−0.2694	−0.2633	−0.2713	−0.2441	−0.2343	−0.2244	−0.2737
	(−0.2522)	(−0.3170)	(−0.3105)	(−0.2809)	(−0.3039)	(−0.2672)	(−0.2784)	(−0.2417)	(−0.2295)	(−0.2199)	(−0.3546)[f]
C(2)	0.1220	0.3148	0.3270	0.3236	0.3193	0.1981	0.3363	0.1512	0.1927	0.2704	0.3722
	(0.1220)	(0.1335)	(0.1342)	(0.1357)	(0.1311)	(0.1220)	(0.1334)	(0.1253)	(0.1270)	(0.1303)	(0.1817)
H(C²)	(0.0979)	(0.0907)	(0.0929)	(0.1004)	(0.0959)	(0.0953)	(0.1022)	(0.1034)	(0.1076)	(0.1122)	(0.1056)
N(3)	−0.2507	−0.3130	−0.3071	−0.3034	−0.2995	−0.2653	−0.2751	−0.2423	−0.2296	−0.2184	−0.3619[g]
	(−0.2507)	(−0.2885)	(−0.2844)	(−0.2679)	(−0.2689)	(−0.2580)	(−0.2581)	(−0.2422)	(−0.2359)	(−0.2287)	(−0.2817)
C(4)	0.1841	0.1955	0.1956	0.1944	0.1927	0.1848	0.1948	0.1881	0.1891	0.1931	0.2323
	(0.1841)	(0.1915)	(0.1925)	(0.1936)	(0.1905)	(0.1841)	(0.1921)	(0.1876)	(0.1887)	(0.1905)	(0.1837)
C(5)	0.0760	0.0471	0.0497	0.0609	0.0607	0.0701	0.0686	0.0811	0.0862	0.0904	0.0300
	(0.0760)	(0.0407)	(0.0441)	(0.0407)	(0.0590)	(0.0654)	(0.0572)	(0.0818)	(0.0931)	(0.0993)	(0.0364)
C(6)	0.0384	0.0495	0.0501	0.0530	0.0518	0.0383	0.0518	0.0428	0.0459	0.0509	0.0649
	(0.0384)	(0.2330)	(0.2447)	(0.2394)	(0.2326)	(0.1165)	(0.2497)	(0.0645)	(0.1057)	(0.1798)	(0.2968)
H(C⁶)	0.0931	0.0889	0.0903	0.0967	0.0958	0.0909	0.0985	0.0987	0.1027	0.1076	0.0973
N(7)	−0.3569	−0.3596	−0.3592	−0.3573	−0.3574	−0.3578	−0.3563	−0.3555	−0.3539	−0.3526	−0.3524
	(−0.3569)	(−0.3614)	(−0.3585)	(−0.3601)	(−0.3535)	(−0.3580)	(−0.3540)	(−0.3558)	(−0.3531)	(−0.3506)	(−0.3446)
H(N⁷)	0.2503	0.2431	0.2440	0.2487	0.2483	0.2485	0.2511	0.2537	0.2562	0.2587	0.2505
	(0.2503)	(0.2448)	(0.2384)	(0.2402)	(0.2536)	(0.2478)	(0.2541)	(0.2563)	(0.2605)	(0.2770)	(0.2554)
C(8)	0.0984	0.0903	0.0914	0.0968	0.0961	0.0962	0.1005	0.1033	0.1069	0.1103	0.0913
	(0.0984)	(0.0865)	(0.0917)	(0.0998)	(0.0949)	(0.0960)	(0.1005)	(0.1042)	(0.1078)	(0.1092)	(0.0846)
N(9)	−0.3561	−0.3592	−0.3584	−0.3568	−0.3571	−0.3571	−0.3549	−0.3543	−0.3532	−0.3516	−0.3548
	(−0.3561)	(−0.3576)	(−0.3567)	(−0.3552)	(−0.3560)	(−0.3568)	(−0.3548)	(−0.3543)	(−0.3534)	(−0.3527)	(−0.3511)
H(N⁹)	0.2559	−0.2504	−0.2517	0.2547	0.2541	0.2544	0.2584	0.2595	0.2620	0.2654	0.2508
	(0.2559)	(0.2521)	(0.2537)	(0.2579)	(0.2556)	(0.2547)	(0.2587)	(0.2591)	(0.2616)	(0.2632)	(0.2527)
X(C²)/	0.0979	0.0472	0.0175	−0.0416	−0.0354	0.0623	−0.1024	0.0176	−0.0708	−0.1997	−0.2962
Y(C⁶)	(0.0931)	(0.0518)	(0.0179)	(−0.0436)	(−0.0308)	(0.0585)	(−0.1024)	(0.0117)	(−0.0801)	(−0.2098)	(−0.3003)

[a] Net charges are for X ≡ variable, Y ≡ H, R ≡ H; charges for R ≡ CH_2OH species appear in parentheses. Standard geometries used throughout. [b] Net charges for $H_{N(3)}$ are 0.1329 for R ≡ H and 0.1315 for R ≡ CH_2OH species. [c] Net charges for Y ≡ variable, X ≡ H, R ≡ H; charges for R ≡ CH_2OH species appear in parentheses. Standard geometries used throughout. [d] Net charges for $H_{N(1)}$ are 0.1194 for R ≡ H and 0.1197 for R ≡ CH_2OH species. [e] Net charges are for R ≡ H, X ≡ variable, Y ≡ H species; charges for R ≡ H, Y ≡ variable, X ≡ H species appear in parentheses. Standard geometries used throughout. [f] Net charge for $H_{N(1)}$ is 0.2352 for X ≡ H, Y ≡ =O. [g] Net charge for $H_{N(3)}$ is 0.2496 for Y ≡ H, X ≡ =O.

inversely related to the experimental C(8)H lability; i.e., the more stable the lone pair of intermediate III, the greater the C(8)H isotope exchange rate. In addition, the carbanion lone pair has pronounced s character with almost exclusive contributions from the 2s function on C(8) and a 2p function on C(8) oriented along the C(8)H bond axis. Because of its orientation in the σ plane of the aromatic system, direct overlap with the delocalized pπ system is precluded. In sulfur and phosphorus ylides,[41-43] π overlap with p- or d-type orbitals can become an important mechanism of stabilization. Nevertheless, the unit positive charge introduced formally at N(7) and the unit negative charge appearing formally at C(8) are offset by polarization of the π-electron cloud (vide infra).

The atomic net charges (Tables VI and VII) reveal substantially reduced net charges at N(7)H and C(8), demonstrating only partial zwitterion character. INDO net charges at C(8) are typically in the range −0.17 to −0.18 for R ≡ H purines and −0.16 to −0.17 for R ≡ CH_2OH derivatives. The STO-3G results are even more astonishing, showing actually a slight positive charge at C(8). Further surprises are evident at N(7) which is either slightly negative (INDO) or considerably negative (STO-3G) for both electron-withdrawing and -releasing substituents. When the charges at N(7) and H(7) are considered together, the charges become slightly positive with INDO wave functions but remain slightly negative with STO-3G wave functions. Electron-withdrawing substituents (CN, F, NO_2, =O, etc.) at C(2) and C(6) leave slightly more positive charge at N(7)H than electron-releasing groups (CH_3, NH_2, etc.). Substituents at C(2) appear slightly better able to reduce positive charge at N(7)H. A similar pattern is observed at N(9), with N(9) slightly negative and N(9)R slightly positive (INDO). (STO-3G results are again more negative for N(9)R.) Greater positive charge is apparent at N(9)R for the electron-withdrawing groups with the location of the substitution (C(2) or C(6)) having little effect. Elsewhere in the purine system, the pyrimidine ring and substituent(s) in general remain slightly positive for electron-withdrawing and -releasing groups alike with the exception of 2- and 6-nitropurine derivatives. However, the presence of electron-releasing groups tends to accompany greater positive charge accretion in the pyrimidine ring.

The unusual charge distributions for ylide species III cannot be fully understood by mere examination of net atomic charges. Separation of the total charge into σ and π components, on the other hand, does reveal an interesting pattern. The expected charge separation (positive at N(7)H and N(9)R and negative at C(8)) are clearly visible in the σ charges in both the INDO and STO-3G results (Table VIII). These σ charges induce an alteration in the π-electron distribution to counterbalance these charges. The π charges at C(8) beocme uniformly positive and those at N(7) are uniformly negative. This reverse polarization effect, thus, stabilizes the ylide species III not only by reducing the total charges at N(7)H and C(8) but also by redistributing charge throughout the aromatic system. A similar phenomenon has been reported for vinyl and ethynyl carbanions[45] and might reasonably be expected for phenyl carbanions. However, in these purine carbanions, greater stability can be achieved due to the presence of polarizable heteroatoms and the additional positive charge.

Density difference maps are also useful in assessing electron reorganization in deprotonated species III. The differences in integrated electron density between protonated and deprotonated species, $\delta P(x,z)$, where

$$\delta P(x,z) = P(x,z)_{III} - P(x,z)_{II} \quad (8)$$

were plotted for several substituted purines and are displayed in Figure 9. The singular, massive depression in the C(8)H bond region is the most salient feature. Electron density, depleted from this region upon proton abstraction, is transferred into other areas of the molecule, principally into the back-lobe of C(8). The development of a carbanion lone pair at C(8) sets off a series of waves of electron polarization throughout the heterocycle. Notable, in this regard, are peaks near N(7) and the depressions in the N(7)H and N(9)R bond regions. Relatively smaller electron

Table VIII. σ and π Charges in Representative Deprotonated Purine Species[a]

atom	Y ≡ H, X ≡ H	Y ≡ H, X ≡ NH_2	Y ≡ H, X ≡ CH_3	Y ≡ H, X ≡ NO_2	Y ≡ H, X ≡ =O	X ≡ H, Y ≡ NH_2	X ≡ H, Y ≡ CH_3	X ≡ H, Y ≡ NO_2	X ≡ H, Y ≡ =O
					A. INDO				
C(8)									
σ	−0.5236	−0.5267	−0.5248	−0.5164	−0.5077	−0.5228	−0.5235	−0.5161	−0.5107
π	+0.3462	+0.3413	+0.3455	+0.3554	+0.3261	+0.3341	+0.3441	+0.3566	+0.3129
N(7)H[b]									
σ	+0.1498	+0.1485	+0.1485	+0.1570	+0.1552	+0.1472	+0.1480	+0.1707	+0.1643
π	−0.0660	−0.0679	−0.0661	−0.0610	−0.0492	−0.0658	−0.0656	−0.0572	−0.0354
N(9)H[b]									
σ	+0.1274	+0.1223	+0.1256	+0.1392	+0.1318	+0.1214	+0.1252	+0.1375	+0.1196
π	−0.0774	−0.0799	−0.0778	−0.0736	−0.0696	−0.0737	−0.0763	−0.0760	−0.0567
N(1)									
σ	−0.1204	−0.0988	−0.1201	−0.1049	−0.0950	−0.0807	−0.1176	−0.1156	−0.5249
π	−0.1333	−0.2281	−0.1490	−0.1123	−0.2289	−0.2686	−0.1548	−0.0979	+0.3440
C(2)									
σ	+0.1947	+0.2723	+0.1860	+0.2500	+0.3280	+0.1868	+0.1893	+0.1994	+0.1772
π	+0.0600	+0.1321	+0.0756	−0.0145	+0.1828	+0.0989	+0.0682	+0.0525	+0.0992
N(3)									
σ	−0.1263	−0.0874	−0.1225	−0.1199	−0.5282	−0.1004	−0.1230	−0.1346	−0.0687
π	−0.1312	−0.2657	−0.1544	−0.0962	+0.3365	−0.2052	−0.1421	−0.0931	−0.2140
C(4)									
σ	+0.1948	+0.1870	+0.1892	+0.1989	+0.1921	+0.1946	+0.1927	+0.1960	+0.1966
π	+0.0306	+0.0633	+0.0379	+0.0265	+0.0379	+0.0504	+0.0341	+0.0279	+0.0314
C(5)									
σ	+0.0827	+0.0971	+0.0850	+0.0739	+0.1363	+0.0937	+0.0833	+0.0850	+0.0816
π	−0.0815	−0.1367	−0.0894	−0.0518	−0.1877	−0.1678	−0.0966	−0.0536	−0.1857
C(6)									
σ	+0.0827	+0.0758	+0.0769	+0.0842	+0.0446	+0.1642	+0.0788	+0.1468	+0.2414
π	+0.0527	+0.0869	+0.0604	+0.0540	+0.1442	+0.1303	+0.0703	−0.0294	+0.1732
					B. STO-3G				
C(8)									
σ	−0.4175	−0.4189	−0.4184	−0.4138	−0.4015	−0.4154	−0.4177	−0.4147	−0.4029
π	+0.5159	+0.5103	+0.5146	+0.5241	+0.4928	+0.5071	+0.5137	+0.5239	+0.4875
N(7)H[b]									
σ	+0.0502	+0.0456	+0.0487	+0.0581	+0.0468	+0.0414	+0.0470	+0.0705	+0.0474
π	−0.1568	−0.1608	−0.1580	−0.1520	−0.1487	−0.1615	−0.1572	−0.1441	−0.1366
N(9)H[b]									
σ	+0.0570	+0.0530	+0.0553	+0.0675	+0.0525	+0.0524	+0.0550	+0.0654	+0.0437
π	−0.1752	−0.1597	−0.1580	−0.1537	−0.1565	−0.1554	−0.1571	−0.1549	−0.1421
N(1)									
σ	−0.2027	−0.1513	−0.1965	−0.1870	−0.3880	−0.1308	−0.1939	−0.1991	−0.6606
π	−0.0495	−0.1412	−0.0668	−0.0374	−0.1298	−0.1797	−0.0733	−0.0208	+0.3060
C(2)									
σ	+0.1328	+0.2771	+0.1768	+0.3499	+0.3375	+0.1129	+0.1269	+0.1449	+0.1258
π	−0.0108	+0.0499	+0.0213	−0.0795	+0.0347	+0.0213	−0.0049	−0.0146	+0.0559
N(3)									
σ	−0.1782	−0.1113	−0.1689	−0.1690	−0.6512	−0.1449	−0.1728	−0.1860	−0.1124
π	−0.0725	−0.1958	−0.0964	−0.0494	+0.2893	−0.1395	−0.0852	−0.0427	−0.1693
C(4)									
σ	+0.2152	+0.1953	+0.2092	+0.2254	+0.2262	+0.2023	+0.2120	+0.2202	+0.2099
π	−0.0311	+0.0003	−0.0244	−0.0323	+0.0061	−0.0098	−0.0279	−0.0297	−0.0262
C(5)									
σ	+0.1171	+0.1507	+0.1231	+0.1062	+0.2084	+0.1672	+0.1219	+0.1193	+0.1619
π	−0.0411	−0.1010	−0.0530	−0.0158	−0.1784	−0.1231	−0.0565	−0.0200	−0.1255
C(6)									
σ	+0.0353	+0.0167	+0.0295	+0.0416	−0.0223	+0.1746	+0.0800	+0.2574	+0.2384
π	+0.0031	+0.0334	+0.0088	+0.0093	+0.0872	+0.0701	+0.0365	−0.0776	+0.0584

[a] Standard geometries used throughout; R ≡ H. [b] Charges are for N + H.

polarization is visible outside the vicinity of the major perturbation. The substituents at C(2) and C(6) receive increased electron density in III principally through the π system (vide infra).

Separation of $\delta P(x,z)$ into σ and π components is again instructive. The major perturbation in the C(8)H bond occurs in the σ-electron system of the molecule. The increase in σ-electron density in the back-lobes of C(8), N(7), and N(9) results in displacement of π electrons away from C(8), as evidenced by the deep "wells" in Figure 10. This pattern is reenacted in other parts of the molecule, as well. Buildup of σ-electron density at N(1), N(3), C(4), C(5), and C(6) in guanine and xanthine, at N(3), C(4), and C(5) in adenine and hypoxanthine, and at C(4) and C(5) in unsubstituted purine displaces π-electron density away from these centers. Similarly, regions of low σ-electron density at C(2), N(7), and N(9) in guanine and xanthine, at N(1), C(2), N(7), and N(9) in adenine and hypoxanthine, and at N(1), C(2), N(3), C(6), N(7), and N(9) in unsubstituted purine are offset by greater π density in proximity to these atoms. Electron density is redistributed to substituents at C(2) and C(6) largely through the π system. Polarization of the mobile π system to counterbalance perturbations in the σ system is seen as an important mechanism for electronic stabilization in these species.

Conclusions

In an overall assessment of both ab initio and semiempirical SCF results, substituents on the purimidine ring of purine nucleotide models have a significant effect upon N(7) basicity of neutral purine I and upon C(8)H acidity of N(7)-protonated purines II. Calculated proton affinities show that electron-releasing substituents enhance N(7) basicity but decrease C(8)H

acidity in protonated purines. In contrast, electron-withdrawing groups are predicted to decrease N(7) basicity but promote C(8)H acidity of the protonated species II. N(7) protonation leaves substantial positive charge in the C(8)H regions. The magnitude of the charge in this region also appears to be directly related to the influence of groups at C(2) and C(6) in the purine system. Guanine, adenine, hypoxanthine, dimethyladenine, and dimethylguanine derivatives exhibit the strongest basicity (at N(7)) along with methyl- and methoxypurines. Xanthine and fluoro-, trifluoromethyl-, or nitropurine derivatives are computed to be among the weakest bases of the group. Ionization at C(8)H was predicted to be most facile for xanthine and fluoro-, trifluoromethyl-, and nitropurines and least facile for adenine, guanine, dimethylguanine, dimethyladenine, and hypoxanthine derivatives. The calculated results are in reasonably good agreement with experimental pK_a's and isotope-exchange rate constants. Further refinement must await computations with inclusion of solvent and conformational effects from the ribofuranosyl ring and phosphate, an on-going project in our group. Finally, the proposed "ylide" intermediate III in the exchange reaction appears to retain zwitterionic character only in the σ-electron system. Considerable stabilization is achieved by polarization of the π-electron system.

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Registry No. I (R, Y = H, X = H), 120-73-0; I (R = Y = H, X = CH_3), 934-23-6; I (R, Y = H, = NH_2), 452-06-2; I (R, Y = H, X = OCH_3), 37432-20-5; I (R, Y = H, X = OH), 95121-01-0; I (R, Y = H, X = $COOCH_3$), 95121-02-1; I (R, Y = H, X = OCF_3), 95121-03-2; I (R, Y = H, X = F), 1598-61-4; I (R, Y = H, X = CF_3), 95121-04-3; I (R, Y = H, X = CN), 95121-05-4; I (R, Y = H, X = NO_2), 95155-85-4; I (R, Y = H, X = =O), 2308-57-8; I (R, Y = H, X = $N(CH_3)_2$), 37432-21-6; I (R, X = H, Y = CH_3), 2004-03-7; I (R, X = H, Y = NH_2), 73-24-5; I (R, X = H, Y = OMe), 1074-89-1; I (R, X = H, Y = OH), 95121-06-5; I (R, X = H, Y = COOMe), 62134-45-6; I (R, X = H, Y = OCF_3), 95121-07-6; I (R, X = H, Y = F), 1480-89-3; I (R, X = H, Y = CF_3), 2268-11-3; I (R, X = H, Y = CN), 2036-13-7; I (R, X = H, Y = NO_2), 95121-08-7; I (R, X = H, Y = =O), 68-94-0; I (R, X = H, Y = $N(CH_3)_2$), 938-55-6; I (R = CH_2OH, X, Y = H), 95121-09-8; I (R = CH_2OH, Y = H, X = CH_3), 95121-10-1; I (R = CH_2OH, Y = H, X = NH_2), 95121-11-2; I (R = CH_2OH, Y = H, X = OCH_3), 95121-12-3; I (R = CH_2OH, Y = H, X = OH), 95121-13-4; I (R = CH_2OH, Y = H, X = $COOCH_3$), 95121-14-5; I (R = CH_2OH, Y = H, X = OCF_3), 95121-15-6; I (R = CH_2OH, Y = H, X = F), 95121-16-7; I (R = CH_2OH, Y = H, X = CF_3), 95121-17-8; I (R = CH_2OH, Y = H, X = CN), 95121-18-9; I (R = CH_2OH, Y = H, X = NO_2), 95121-19-0; I (R = CH_2OH, Y = H, X = =O), 95121-20-3; I (R = CH_2OH, Y = H, X = $N(CH_3)_2$), 95121-21-4; I (R = CH_2OH, X = H, Y = CH_3), 95121-22-5; I (R = CH_2OH, X = H, Y = NH_2), 95121-23-6; I (R = CH_2OH, X = H, Y = OCH_3), 95121-24-7; I (R = CH_2OH, X = H, Y = OH), 95121-25-8; I (R = CH_2OH, X = H, Y = $COOCH_3$), 95121-26-9; I (R = CH_2OH, X = H, Y = OCF_3), 95155-86-5; I (R = CH_2OH, X = H, Y = F), 95121-27-0; I (R = CH_2OH, X = H, Y = CF_3), 95121-28-1; I (R = CH_2OH, X = H, Y = CN), 95121-29-2; I (R = CH_2OH, X = H, Y = NO_2), 95121-30-5; I (R = CH_2OH, X = H, Y = =O), 95121-31-6; I (R = CH_2OH, X = H, Y = $N(CH_3)_2$), 95121-32-7; II (R, Y = H, X = H), 18348-60-2; II (R, Y = H, X = CH_3), 95121-33-8; II (R, Y = H, X = NH_2), 58682-12-5; II (R, Y = H, X = OCH_3), 95121-34-9; II (R, Y = H, X = OH), 95121-35-0; II (R, Y = H, X = $COOCH_3$), 95121-36-1; II (R, Y = H, X = OCF_3), 95121-37-2; II (R, Y = H, X = F), 95121-38-3; II (R, Y = H, X = CF_3), 95121-39-4; II (R, Y = H, X = CN), 95121-40-7; II (R, Y = H, X = NO_2), 95121-41-8; II (R, Y = H, X = =O), 95121-42-9; II (R, Y = H, X = $N(CH_3)_2$), 95121-43-0; II (R, X = H, Y = CH_3), 50291-79-7; II (R, X = H, Y = NH_2), 18444-01-4; II (R, X = H, Y = OCH_3), 95121-44-1; II (R, X = H, Y = OH), 95121-45-2; II (R, X = H, Y = $COOCH_3$), 95121-46-3; II (R, X = H, Y = OCF_3), 95121-47-4; II (R, X = H, Y = F), 95121-48-5; II (R, X = H, Y = CF_3), 95121-49-6; II (R, X = H, Y = CN), 95121-50-9; II (R, X = H, Y = NO_2), 95121-51-0; II (R, X = H, Y = =O), 42007-36-3; II (R, X = H, Y = $N(CH_3)_2$), 80285-14-9; II (R = CH_2OH, Y = H, X = H), 95121-52-1; II (R = CH_2OH, Y = H, X = CH_3), 95121-53-2; II (R = CH_2OH, Y = H, X = NH_2), 95121-54-3; II (R = CH_2OH, Y = H, X = OCH_3), 95121-55-4; II (R = CH_2OH, Y = H, X = OH), 95121-56-5; II (R = CH_2OH, Y = H, X = $COOCH_3$), 95155-87-6; II (R = CH_2OH, Y = H, X = OCF_3), 95121-57-6; II (R = CH_2OH, Y = H, X = F), 95121-58-7; II (R = CH_2OH, Y = H, X = CF_3), 95121-59-8; II (R = CH_2OH, Y = H, X = CN), 95121-60-1; II (R = CH_2OH, Y = H, X = NO_2), 95121-61-2; II (R = CH_2OH, Y = H, X = =O), 95121-62-3; II (R = CH_2OH, Y = H, X = $N(CH_3)_2$), 95121-63-4; II (R = CH_2OH, X = H, Y = CH_3), 95121-64-5; II (R = CH_2OH, X = H, Y = NH_2), 95121-65-6; II (R = CH_2OH, X = H, Y = OCH_3), 95121-66-7; II (R = CH_2OH, X = H, Y = OH), 95121-67-8; II (R = CH_2OH, X = H, Y = $COOCH_3$), 95121-68-9; II (R = CH_2OH, X = H, Y = OCF_3), 95121-69-0; II (R = CH_2OH, X = H, Y = F), 95121-70-3; II (R = CH_2OH, X = H, Y = CF_3), 95121-71-4; II (R = CH_2OH, X = H, Y = CN), 95121-72-5; II (R = CH_2OH, X = H, Y = NO_2), 95121-73-6; II (R = CH_2OH, X = H, Y = =O), 95121-74-7; II (R = CH_2OH, X = H, Y = $N(CH_3)_2$), 95121-75-8.

Communications to the Editor

Structure of Dilithium Tetraphenylallenide

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The way in which a molecular framework distorts to accommodate negative charge provides a valuable reference point for comparison of experiment and theory.[1] Allene, for instance, which has two degenerate orthogonal π^* orbitals, can accommodate two extra electrons in three limiting structures of C_{2v}, D_{2h},[2a] and D_{2d} symmetry. The C_{2v} structure is distinguished from its "linear" counterparts by sp^2 rather than sp hybridization of the central carbon. Recent ab initio calculations of a model "dianion", 2,3-dilithiopropene, predict quasi-C_{2v} symmetry for the hydrocarbon framework and, further, give two energy minima for disposition of the lithium atoms, with a slight preference for a structure of C_s symmetry.[2b] We now present definitive evidence that, for a tetraphenyl derivative of allene dianion, the actual structure is of C_2 symmetry, and we suggest that a structure involving lithium atoms bridging the C(1)–C(2) and C(2)–C(3) bonds coincides with the nuclear magnetic resonance data.

2,3-Dimetallo-1,1,3,3-tetraphenylpropene has been postulated as an intermediate in the reduction of tetraphenylallene with alkali metals in diethyl ether, although the experimental evidence is

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(1) (a) Davidson, E. R.; Borden, W. T. *J. Phys. Chem.* **1983**, *87*, 4783. (b) E.g., for carbon dioxide, see: Kumar, S. V. K.; Venkatasubramanian, V. S. *J. Chem. Phys.* **1983**, *79*, 6423. (c) Games, M. A. F.; Canuto, S. *J. Phys. B* **1984**, *17*, 1711 and references therein. (d) For a general review of polylithium chemistry, see: Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151 and references therein.

(2) (a) The cation-free dianion $C_3H_4^{2-}$ was found to be a planar, linear D_{2h}, species by MNDO calculations: Schleyer, P. v. R.; Kos, A. J. *J. Chem. Soc., Chem Commun.* **1982**, 448. (b) Kost, D.; Klein, J.; Streitwieser, A., Jr.; Schriver, G. W. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3922.

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