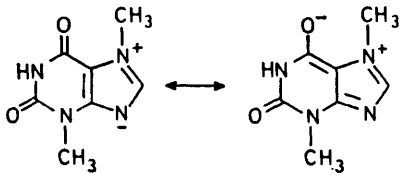
Chemical Reactivity and Electronic Structure of *N*-Methyl Derivatives of Xanthine

By **Aleksander P. Mazurek,*** School of Medicine, Physico-chemical Laboratory, 1 Banacha Street, 02–097 Warsaw, Poland

Calculations of electron density and other indices of reactivity have been performed for *N*-methyl-substituted xanthines using the Hückel, Del Re, and CNDO/2 methods. The considerable difference in chemical reactivity of theophylline, theobromine, and caffeine is probably due either to steric repulsion of the van der Waals type or to the electrostatic effects of a positively charged methyl group in position 7.

THE problem of correlating the molecular electronic structure of various purine derivatives and their chemical reactivity has already been studied by several workers. Veillard and Pullman,[1] Pullman,[2] and Nagata *et al.*[3] have concluded that in purine the C-8 atom is most susceptible to electrophilic substitution. This is due to the high electron density localized on this atom. Quantum



(A) (B)

chemical calculations leading to this conclusion have also been supported by n.m.r. measurements.

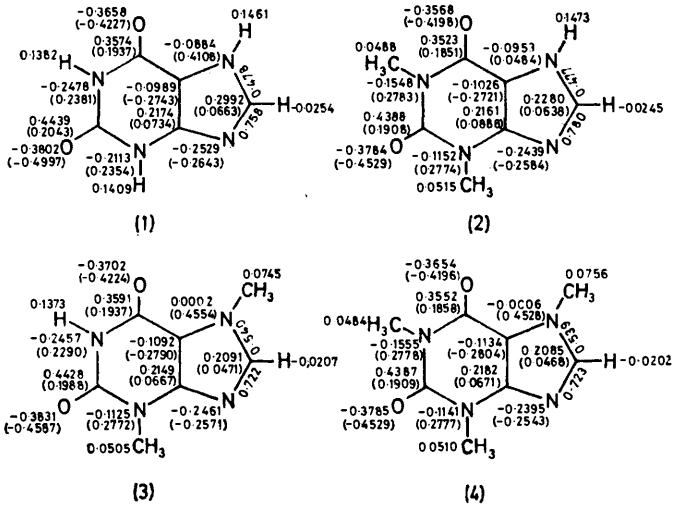
One example of electrophilic substitution is the coupling reaction with diazonium salts. In a review Robins concluded [4] that if N-7 or -9 bears a methyl group, coupling at C-8 in purines does not proceed. However, the presence of bulky methyl groups influences these reactions, by means of their positive inductive effect. The effect will be inconsiderable only for the resonance structures (A) and (B), which are not highly probable. Thus, the statement by Robins on the influence of methyl groups (localized at N-7 and -9) upon coupling at C-8 is not a general rule. Moreover, Robins has overlooked the results of Mazza and Migliardi [5] who were successful in obtaining 8-(*p*-sulphamylphenylazo)theobromine.

RESULTS AND DISCUSSION

In the present paper we have used the common Hückel and Del Re methods [6,7] for xanthine (7- and 9-H forms), theophylline (7- and 9-H forms), theobromine, and caffeine, their 8-halogen derivatives, and also for isocaffeine. For xanthine, theophylline, theobromine, caffeine, and their 8-halogen derivatives the more advanced CNDO/2 method [8,9] was also applied (Figure 1). Calculations were carried out according to the QCPE program. The parameters for the Hückel and Del Re methods are in Table 1. The geometry used was that of ref. 10.

* *Present address*: Drug Institute, Physico-chemical Laboratory, 30/34 Chełmska Street, 00-725 Warsaw, Poland.

From the study of the effect of charge density due to methyl and halogen substituents, the following conclusions may be drawn. (1) For the four parent compounds examined, *i.e.* xanthine, theophylline, theobromine, and caffeine the total charge on the carbon atoms is as follows: C-2 < C-6 < C-8. (2) Substitution of a nitrogen atom in the imidazole ring by a methyl group causes a characteristic inductive effect. The electron density on the nitrogen atom adjacent to the methyl group is apparently lowered, but increases slightly on the adjacent carbon atoms. This is almost entirely due to a π-electron effect. The distribution of the σ-electron density is little disturbed. It is worth mentioning that when the methyl group is present in position 7 (theobromine and caffeine) the increase in electron density is accompanied by a bond order increase of the N-7–C-8 bond. This is to say that additional electron density is displaced significantly toward this bond and the C-8 atom is probably slightly active in electrophilic substitution reactions. (3) A halogen atom



(1) (2)

(3) (4)

FIGURE 1 The distribution of total effective charges, π-electron charges (in parentheses), and π-electron bond orders (CNDO/2 method) for 7*H*-xanthine (1), 7*H*-theophylline (2), theobromine (3), and caffeine (4)

at C-8 causes displacement of the electron charge from C-8 towards the halogen atom; in this way the positive charge on the carbon atom is increased. These changes in density either do not affect the surrounding atoms (CNDO/2) or do, but very slightly (Del Re). As ex-

TABLE 1
Parameters used

(*a*) Hückel method $\alpha_x = \alpha + h_x\beta$ $\beta_{xy} = k_{xy}\beta$

Bond	C–C	C=N–	C–N=	C=O	C–F	C–Cl	C–Br	C–I	H–N(C)(C)	C–N(C)(H)	=N–CH$_3$
	$h_C = 0.0$	$h_N = 0.4$	$h_N = 1.0$	$h_O = 0.7$	$h_F = 2.3$ $h_C = 0.1$	$h_{Cl} = 2.2$ $h_C = 0.2$	$h_{Br} = 2.1$ $h_C = 0.2$	$h_I = 2.0$ $h_C = 0.1$	$h_N = 1.6$	$h_N = 1.8$	$h_N = 1.1$ $h_C = -0.2$ $h_{H_3} = -0.4$
	$k_{CC} = 1.0$	$k_{CN} = 0.1$	$k_{CN} = 0.9$	$k_{CO} = 2.0$	$k_{CF} = 0.7$	$k_{CCl} = 0.7$	$k_{CBr} = 0.7$	$k_{CI} = 0.6$	$k_{CN} = 0.8$	$k_{CN} = 0.8$	$k_{NC} = 0.8$ $k_{C=H_3} = 2.0$

(*b*) Del Re method

Bond C–X

X=	C	N	O
δ°_x	0.07	0.24	0.40
ε_{cx}	1.00	1.00	0.95
$\gamma_{cx} = \gamma_{xc} =$	0.10		

C–X

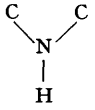
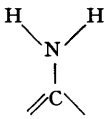
X=	Cl	Br	I
δ°_x	0.35	0.29	0.26
ε_{CX}	0.60	0.45	0.45
γ_{CX}	0.20	0.20	0.20
γ_{XC}	0.40	0.40	0.40

X=	C
ε_{HX}	1.00
$\delta_H = 0.00$	

H–X

	N	O
$\gamma_{HX} =$	0.40	0.45
$\gamma_{XH} =$		0.30

Other types of bonds

X	Type	δ°_x	X–B	ε_{XB}
C		0.12	C–H	1.00
N		0.38	C=N	0.70
N		0.30	C–N N–H	0.70 0.60
N		0.24	C–N N–H	1.00 0.45
O	O=	0.28	C=O	0.70

pected, the electron density on the halogen atom diminishes with decreasing electronegativity. Based on the present calculations and for corresponding coupling experiments of various diazonium salts with caffeine, it might be thought that the coupling method of Bystricka,[11] which has been applied to similar systems to those examined by us, cannot be used for purines. This does not mean, however, that for the other groups of compounds, the reaction of diazonium salts with suitable bromo derivatives does not increase the yield.

The conclusions obtained from the present calculations and based on the Hückel, Del Re, and CNDO/2 methods are consistent qualitatively. It proves the correctness of the results (Figure 2).

The calculated electron densities are also well correlated with the chemical shifts of the ^{1}H n.m.r. signals for the methyl groups of theophylline, theobromine, caffeine, isocaffeine, and 3,9-dimethylxanthine [12] (Table 2). Similar results have been obtained upon applying the CNDO/2 method.

Reactivity of the Purine System.—One of the most frequently applied reactivity indices is the localization energy index for Wheland complexes.[13] This energy has been calculated for electrophilic substitution at C-8 in theophylline and theobromine: E_{loc} (theophylline) 2.083 β; E_{loc} (theobromine) 2.086 β. These values are practically identical. It suggests that there is no difference in reactivity in the compounds examined. Other

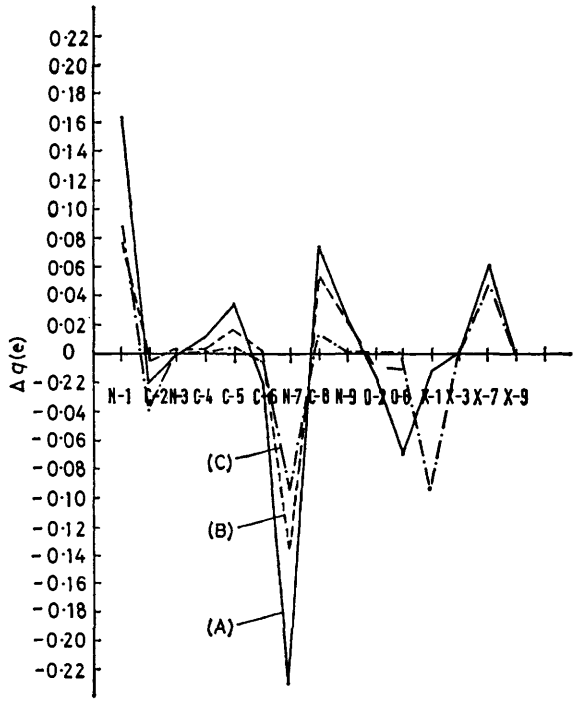


FIGURE 2 Changes in electron density on particular atoms: (A) total Hückel and Del Re; (B) π Hückel; (C) total CNDO/2. Δq = electron density on the ith atom of theophylline — electron density on the ith atom of theobromine, q_i-(theophylline) — q_i-(theobromine)

reactivity indices are (a) the charge on the atom which is subjected to attack, (b) the electron density on this atom derived from the highest occupied orbital (HOMO), *i.e.* the index of frontier electrons, (c) the HOMO energy. It has been established that, for instance, a comparison of the effective charges in the purine ring leads to wrong conclusions regarding the position of electrophilic attack.[14] To obtain a proper view of the problem it is necessary to invoke more detailed reactivity theory.

TABLE 2

^{1}H N.m.r. chemical shifts (δ) of xanthines

Xanthine	1-CH_3	3-CH_3	7-CH_3	9-CH_3
1,3-Dimethyl	3.30	3.48		
3,7-Dimethyl		3.49	3.95	
1,3,7-Trimethyl	3.32	3.50	3.95	
1,3.9-Trimethyl	3.35	3.76		3.99
3,9-Dimethyl		3.65		3.96
Electron charge density (Hückel and Del Re methods)				
	1-CH_3	3-CH_3	7-CH_3	9-CH_3
1,3-Dimethyl	0.0898	0.0915		
3,7-Dimethyl		0.0910	0.1119	
1,3,7-Trimethyl	0.0898	0.0909	0.1118	
1,3,9-Trimethyl	0.0898	0.0922		0.1110
3,9-Dimethyl		0.0900		0.1110

The change of energy during a reaction (proportional to ΔH, *i.e.* the heat of formation of an acid–base complex) for a second-order perturbation calculation is given by equation (1) [15] where r and s are the reacting atoms,

$$\Delta E = \sum_{n}^{\text{unocc}} \sum_{m}^{\text{occ}} \frac{2(Cr^m)^2(Cs^n)^2\beta^2}{E_m^* - E_n^*} \quad (1)$$

E_m^* is the energy of the occupied electron level of the donor nucleophilic, E_n^* is the energy of the occupied electron level of the acceptor electrophile, and β is the resonance parameter value.

One can distinguish two extreme cases. (1) When $|E_m^* - E_n^*| \gg 4\beta^2$, one can take the average difference of energy $|E_m^* - E_n^*|_{av}$, and hence equation (2) is

$$\Delta E = 2 \sum_{m}^{\text{occ}} (Cr^m)^2 \sum_{n}^{\text{unocc}} (Cs^n)^2\gamma \quad (2)$$

$$\gamma = \frac{\beta^2}{(E_m^* - E_n^*)_{av}} \quad (3)$$

obtained where relationship (3) applies. In this case the reaction is controlled by the charge on the atom examined $[2\sum^{\text{occ}}(Cr^{m*})^2]$. (2) When $|E_m^* - E_n^*| \approx 0$, one has a case which is almost degenerate, giving the approximation (4).

$$\Delta E \approx (Cr^m)^2(Cs^n)^2\beta rs \quad (4)$$

In this case the reaction is controlled by the density of frontier electrons $[(Cr^m)^2]$.

Any intermediate situation, which may be regarded as a combination of (1) and (2), is described by equation (5) which corresponds to an empirical correlation.[16]

$$\Delta E = 2\sum_{m}^{\text{occ}} (Cr^m)^2 \sum_{n}^{\text{unocc}} (Cs^n)^2\gamma + (Cr^m)^2(Cs^n)^2\beta rs \quad (5)$$

Assuming that the attacking electrophilic agent is always the same, ΔE should depend only on the electron density at C-8 (Table 3).

Analysis of the results from our theoretical calculations shows that neither of the indices in Table 3 allows the reactivity of theobromine to be distinguished from that of caffeine. It follows that dissimilarities in reactivity, particularly for the reaction considered here, are not due to changes in the electronic structure of these molecules, but rather to the influence of steric effects. The latter effects might be of two types. (a) The presence of a bulky 7-methyl group in theobromine makes the approach of the electrophile difficult. This is due to a steric repulsion of the van der Waals type. (b) Positively charged protons in the methyl group create a potential which forbids positively charged species to approach C-8, owing to simple electrostatic repulsion. An additional argument in support of such an interpretation is that the rate of electrophilic attack by halogen is comparable for both theophylline and theobromine. If nitronium ion is the attacking agent, the differences in reactivities are more considerable.[17] In this case the electrostatic potential diagrams, calculated for the molecules under discussion by *ab initio* and semi-empirical methods should provide quite an accurate reactivity index. For the purposes of the quantum chemical calculations, it was assumed that the coupling reaction

TABLE 3

Densities of frontier electrons at C-8 and energies of the highest occupied molecular orbital (HOMO) in β units

Xanthine	Frontier electrons CNDO/2 method	HOMO (β units) CNDO/2 method
Xanthine	0.0957	+0.4044
1,3-Dimethyl	0.0684	+0.3933
3,7-Dimethyl	0.0701	+0.3889
1,3,7-Trimethyl	0.0686	+0.3902

was carried out in the presence of pyridine. The latter may be a useful catalyst, particularly for those structures in which the centre of coupling is subjected to overcrowding by the surrounding substituents.[18,19] Applying the above method we succeeded in preparing 8-(*p*-nitrophenylazo)caffeine. The reaction was carried out in pure pyridine, which also constituted a good solvent for the sparingly soluble caffeine. It is evident that the coupling reaction of diazonium salts occurs with the base itself which is unable to provide an anion. 8-(*p*-Nitrophenylazo)caffeine was synthesized in 8% yield after coupling for 24 h. Under similar conditions, 8-(*p*-nitrophenylazo)theophylline was synthesized in 36% yield after 24 h. The structure and composition of the new compounds was confirmed by elemental analyses and i.r. and ^{1}H n.m.r. spectra.[20,21]

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