

Some Remarks on Position-Conditioned Differences of the Ultraviolet Spectra and Chemical Reactivities of Disubstituted Pyrimidines and Purines

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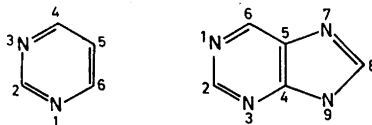
A survey is given of position-conditioned differences of the ultraviolet spectra and chemical reactivities of disubstituted pyrimidines and purines. Special attention is paid to the spectral shifts observed when oxygen is replaced by sulfur or selenium in compounds of the above-mentioned type. Uracil, 2-thiouracil, 4-thiouracil and 2,4-dithiouracil are examined by the Hückel MO-LCAO method, which is found to give account of the spectral peculiarities in a semi-quantitative manner.

It has been known for some time that the wavelengths of maximum absorption of thiocarbonyl compounds are greater than those of isologous carbonyl compounds¹. A further bathochromic shift is seen when sulfur is replaced by selenium. Since wavelength is inversely proportional to the energy difference between the ground state and the excited state, it has been proposed that in sulfur and presumably to a greater extent in selenium analogs of carbonyl compounds either labilization of the ground state (attributable to the increased difficulty of forming π -bonds) or stabilization of the excited state, possibly because octet expansion occurs^{2,3}.

Studies of isologous non-cyclic⁴ and cyclic⁵⁻⁷, oxo-, thio-, and seleno-carbamyl compounds and of isologous acyl, thioacyl, and selenoacyl compounds⁸ showed the aforementioned bathochromic shift on descending the periodic table in the spectra of all the series of compounds investigated. This effect has been attributed to the increased importance of polarized forms, as oxygen is successively replaced by sulfur and by selenium. This view is sup-

ported by measurements of ultraviolet spectra,^{4,5} of acid dissociation constants,^{5,6,9} and of dipole moments^{4,10}.

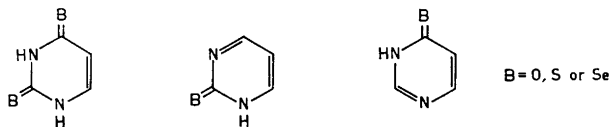
In studying the effects of replacing oxygen by sulfur or by selenium in 2,4-disubstituted pyrimidines and 2,6-disubstituted purines it was noted that such substitution caused much greater bathochromic shifts in the ultraviolet



spectra when permitted to take place in the 4-position of pyrimidines or the corresponding 6-position of purines than when taking place in the 2-positions of these compounds. This effect can be observed by noting the colors of isologous 2,4- (2,6-) disubstituted oxo-, thio-, and seleno-pyrimidines and purines. 2-Thio and 2-seleno compounds are colorless as are the parent compounds. On the other hand, introduction of sulfur into the 4-position of pyrimidines or the 6-position of purines yields compounds that are yellow, while the corresponding selenium compounds are orange. Some pertinent data are summarized in Table 1.

It is interesting that a study of 2- and 4-monosubstituted pyrimidines and of 2- and 6-monosubstituted purines does not show equivalent positional effects. Unfortunately, except for 6-selenopurine,⁵ none of the pertinent monosubstituted seleno compounds have been made. Ultraviolet data for some monosubstituted pyrimidines and purines are given in Table 2.

It appears that a bathochromic effect is observed only when sulfur (or selenium) is present in the —NH—CS—C= or —NH—CS—N= groups (conjugated "amidic" sulfur), but not in the —NH—CS—NH— group ("ureidic" sulfur). In 2,4-disubstituted pyrimidines or 2,6-disubstituted purines sulfur and selenium are "ureidic" in the 2-position, but "amidic" in the 4- or 6-position respectively. In monosubstituted pyrimidines they are "amidic" in either position.



It has been noted that the chemical reactivity of oxygen, sulfur and selenium differs when these elements are introduced into the 2- or the 4- (6-) position of disubstituted pyrimidines and purines.

For instance, the thiation of uracil with phosphorus pentasulphide yields 4-thiouracil and 2,4-dithiouracil, but no 2-thiouracil¹¹. In analogous fashion the thiation of xanthine (2,6-diketopurine) yields 6-thioxanthine and 2,6-dithioxanthine, but no 2-thioxanthine¹². Position-conditioned differences in reactivity are also found in the treatment of 2,4-dithiopyrimidine with ammo-

Table 1. Ultraviolet data for some disubstituted purines and pyrimidines.

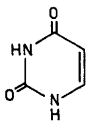
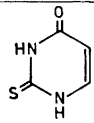
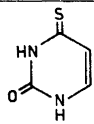
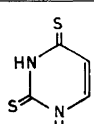
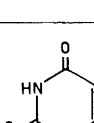
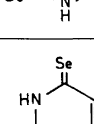
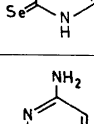
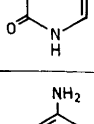
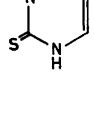

Compound	Species charge	λ_{\max}	ϵ_{\max}	Color	Reference
	+	203	8 300	Colorless	5,24,26
	0	258	7 800		
	0	203	8 300		
	0	258	7 980		
	+	216	8 750	Colorless	5,25
	0	284	6 150		
	+	273	13 800		
	0	271	13 700		
	+	233	11 000	Yellow	25,26
	0	259	10 200		
	0	310	6 950		
	+	242	3 500		
	0	326	19 200	Yellow	5,25
	0	249	2 400		
	0	330	15 500		
	+	334	17 900		
	+	280	22 300	Yellow	5,25
	0	345	10 000		
	0	284	21 600		
	0	361	8 770		
	0	321	6 000	Colorless	5
	0	360	8 900		
	0	315	12 600	Colorless	5
	0	314	16 070		
	0	400	10 040	Orange	5
	0	314	16 070		
	+	275	10 450	Colorless	16
	+	225	15 900		
	+	278	20 650	Colorless	26,16
	+	225	15 900		

Table 1. (Continued)

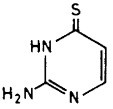
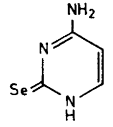
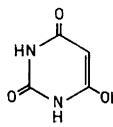
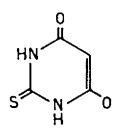
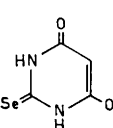
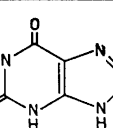
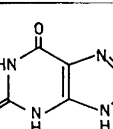
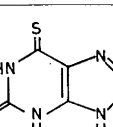
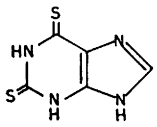
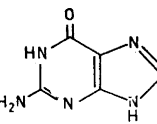
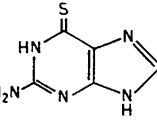
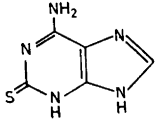
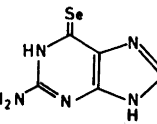
Compound	Species charge	λ_{\max}	ϵ_{\max}	Color	Reference
	+	256 325	4 800 14 700	Yellow	25
	+	308	17 600	Colorless	7
	0	257	19 800	Colorless	6
	0	240 265 280	7 460 14 760 12 600	Colorless	6
	0	263 298	10 050 12 800	Colorless	6
	-	240 277	8 900 9 300	Colorless	15
	-	278	16 600	Colorless	12
	-	340	21 380	Yellow	12

Table 1. (Continued)





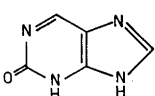
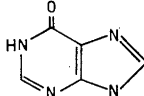
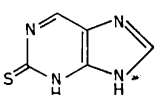
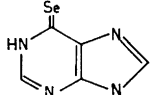
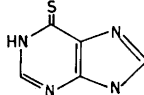
Compound	Species charge	λ_{\max}	ϵ_{\max}	Color	Reference
	—	252 285 346	20 900 14 130 13 490	Yellow	12
	+	248 271	10 720 7 080	Colorless	15
	+	258 347	8 100 20 900	Yellow	13
	+	230 285	9 640 12 600	Colorless	14
	+	263 372	5 620 16 500	Orange	7

nia which yields 2-thiocytosine (2-thio-4-aminopyrimidine¹⁶). Similarly, 2,4-diselenopyrimidine yields 2-selenocytosine⁷. In both cases substitution occurs in the 4-, but not in the 2-position.

A study of the oxidation with iodine of 2-thiouracil and of 4-thiouracil showed that here too positional differences in the reactivity of sulfur could be seen¹⁷. 4-Thiouracil is oxidized by iodine to the stable disulfide which undergoes further oxidation only with difficulty. However, 2-thiouracil reacts rapidly with several equivalents of iodine, while the 2,2'-disulfide is very unstable and could be isolated only as the disodium salt.

The observation that 2-thiouracil, but not 4-thiouracil has antithyroid activity has been attributed to the aforementioned difference in reactivity with iodine.

Table 2. Ultraviolet data for some monosubstituted purines and pyrimidines.

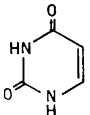
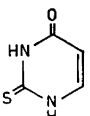
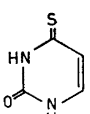
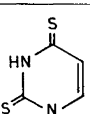
Compound	Species charge	λ_{\max}	ϵ_{\max}	Color	Reference
	0	215 299	10 000 4 570	Colorless	15
	0	228 357 infl.	9 330 5 500	Colorless	15
	0	278 346	21 380 2 630	Yellow	15
	0	285 327	10 720 18 130	Yellow	15
	0	238 315	2 880 4 900	Colorless	15
	0	249	10 480	Colorless	15
	0	241 285 348	12 590 17 800 1 510	Yellow	15
	0	225 325	7 410 18 600	Yellow	15
	0	361	14 550	Orange	4

It seems difficult to account for the position-conditioned differences discussed above within the framework of classical electronic theory of organic chemistry. Accordingly it appeared worth while to determine whether the Hückel linear combination of atomic orbitals molecular orbital (MO—LCAO) method could be utilized to describe these effects. Since the experimental material is extensive, it was decided to deal only with restricted aspects of the problem, namely the ultraviolet peculiarities of the 2,4-disubstituted pyrimidines.

Many theoretical investigations of purines and pyrimidines have been made; uracil and 2-thiouracil, *e.g.*, have been treated by Pullman and Pullman²⁰ using the Hückel method. Quite recently, Ladik and Appel²¹ have investigated the π -electron system of uracil with different semi-empirical methods, *viz.* simple Hückel, Hückel-CI, semi-empirical self consistent field SCF—LCAO—MO and SCF—LCAO—MO—CI.

The curious spectroscopic properties of mono-substituted purines, *e.g.* the fact that certain substituents in the 6-position cause a hypsochromic shift if compared to purine itself ($\lambda_{\max} = 263 \text{ m}\mu$), have been successfully treated with Hückel theory by Pullman²². As far as we know, however, nobody has pointed out the specific positional differences in disubstituted pyrimidines.

Table 3. Calculated excitation energies and wavelengths of maximum absorption.

Molecule	ΔE (calc.) β_0		ΔE (calc.) kcal mole ⁻¹		λ_{\max} (calc.)		λ_{\max} (observed)	
	ΔE_1	ΔE_2	ΔE_1	ΔE_2	λ_1	λ_2	λ_1	λ_2
	-1.557 *	-2.015	110.85 *	143.5	(258 *)	199	258*	203
	-1.317	-1.743	93.8	124.1	305	230	271	233 259 (in base only)
	-1.254	-1.756	89.3	125.0	320	229	330	249
	-1.228	-1.348	87.4	96.0	327	298	361	284

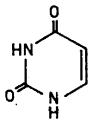
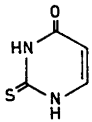
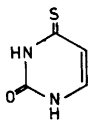
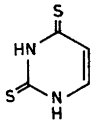
* The observed value for uracil ($258 \text{ m}\mu = 110.85 \text{ kcal mole}^{-1}$) has been used to determine β_0 from the relation $-1.557\beta_0 = 110.85$.

From the difference in charge and bond-order of the two C=O groups in uracil,^{20,21} one might expect a specific position effect upon replacement of oxygen by sulfur. Since the atom- and bond-parameters for C=S and C=O are rather different, however, it appeared unwise to rely on a simple perturbation treatment, accordingly we calculated the orbital energies for uracil, 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil by solving the secular equations occurring in the simple Hückel theory neglecting overlap*. The parameters recommended by Pullman and Pullman²³ were used.

The results of these calculations are given in Tables 3 and 4. Since the molecules under consideration contain ten π -electrons spaced over eight atomic nuclei, there are eight π -molecular orbitals (MO), five of which are doubly occupied in the ground state. The first excitation energy (ΔE_1) corresponds to an electron jump from the highest occupied MO of the ground state to the lowest unoccupied orbital. In all of these molecules the second excitation energy (ΔE_2) comes from an electron jump from the next highest occupied MO to the lowest unoccupied orbital.

The calculations give correct relative order of the first excitation energy (ΔE_1) within the series of molecules investigated (Table 3, column 1). It is a

Table 4. Total π -electron energy of the ground state and the first two excited states. [Energy unit = β_0].

Molecule	E_0	E_1	E_2
	-18.670	-17.113	-16.655
	-13.660	-12.323	-11.917
	-15.308	-14.454	-13.952
	-12.698	-11.470	-11.350

* We are indebted to Professor Per-Olov Löwdin for the loan of the Alwac-III computer at the Quantum Chemistry Group, University of Uppsala, and to Dr. Klaus Appel for carrying out the machine computations.

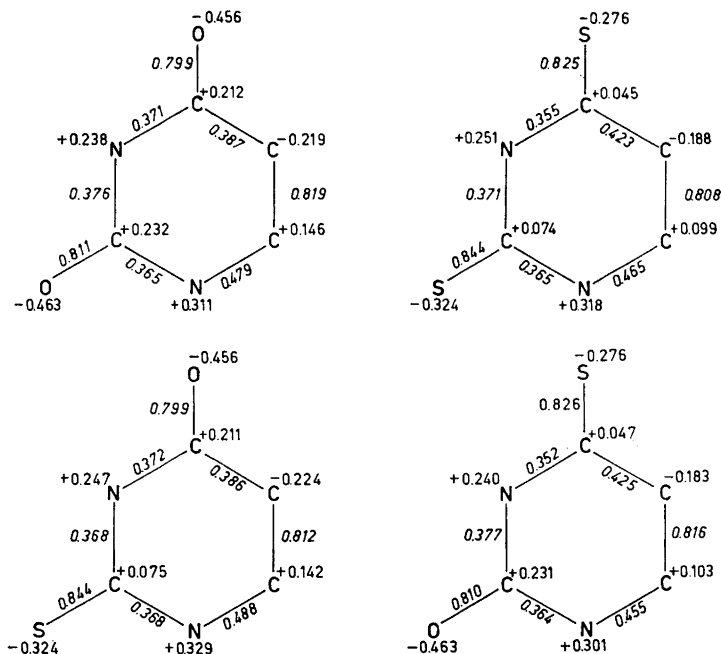


Fig. 1. Net-charges and bond-orders.

well-known fact however, that the simple Hückel-theory gives a very poor agreement between calculated and observed excitation energies measured on an absolute scale,²¹ and this is true here also. In order to transform in a proper way the values given in units of the resonance integral, β_0 , into kcal mole⁻¹ or wavelengths, we should determine β_0 from one of the observed excitation energies. Therefore, the observed first excitation energy for uracil ($258 \text{ m}\mu = 110.85 \text{ kcal mole}^{-1}$) was used to determine the resonance integral β_0 ($-1.557\beta_0 = 110.85$). The value of β_0 obtained in this manner was used in the calculation of the other excitation energies and wavelengths. It is evident from Table 3 that a significant difference exists between the first ultraviolet absorption peak of 2- and 4-thiouracil, although the calculated difference is not as large as that observed experimentally. The presence of two distinct peaks for 2,4-dithiouracil and 4-thiouracil is interesting, and the calculations correctly predict this phenomenon. The calculations also predict a peak at $199 \text{ m}\mu$ for uracil. Since the literature gives no information at this point, the spectrum of uracil has been checked with a Cary recording spectrometer, and a strong absorption band with maximum at $203 \text{ m}\mu$ was indeed detected.

In conclusion it may be stated that the simple Hückel theory accounts qualitatively for the spectral peculiarities of the 2,4-disubstituted pyrimidines. The total π -electron energies of the ground and the two first excited states

of the molecules under consideration as given in Table 4, furthermore tells us that it is impossible to interpret the bathochromic shift observed when going from oxygen to sulfur compounds entirely in terms of either a labilization of the ground state or a stabilization of the excited state as previously proposed ^{2,3}. As seen from Table 4 the ground state as well as the excited state is labilized when oxygen is replaced by sulfur.

In Fig. 1 the net-charges and bond-orders for the disubstituted pyrimidine derivatives studied (*cf.* Ref.²⁰), are given. It is evident that there are specific positional differences. An extrapolation from the differences in bond order and electron density noted in substituents in the 2- and 4-positions of disubstituted pyrimidines to the positional differences in chemical reactivity, already noted, of substituents in these positions, is tempting. However, such speculations seem inappropriate in view of the scanty knowledge of the reaction mechanisms involved.

It is interesting to note that the electronic characteristics of the C=S bond of 2-thiouracil are similar to those of the corresponding bond in 2,4-dithiouracil; the same relationship is seen in comparing 4-thiouracil and 2,4-dithiouracil.

The charge differences noted in these calculations should be useful in estimating the relative strengths of hydrogen bonds formed by substituents in the 2- and 4-positions of pyrimidines, a problem of great importance in understanding the replication of nucleic acids. It should be noted that hydrogen bonding has been postulated as being involved in the mechanism of action of 6-thioguanine,¹⁸ the antineoplastic activity of which has been claimed to parallel its ability to be incorporated into deoxyribonucleic acid ¹⁹.

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