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Mesoionic Purinone Analogs. I. Initial Theoretical Considerations

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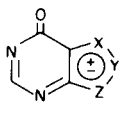
Thirty mesoionic analogs of purin-6-one, -2-one and -2,6-dione have been formulated based upon reported simple monocyclic mesoionic systems and factors influencing their stability. Hückel molecular orbital calculations were performed for these structures employing the ω, ω'-technique and the variation of resonance integrals with bond orders. The results provide predictions concerning the properties and stability of the analogs, assist the determination of reasonable synthetic goals, and serve as input for more sophisticated theoretical treatments.

The term "mesoionic" was proposed by Baker *et al.* (1,2) for a novel group of heterocyclic compounds which cannot be satisfactorily represented by any one covalent or dipolar structure. Although the term was intended for five- or six-membered rings possessing a sextet of π-electrons, it seems appropriate to extend this definition to any heterocyclic system regardless of ring size when π-electron delocalization may be extensive and no single dipolar or covalent structure conveys a proper indication of the molecular properties (3).

A large number of simple five-membered ring mesoionic systems have been prepared (4). Many of these systems have been reported to display a wide variety of biological or pharmacological activity (5,6). Based upon the chemical properties of these simple systems one can formulate a number of structures in which these systems are incorporated within an analogous purinone structure. This is accomplished by ring-fusing the mesoionic 5-membered ring imino-structure to a pyrimidine ring.

The resulting systems are isoelectronic with various purinone and xanthine structures. We have limited the extent of such formulations to structures whose 5-membered ring mesoionic systems have been reported and a few proposed new systems. In addition, the choice of the pyrimidine ring selected for ring fusion is based upon the observation that, in general, 5-membered mesoionic imino derivatives are stabilized by substitution with electron withdrawing groups on the exocyclic-imino nitrogen. Thus many mesoionic imines can be isolated as neutral compounds, rather than salts, only by *N*-acylation. For many mesoionic structures of the sydnone type, substitution ortho to the exo-cyclic atom or group in the π-system leads to stabilization when the substituent is again electron-withdrawing. Note that 3-methyl-4-(2′,4′-dinitrophenyl)-sydnone is stable towards hot concentrated nitric acid,



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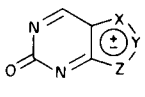

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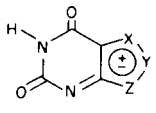

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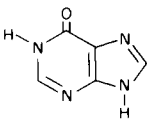
System	X	Y	Z	Reference (a)
a	N-R	N	O	9
b	O	C-R	N-R′	10
c	S	C-R	N-R′	11
d	N-R	C-R′	N-R″	12
e	O	N	N-R	(b)
f	N-R	C-R′	O	13
g	N-R	C-R′	S	14
h	S	C-R′	S	15
i	N-R	N	S	(b)
j	N-R	N	N-R′	16

(a) Reference to reported monocyclic mesoionic system. (b) Proposed monocyclic mesoionic system not yet reported.

conditions which readily hydrolyze other sydnones to hydrazines (7), while attempts to prepare 4-amino sydnones have been unsuccessful (8).

Structures **1**, **2** and **3** (**a-j**) represent the mesoionic analogs of purin-6-one, purin-2-one, and xanthine, respectively (**4**, **5** and **6**).



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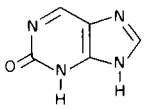

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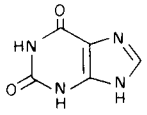

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The known monocyclic mesoionic systems undergo many examples of interesting ring opening reactions. These may proceed through polar addition-elimination mechanisms or *via* isopolar 1,3-dipolar cycloadditions. The analogous hydrolytic products of the sydnonimine system, corresponding to **1-3a**, might be 5-nitrosamino- and 5-hydrazino pyrimidones. Many of the analogs possess substitution patterns allowing formation of nucleosides corresponding to those of the purinones.

Although it is intriguing to comtemplate the biochemical and potential pharmacological properties of these analogs, such considerations should properly await the

TABLE I

Calculated Charge Densities for Purinones and Mesoionic Analogs

System	Positions (a)										
	1	2	3	4	5	6	7	8	9	10	11
4	.247	.176	-.238	.080	-.049	.185	-.260	.108	.252	-.502	
1a	-.283	.117	-.282	.125	.043	.113	.424	.090	.185	-.536	
1b	-.303	.095	-.294	.074	.008	.092	.186	.394	.354	-.605	
1c	-.304	.094	-.295	.073	.002	.092	.234	.369	.339	-.606	
1d	-.307	.092	-.297	.071	-.010	.092	.329	.322	.315	-.608	
1e	-.296	.108	-.292	.103	.072	.105	.219	.131	.400	-.552	
1f	-.298	.098	-.291	.089	-.007	.096	.366	.372	.173	-.598	
1g	-.301	.096	-.294	.083	-.008	.094	.353	.356	.222	-.602	
1h	-.300	.097	-.293	.085	.006	.094	.257	.402	.241	-.598	
1i	-.289	.113	-.287	.117	.042	.111	.411	.087	.241	-.547	
1j	-.300	.106	-.295	.099	.037	.105	.387	.071	.354	-.565	
5	-.243	.194	.237	.150	-.057	.140	-.262	.105	.254	-.517	
2a	-.222	.126	-.300	.133	.037	.101	.423	.091	.176	-.566	
2b	-.260	.105	-.314	.096	.000	.070	.182	.411	.352	-.641	
2c	-.261	.104	-.316	.095	-.004	.070	.233	.385	.336	-.642	
2d	-.264	.103	-.319	.093	-.014	.071	.327	.337	.309	-.643	
2e	-.215	.118	-.317	.114	.060	.092	.215	.138	.390	-.596	
2f	-.261	.102	-.308	.109	-.012	.075	.365	.381	.168	-.626	
2g	-.262	.106	-.313	.104	-.013	.074	.352	.368	.217	-.633	
2h	-.257	.108	-.312	.105	-.001	.074	.255	.421	.237	-.630	
2i	-.225	.122	-.309	.126	.034	.097	.411	.091	.233	-.581	
2j	-.230	.115	-.320	.111	.028	.092	.385	.081	.343	-.606	
6	.213	.251	.205	.116	-.091	.200	-.264	.087	.252	-.493	-.476
3a	.213	.180	-.343	.137	.019	.185	.418	.032	.167	-.541	-.468
3b	.206	.157	-.382	.091	-.032	.160	.186	.378	.344	-.592	-.518
3c	.206	.157	-.383	.090	-.034	.161	.237	.352	.329	-.593	-.519
3d	.206	.156	-.384	.088	-.050	.161	.330	.304	.305	-.594	-.522
3e	.211	.168	-.372	.116	.049	.181	.220	.090	.370	-.569	-.464
3f	.208	.163	-.369	.106	-.046	.164	.364	.340	.165	-.578	-.517
3g	.207	.161	-.375	.100	-.048	.163	.352	.329	.213	-.584	-.518
3h	.207	.162	-.374	.103	-.033	.163	.257	.380	.231	-.582	-.514
3i	.212	.175	-.357	.129	.016	.184	.408	.036	.222	-.553	-.471
3j	2.10	.166	-.376	.113	.009	.181	.387	.034	.330	-.574	-.478
7	.212	.251	.197	.056	-.043	.193	-.252	.123	-.273	-.496	-.473
8	-.204	.106	-.212	.104	-.002	.089	-.260	.138	.241		(-.531) (b)
9	.211	.249	.206	.111	-.069	.181	.193	.227	.214	-.497	-.496
10	.216	.255	.190	.072	-.002	.225	-.133	.290	-.209	-.485	-.419
11	.233	.226	-.314	.111	-.061	.187	-.165	-.118	.268	.129	-.496

(a) Positions numbered according to the IUPAC convention for purine. (b) Position **12** for system **9**.

determination of their fundamental structural and chemical properties. In order to estimate the perturbation of these properties with respect to well-known purinones we report the application of the Hückel molecular orbital treatment of the π-electron system.

HMO Calculations.

The estimation of the stability, physical and chemical properties of these analogs based upon their valence-bond representations is made extremely difficult by their unusual structure. The application of LCAO molecular orbital calculations obviates the problem of dealing with these molecular systems *via* the classical valence-bond approach.

The assumptions inherent in the simple HMO method lead to cancellation of nonexplicitly considered factors when alternate cyclic hydrocarbons are treated with this method. Dewar has critized the application of HMO methods to heterocyclic systems, especially with regard to

TABLE II

Calculated Bond Orders for Purinones and Mesoionic Analogs

System	Bonds											
	1-2	2-3	3-4	4-5	5-6	6-1	5-7	7-8	8-9	9-4	6-10	2-10
4	.407	.818	.438	.679	.436	.381	.457	.806	.429	.400	.749	
1a	.688	.639	.592	.604	.448	.523	.450	.637	.395	.319	.661	
1b	.659	.678	.532	.678	.485	.538	.284	.461	.640	.347	.625	
1c	.658	.679	.531	.674	.481	.539	.314	.517	.616	.352	.626	
1d	.656	.680	.530	.668	.476	.540	.357	.601	.574	.359	.628	
1e	.665	.700	.545	.622	.460	.537	.354	.456	.618	.404	.645	
1f	.669	.664	.558	.669	.476	.533	.357	.657	.428	.283	.633	
1g	.664	.670	.547	.669	.476	.536	.357	.638	.485	.314	.631	
1h	.665	.669	.548	.671	.480	.535	.319	.553	.524	.312	.630	
1i	.679	.650	.576	.607	.451	.529	.444	.620	.453	.356	.653	
1j	.662	.671	.541	.618	.449	.538	.437	.543	.553	.410	.649	
5	.465	.386	.380	.653	.522	.757	.431	.822	.410	.428		.739
2a	.471	.526	.668	.546	.545	.749	.438	.638	.381	.305		.653
2b	.502	.546	.626	.598	.612	.701	.270	.462	.639	.338		.616
2c	.501	.547	.624	.596	.606	.703	.299	.520	.613	.343		.616
2d	.500	.549	.622	.591	.600	.706	.340	.607	.568	.349		.615
2e	.475	.547	.627	.561	.767	.738	.340	.455	.609	.386		.636
2f	.500	.536	.650	.591	.597	.709	.343	.662	.419	.275		.624
2g	.500	.541	.639	.591	.597	.708	.342	.643	.477	.305		.621
2h	.500	.540	.640	.593	.602	.707	.306	.556	.517	.303		.622
2i	.471	.535	.651	.550	.548	.747	.432	.626	.443	.341		.646
2j	.473	.549	.623	.558	.554	.743	.420	.598	.544	.393		.635
											6-11	2-10
6	.370	.385	.322	.708	.426	.355	.444	.814	.416	.421	.772	.794
3a	.350	.533	.631	.576	.439	.369	.466	.618	.357	.310	.753	.713
3b	.344	.583	.553	.654	.494	.362	.283	.465	.620	.349	.717	.678
3c	.344	.584	.551	.651	.491	.362	.313	.521	.596	.354	.718	.677
3d	.343	.586	.548	.646	.487	.362	.355	.605	.553	.361	.719	.675
3e	.344	.565	.581	.597	.451	.371	.363	.453	.574	.394	.746	.694
3f	.347	.566	.584	.642	.484	.362	.362	.653	.407	.283	.723	.688
3g	.346	.573	.571	.643	.485	.362	.359	.637	.464	.314	.722	.683
3h	.346	.571	.573	.645	.487	.362	.322	.553	.500	.312	.721	.685
3i	.347	.547	.610	.581	.441	.370	.460	.609	.416	.348	.751	.705
3j	.343	.569	.575	.592	.445	.370	.447	.588	.515	.404	.747	.691
7	.370	.390	.291	.712	.437	.353	.357	.466	.770	.508	.792	.766
8	.625	.691	.593	.578	.610	.678	.426	.823	.420	.382		(.757) (a)
9	.374	.386	.322	.763	.462	.347	.267	.416	.393	.347	.791	.749
10	.362	.386	.283	.485	.350	.368	.746	.444	.393	.775	.799	.813
11	.394	.732	.476	.639	.436	.374	.508	.789	.398	.431	.395	.753

(a) Bond **8-12** for system **9**.

π-electron energies (17).

These shortcomings can be reduced by modifying techniques. Kier (18) and Roche (19) have applied the ω-technique (20) to mesoionic systems in which coulomb integrals are modified by calculated charge densities in an iterative fashion. They were able to calculate reasonable charge densities, bond orders, dipole moments, localization energies and spectral transitions as well as predict fragmentation modes upon electron bombardment (21).

Pullman has shown reasonably good correlations between HMO bond order and bond lengths in the purine series (22). An additional refinement to the HMO ω-technique is the modification of resonance integrals by calculated bond orders. Boyd and Singer have shown that this $\omega\beta$ method is in some ways superior to the Pariser-Parr-Pople SCF method (23). Thus the sensitivity of the results to the choice of heteroatom parameters is reduced. The number of parameters employed in the modified Hückel method is considerably less than that required for a semi-empirical SCF-MO treatment.

TABLE III

HMO Energies and Charge Separation (a)

System	E^{π}_{Total} (b)	$E^{\pi}_{Deloc.}$	E_{Homo}	E_{Lemo}	$\Delta E_{Homo-Lemo}$	$\Sigma\|Q\|$
4	20.5229	4.623	0.532	-0.697	1.229	2.097
1a	23.0268	5.127	0.448	-0.088	0.536	2.198
1b	22.2170	5.117	0.352	-0.323	0.675	2.405
1c	21.3852	4.785	0.348	-0.391	0.739	2.408
1d	20.2887	4.389	0.340	-0.508	0.848	2.443
1e	22.9764	5.076	0.424	-0.031	0.455	2.278
1f	22.2505	5.150	0.358	-0.360	0.718	2.388
1g	21.4042	4.804	0.351	-0.413	0.764	2.409
1h	22.4707	5.171	0.360	-0.281	0.641	2.373
1i	22.1740	4.774	0.433	-0.133	0.566	2.245
1j	21.0946	4.395	0.405	-0.224	0.629	2.319
5	20.4780	4.578	0.542	-0.527	1.069	2.159
2a	22.9838	5.083	0.430	-0.066	0.496	2.175
2b	22.1523	5.052	0.320	-0.273	0.593	2.431
2c	21.3184	4.718	0.316	-0.337	0.653	2.446
2d	20.2198	4.320	0.309	-0.448	0.757	2.480
2e	22.9093	5.009	0.393	0.006	0.387	2.255
2f	22.2005	5.101	0.333	-0.327	0.660	2.407
2g	21.3463	4.746	0.324	-0.371	0.695	2.442
2h	22.4132	5.113	0.333	-0.242	0.575	2.400
2i	22.1357	4.736	0.409	-0.105	0.514	2.229
2j	21.0236	4.324	0.375	-0.179	0.554	2.311
6	24.4224	6.522	0.540	-0.756	1.296	2.648
3a	26.8202	6.920	0.385	-0.162	0.547	2.703
3b	25.9397	6.840	0.275	-0.330	0.605	3.046
3c	25.1083	6.508	0.269	-0.399	0.668	3.061
3d	24.0119	6.119	0.260	-0.520	0.780	3.100
3e	26.7208	6.821	0.352	-0.065	0.417	2.810
3f	26.0044	6.904	0.284	-0.405	0.689	3.020
3g	25.1457	6.546	0.275	-0.447	0.722	3.050
3h	26.2141	6.914	0.286	-0.312	0.598	3.006
3i	25.9643	6.564	0.366	-0.196	0.562	2.763
3j	24.8401	6.140	0.333	-0.262	0.595	2.858
7	24.3677	6.468	0.568	-0.642	1.210	2.372
8	16.7862	4.886	0.840	-0.658	1.498	1.356
9	28.1185	6.219	0.409	-0.746	1.155	3.185
10	25.2050	6.505	0.840	-0.495	1.335	2.496
11	24.7050	6.505	0.516	-0.704	1.220	2.308

(a) All energy terms in units of β. (b) Total energy expressed in terms of K_i, where: $E_T = n_e\alpha + K_i\beta$

The method employed in this study is an ω- (1.4), ω'- (0.1), variable resonance integral (23) calculation employing the heteroatom Hückel parameters used by Kier in treating other mesoionic systems (21).

One of the objectives of the application of these elementary calculations is the prediction of molecular geometries required for the establishment of the semi-empirical parameters for the π-SCF-MO and all-valence electron methods. To this end, rather than neglecting the σ-bonding system, one can attempt to calibrate a bond order *vs.* bond length relationship for each bond type using structures of known geometry. The following compounds were used for this purpose: 9-ethylhypoxanthine (24), theophylline **7** (25), purine-9*H* **8** (26), uric acid **9** (27), xanthole **10** (28), and 8-azaguanine **11** (29). Calculated bond orders were plotted *vs.* reported bond lengths for each bond type, *i.e.* N_1-C_2, C_2-N_3, etc. From these plots bond lengths can be estimated for the analogs. Since these predicted geometries will serve primarily as a point of departure for refinement by methods which give reliable geometries (such as CNDO/2) they will not be reported here.

The ω-technique leads to significant reduction of the exaggerated charge separations predicted by the HMO method. The absolute sum of the net π-electron charge on each atom was calculated as an index of the charge separation since the polarity of these mesoionic analogs relative to that of the purinones is of prime interest.

Results.

Charge densities and bond orders for the purinones and the mesoionic analogs are given in Tables I and II. In the purin-6-one analogs the electron densities on the two nitrogen atoms in the 6-membered ring are nearly equal, while in the purin-2-one series the densities at N-3 exceed those at N-1. In both cases electron density on the exocyclic oxygen increases.

In the 6-one series position 1 becomes electron rich instead of electron deficient as in purin-6-one itself, while position 8 is strongly electron deficient for all except the 8-aza analogs, **1-3a**, **e**, **i**, and **j**. For both the 2-one and 6-one series the 6-membered ring becomes electron rich and the 5-membered ring very strongly electron deficient. The 6-membered ring in the xanthine analogs is only slightly electron deficient (0.2) compared to that of xanthine (0.89).

The comparison of bond orders and charge densities for the simple monocyclic mesoionic systems and the corresponding purinone analogs can be exemplified in the case of **1-3a**. Kier and Roche (30) have reported ω-HMO calculations for sydnonimines. The N_3-C_4 bond of the analogs, which corresponds to the C_5-N exocyclic bond in sydnonimine, shows a decrease in double-bond character (0.744 in sydnonimine). However, this bond order is substantially greater than that of the N_3-C_4 bond in the parent purinones. The 5-membered rings in the analogs **1-3a** are much more electron deficient (+0.77 to +0.87) than in sydnonimine (+0.33). This is also true for the remaining analogs.

Inspection of the calculated charge densities and bond orders reveals that no single dipolar valence-bond representation would adequately reflect these properties. In most systems many adjacent bonds possess comparably high bond orders. The bond orders of the exocyclic C-O bonds decrease by an average of 0.1, while the electron density on the exocyclic oxygen increases, on the average, by 0.09 **e**. In the xanthine analogs, however, the C_6-O bond is not so substantially affected. Some of the systems exhibit features peculiar to themselves, such as the unusually high bond order for the C_5-C_6 bond in system **2e**.

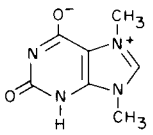
The delocalization energies represent the difference between total π-electron energy and the energy of the π-electrons isolated on the atoms contributing them to the π-system. Resonance energies cannot be calculated without a good method of approximating the energy of the most stable valence bond structure. The value of β depends upon the method and choice of heteroatom parameters and therefore direct comparisons cannot be made with previously reported HMO calculations of purine derivatives. It is interesting to note that the majority of the analogs have calculated delocalization energies which exceed that of their parent system. Another possible index of stability is the energy separation between highest occupied molecular orbital and lowest empty molecular orbital. This difference has been correlated with the longest wavelength $\pi \rightarrow \pi^*$ singlet transition (18). E_{HOMO} has been used as an index of the oxidation potential of the molecule. It appears that these analogs should be both better electron donors and acceptors than the purinones and should absorb at longer wavelengths. One might also anticipate an enhansed ability of these analogs to participate in charge-transfer modes of binding.

With respect to over-all charge separation, **1-3a**, **e**, and **i** exhibit absolute sums of the charge densities comparable with that of the parent system, while the others seem to be more polar.

Discussion.

A number of questions of immediate concern come to mind when considering these mesoionic analogs. Will they be stable as isolated molecules at normal temperatures? Will they be very much more polar than their corresponding purinones, as implied by their valence-bond representations? In what manner will their physical and chemical properties differ from the purinones?

The results of the HMO calculations provide only limited answers to these questions. Most of the analogs exhibit calculated delocalization energies which exceed that of their analogous purinone. In one of the few cases where this is not true, **1-3d**, experimental evidence indicates that this system is thermally, photochemically, and chemically stable under normal conditions. Bredereck, *et al.*, have reported the preparation of **12** and **13**, a "xanthinium betaine" (31) and a natural product, herbipolin (32),



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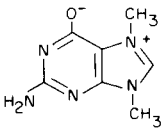


13

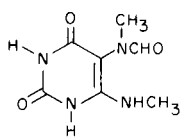
respectively. In comparing the properties of these compounds with the results of the HMO calculations for **1d** and **3d** one may be encouraged concerning the feasibility of preparing many of the other analogs.

Although all of the analogs may be expected to be more polar than the corresponding purinone, many of them are only slightly more polar based on π-electron considerations. Thus, the difference is a matter of degree rather than kind. The use of valence-bond notation is uniformly misleading in cases such as these.

When one considers the σ-bonding system as well as the π-system, it is conceivable that the overall dipole moment may be reduced rather than increased in some of the analogs.

The substantial decrease in the energy separation between highest occupied and lowest empty molecular orbitals can be interpreted as an indication of enhanced reactivity, in a general sense. Few generalizations concerning the chemistry of these analogs would seem appropriate since predictions based upon ground state properties of only the π-system are theoretically unsound. These properties, however, may be significant in less energetic interactions such as base-pairing and base-stacking observed for the purinone components of nucleic acids. The electron donor property of the analogs increases slightly but the electron affinity increases to a point surpassing that of the pyrimidines; uracil, cytosine, and alloxane.

Mesoionic xanthine **3d** undergoes ring opening in alkaline solution to give **14** (31), breaking the 8,9-bond which is found to be of lower bond order than the 7,8-bond.



14

Corresponding products expected from the alkaline hydrolysis of **2f**, **g**, and **h** would be *N'*-alkyl-5-acylaminouracil, *N'*-alkyl-5-acylamino-4-thiouracil, and 5-acylmercapto-4-thiouracil, respectively.

The 8-aza analogs, in which the 8-position is not as electron deficient as in the other analogs, may be expected to undergo nucleophilic attack in the 6-membered ring as in the case of triazolopyrimidines (33). Sydnonimines undergo base-catalyzed ring cleavage to give *N*-nitroso-α-amino amides. Although the analogous reaction of **2a** would produce *N'*-alkyl-5-nitrosaminouracil, the present calculations provide no means of estimating the probability of this reaction.

More pertinent to the discussion of the chemistry of these analogs would be the localization energies for nucleophilic and electrophilic attack at all positions. These data will be calculated with the SCF methods which take electron repulsions into explicit consideration.

Although the concept of mesoionic purinones is not entirely new (34), much theoretical and experimental work remains to be accomplished before an understanding of this class of compounds is achieved.

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