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QUANTUM CHEMICAL STUDY OF 2-SUBSTITUTED 4-OXO- AND 4-THIOXOSPIRO(BENZO[h]QUINAZOLINE-5,1'-CYCLOALKANES) IN ALKYLATION REACTIONS

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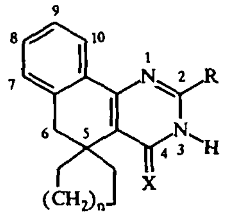
The steric and electronic structures of 2-substituted 4-oxo- and 4-thioxospiro(benzo[h]quinazoline-5,1'-cycloalkanes and their deprotonated forms have been calculated by the semiempirical PM-3 quantum chemical method. Using the conclusions of limiting orbital theory, a quantum chemical explanation has been derived, based on the calculations made, for the selectivity of alkylation of the systems investigated.

No quantum chemical investigation has been carried out hitherto on 2-substituted 4-oxo and 4-thioxospiro-(benzo[h]quinazoline-5,1'-cycloalkane) systems. However, a study of the alkylation of these systems is of interest from the viewpoint of quantum chemical consideration of the accumulated experimental material.



I X = O, n = 1, R = H; II X = O, n = 1, R = Et; III X = O, n = 1, R = Ph; IV X = O, n = 1, R = Bz;
V X = O, n = 2, R = H; VI X = O, n = 2, R = Et; VII X = O, n = 2, R = Ph; VIII X = O, n = 2, R = Bz;
XI X = S, n = 1, R = H; X X = S, n = 1, R = Et; XI X = S, n = 1, R = Ph; XII X = S, n = 1, R = Bz;
XIII X = S, n = 2, R = H; XIV X = S, n = 2, R = Et; XV X = S, n = 2, R = Ph;
XVI X = S, n = 2, R = Bz

The aim of the present work was a quantum chemical study of the electronic structure and reactivity of 2-substituted 4-oxo- and 4-thioxospiro(benzo[h]quinazoline-5,1'-cycloalkanes) in alkylation reactions. Calculations carried by the PM-3 method for a wide range of compounds have shown that the present method, out of all the semiempirical methods, gives results closest to those obtained by nonempirical methods [1, 2].

According to the calculations, the pyrimidine ring emerges from the plane of the benzene ring in the molecules of (I) and (V) by 18°, in (II) and (VI) by 17.6°, in (III) and (VII) by 4.6° and in (IV) and (VIII) by 4°. For the deprotonated molecules (Ii)-(VIIIi) the angle of emergence from the benzene plane depends less on the structure of the substituent R and on average was 18°. Calculation of the bond lengths in molecules (I)-(VIII) and their corresponding anions (Ii)-(VIIIi) showed that on deprotonation the greatest changes in length occurred in the bonds $N_{(1)}-C_{(2)}$, $C_{(2)}-N_{(3)}$, $N_{(3)}-C_{(4)}$, and $C_{(4)}-O$, which may be explained by the resonance stabilization of the anions obtained on deprotonation.

The quantum chemical calculation of 2-substituted 4-thioxospiro(benzo[h]quinazoline-5,1'-cycloalkanes) (IX)-(XVI) indicated that the pyrimidine ring emerges from the plane of the benzene by 20° on average (this also applies to the corresponding anions (IXi)-(XVIi) formed on deprotonation of the $N_{(3)}$ nitrogen atom).

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TABLE 1. Calculated Data on 2-Substituted 4-Oxospiro(benzo[h]quinazoline-5,1'-cycloalkanes) (I)-(VIII)

Molecule	π-Density	Atom number									T_{form}, ΔH, kcal/mole	ΔE, eV, $E_{HOMO}-E_{LUMO}$	Dipole moment
		1	2	3	4	O (oxygen)	7	8	9	10			
1	2	3	4	5	6	7	8	9	10	11	12	13	14
I	Charge	-0,1538	-0,0652	0,0618	0,2889	-0,3764	-0,1138	-0,0796	-0,1226	0,0460	0,6390	-8,15	1,586
	HOMO	0,2269	0,2104	0,2095	0,0764	0,3204	0,0639	0,2921	0,1712	0,1569			
	LUMO	0,0679	0,3628	0,2842	0,1672	0,1524	0,0745	0,2733	0,0955	0,2166			
Ii	Charge	-0,333	0,027	-0,332	0,350	-0,482	-0,126	-0,126	-0,137	-0,07	-39,9	-7,05	9,217
	HOMO	0,5181	0,0778	0,4108	0,1230	0,4276	0,0012	0,0249	0,0025	0,0244			
	LUMO	0,1466	0,0621	0,1472	0,0573	0,0547	0,1921	0,5076	0,3232	0,1907			
II	Charge	-0,153	-0,045	0,07	0,29	-0,381	-0,114	-0,08	-0,123	-0,047	-13,75	-8,1	2,113
	HOMO	0,2633	0,2259	0,2207	0,0825	0,3369	0,0593	0,2675	0,1520	0,1495			
	LUMO	0,0702	0,3766	0,2894	0,1613	0,1476	0,0748	0,2712	0,0954	0,2139			
IIi	Charge	-0,316	0,039	-0,315	0,350	-0,483	-0,127	-0,126	-0,137	-0,071	-52,56	-7,04	7,585
	HOMO	0,5242	0,0815	0,4068	0,1261	0,4393	0,0014	0,0246	0,0022	0,0235			
	LUMO	0,1522	0,0658	0,1532	0,0572	0,0545	0,1931	0,5055	0,3194	0,1928			
III	Charge	-0,157	0,015	0,06	0,295	-0,382	-0,114	-0,008	-0,123	-0,048	25,31	-7,78	2,6
	HOMO	0,3132	0,2329	0,2021	0,0853	0,3302	0,0522	0,2273	0,1219	0,1358			
	LUMO	0,2045	0,4130	0,2879	0,0869	0,0868	0,0433	0,1713	0,0526	0,1450			
IIIi	Charge	-0,306	0,071	-0,308	0,349	-0,479	-0,126	-0,123	-0,136	-0,007	-15,18	-7,07	6,021
	HOMO	0,5226	0,0872	0,4034	0,1247	0,4455	0,0018	0,0273	0,0031	0,0262			
	LUMO	0,0726	0,1445	0,2369	0,0268	0,0265	0,1705	0,4387	0,2640	0,1862			
IV	Charge	-0,157	-0,041	0,074	0,290	-0,379	-0,115	-0,08	-0,123	-0,048	19,99	-8,09	2,088
	HOMO	0,2615	0,2247	0,2206	0,0824	0,3393	0,0587	0,2615	0,1473	0,1472			
	LUMO	0,0725	0,3789	0,2885	0,1591	0,1472	0,0729	0,2651	0,0924	0,2102			

TABLE 1 (continued)

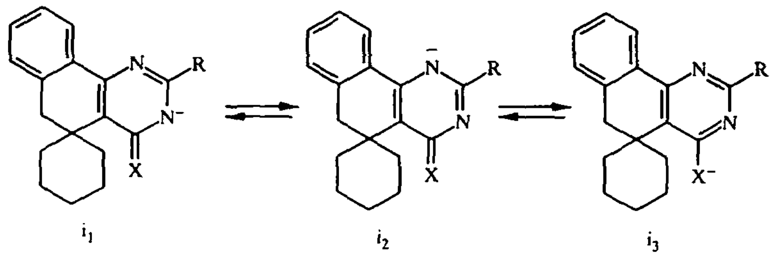
1	2	3	4	5	6	7	8	9	10	11	12	13	14
IVi	Charge	-0,314	0,034	-0,313	0,347	-0,477	-0,128	-0,124	-0,137	-0,07	-18,42	-7,08	5,7
	HOMO	0,5213	0,0795	0,4109	0,1232	0,4502	0,0014	0,0257	0,0028	0,0243			
	LUMO	0,1559	0,0725	0,1606	0,0589	0,0562	0,1887	0,4945	0,3060	0,1990			
V	Charge	-0,150	-0,067	0,067	0,288	-0,379	-0,115	-0,079	-0,123	-0,047	-1,43	-8,15	1,899
	HOMO	0,1779	0,1771	0,1524	0,0655	0,2395	0,0555	0,2879	0,1785	0,1484			
	LUMO	0,0565	0,3082	0,2428	0,1369	0,1180	0,0725	0,2528	0,0824	0,2090			
Vi	Charge	-0,333	0,028	-0,332	0,349	-0,482	-0,127	-0,126	-0,137	-0,07	-43,72	-7,08	9,36
	HOMO	0,4552	0,0697	0,3481	0,0960	0,3219	0.0019	0,0242	0,0013	0,0226			
	LUMO	0,1310	0,0507	0,1270	0,0469	0,0417	0,1855	0,4768	0,2981	0,1856			
VI	Charge	-0,148	-0,047	0,075	0,290	-0,384	-0,115	-0,08	-0,123	-0,047	-16,05	-8,12	2,455
	HOMO	0,2095	0,1920	0,1631	0,0711	0,2559	0,0533	0,2681	0,1610	0,1438			
	LUMO	0,0620	0,3243	0,2491	0,1326	0,1151	0,0728	0,2510	0,0824	0,2060			
VIl	Charge	-0,315	0,04	-0,315	0,349	-0,482	-0,127	-0,126	-0,137	-0,07	-56,48	-7,07	7,61
	HOMO	0,4610	0,0727	0,3389	0,0980	0,3265	0,0017	0,0236	0,0012	0,0216			
	LUMO	0,1340	0,0538	0,1297	0,0459	0,0406	0,1837	0,4723	0,2951	0,1836			
VII	Charge	-0,154	0,013	0,066	0,294	-0,385	-0,115	-0,08	-0,124	-0,048	23,14	-7,79	2,96
	HOMO	0,2542	0,1968	0,1519	0,0732	0,2521	0,0466	0,2242	0,1279	0,1286			
	LUMO	0,1749	0,3525	0,2439	0,0686	0,0650	0,0424	0,1562	0,0438	0,1375			
VIIl	Charge	-0,306	0,072	-0,308	0,349	-0,478	-0,126	-0,123	-0,136	-0,07	-19,30	-7,1	5,87
	HOMO	0,4464	0,0759	0,3294	0,0946	0,3221	0,0023	0,0261	0,0020	0,0238			
	LUMO	0,0622	0,1216	0,1958	0,0193	0,0169	0,1610	0,4003	0,2356	0,1751			
VIII	Charge	-0,131	-0,049	0,067	0,286	-0,387	-0,118	-0,079	-0,127	-0,049	14,20	-8,11	2,33
	HOMO	0,1072	0,0966	0,0829	0,0389	0,1472	0,0346	0,1773	0,1105	0,0963			
	LUMO	0,0401	0,1743	0,1380	0,0836	0,0747	0,0423	0,1597	0,0568	0,1289			
VIIIi	Charge	-0,306	0,035	-0,314	0,346	-0,483	-0,128	-0,123	-0,137	-0,069	-24,62	-7,14	5,93
	HOMO	0,4914	0,0839	0,3850	0,1198	0,4234	0,0026	0,0253	0,0027	0,0238			
	LUMO	0,1394	0,0691	0,1526	0,0578	0,0550	0,1837	0,4738	0,2901	0,1952			

TABLE 2. Calculated Data on 2-Substituted 4-Thioxospiro(benzo[h]quinazoline-5,1′-cycloalkanes) (IX)-(XVI)

Molecule	π-Density	Atom number 1	2	3	4	S (sulfur)	7	8	9	10	T_{form}, ΔH, kcal/mole	ΔE, eV $E_{HOMO}-E_{LUMO}$	Dipole moment
1	2	3	4	5	6	7	8	9	10	11	12	13	14
IX	Charge	−0,115	−0,108	0,220	−0,075	−0,293	−0,113	−0,071	−0,124	−0,04	73,5	−7,0	4,0
	HOMO	0,0201	0,0585	0,0657	0,0164	0,1357	0,0028	0,0178	0,0048	0,0148			
	LUMO	0,0002	0,0164	0,0303	0,0381	0,0360	0,0152	0,0392	0,0056	0,0529			
IXi	Charge	−0,213	−0,037	−0,168	−0,041	−0,524	−0,124	−0,115	−0,137	−0,068	13,6	−6,2	11,1
	HOMO	0,0107	0,0406	0,0292	0,0086	0,2166	0,0069	0,0040	0,0042	0,0047			
	LUMO	0,0020	0,0027	0,0109	0,0105	0,0128	0,0422	0,0920	0,0459	0,0596			
X	Charge	−0,114	−0,085	0,229	−0,073	−0,304	−0,114	−0,072	−0,124	−0,042	58,7	−7,0	4,5
	HOMO	0,0230	0,0488	0,0539	0,0153	0,1244	0,0021	0,0159	0,0045	0,0138			
	LUMO	0,0038	0,0085	0,0207	0,0281	0,0285	0,0145	0,0357	0,0052	0,0491			
Xi	Charge	−0,196	−0,023	−0,153	0,042	−0,526	−0,125	−0,115	−0,137	−0,068	1,3	−6,2	10,2
	HOMO	0,0132	0,0405	0,0250	0,0101	0,2403	0,0070	0,0037	0,0041	0,0051			
	LUMO	0,0004	0,0032	0,0322	0,0241	0,0263	0,0371	0,0817	0,0406	0,0510			
XI	Charge	−0,121	−0,021	0,218	−0,066	−0,309	−0,114	−0,072	−0,125	−0,043	97,8	−7.3	5,2
	HOMO	0,0039	0,0425	0,0548	0,0088	0,1829	0,0037	0,0154	0,0061	0,0156			
	LUMO	0,0159	0,0332	0,0446	0,0490	0,0482	0,0128	0,0296	0,0036	0,0400			
XIi	Charge	−0,189	0,013	−0,147	0,042	−0,518	−0,126	0,113	−0,136	−0,068	40,1	−6,2	9,4
	HOMO	0,0141	0,0392	0,0073	0,0132	0,2584	0,0065	0,0033	0,0043	0,0050			
	LUMO	0,0129	0,0286	0,0654	0,0191	0,0288	0,0320	0,0686	0,0330	0,0457			
XII	Charge	−0,117	−0,083	0,238	−0,073	−0,302	−0,116	−0,071	−0,125	−0,042	93,0	−7,0	4,5
	HOMO	0,1614	0,0508	0,0998	0,0266	0,3048	0,0199	0,0593	0,0211	0,0470			
	LUMO	0,0981	0,1912	0,2653	0,2632	0,1826	0,0306	0,1497	0,0392	0,1277			

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
XIIi	Charge	−0,198	−0,026	−0,149	0,038	−0,517	−0,124	−0,114	−0,136	−0,068	34,1	−6,2	9,5
	HOMO	0,0368	0,0285	0,0120	0,0093	0,2670	0,0106	0,0020	0,0027	0,0060			
	LUMO	0,1767	0,0609	0,1880	0,1053	0,0603	0,1197	0,2953	0,1544	0,1483			
XIII	Charge	−0,112	−0,109	0,224	−0,084	−0,288	−0,115	−0,071	−0,124	−0,042	69,6	−7,1	3,8
	HOMO	0,1866	0,1356	0,2401	0,0199	0,4764	0,0293	0,1187	0,0513	0,0858			
	LUMO	0,1086	0,1865	0,3015	0,3264	0,2385	0,0477	0,1998	0,0454	0,1870			
XIIIi	Charge	−0,225	−0,032	−0,177	0,05	−0,557	−0,123	−0,117	−0,135	−0,067	14,2	−6,5	11,1
	HOMO	0,1253	0,0214	0,1463	0,0053	0,3683	0,0010	0,0067	0,0026	0,0056			
	LUMO	0,1828	0,0421	0,1731	0,0922	0,0526	0,1908	0,4569	0,2465	0,2295			
XIV	Charge	−0,114	−0,085	0,232	−0,08	−0,301	−0,116	−0,072	−0,125	−0,042	55,2	−7,0	4,5
	HOMO	0,2021	0,1395	0,2459	0,0178	0,5600	0,0257	0,1025	0,0414	0,0757			
	LUMO	0,1054	0,2201	0,3319	0,3509	0,2577	0,0487	0,1993	0,0463	0,1840			
XIVi	Charge	−0,209	−0,017	0,162	−0,05	−0,561	−0,124	−0,116	−0,136	−0,067	1,4	−6,5	10,1
	HOMO	0,1326	0,0172	0,1431	0,0082	0,4551	0,0008	0,0063	0,0028	0,0048			
	LUMO	0,1864	0,0482	0,1814	0,0919	0,0526	0,1882	0,4476	0,2402	0,2247			
XV	Charge	−0,120	−0,022	0,222	−0,075	−0,306	−0,116	−0,072	−0,125	−0,043	94,1	−6,9	5,1
	HOMO	0,2193	0,1405	0,2308	0,0141	0,5663	0,0246	0,1018	0,0413	0,0759			
	LUMO	0,0095	0,2928	0,3324	0,2601	0,1945	0,0420	0,1741	0,0374	0,1637			
XVi	Charge	−0,201	0,018	−0,156	0,046	−0,554	−0,125	−0,114	−0,135	−0,067	38,7	−6,5	8,8
	HOMO	0,0959	0,0204	0,1078	0,0074	0,4490	0,0007	0,0054	0,0033	0,0035			
	LUMO	0,0744	0,1424	0,2257	0,0306	0,0081	0,1569	0,3642	0,1828	0,1983			
XVI	Charge	−0,100	−0,089	0,246	−0,087	−0,290	−0,115	−0,070	−0,125	−0,040	90,1	−6,6	4,8
	HOMO	0,0450	0,0379	0,0866	0,0163	0,2366	0,0099	0,0152	0,0069	0,0157			
	LUMO	0,1030	0,2545	0,3553	0,4091	0,2971	0,0454	0,1948	0,0428	0,1820			
XVIi	Charge	−0,187	−0,019	−0,165	0,039	−0,535	−0,127	−0,114	−0,137	−0,067	28,3	−6,3	10,7
	HOMO	0,0256	0,0114	0,1158	0,0147	0,5992	0,0100	0,0024	0,0001	0,0055			
	LUMO	0,0816	0,0414	0,1123	0,0663	0,0416	0,0009	0,2692	0,1409	0,1482			

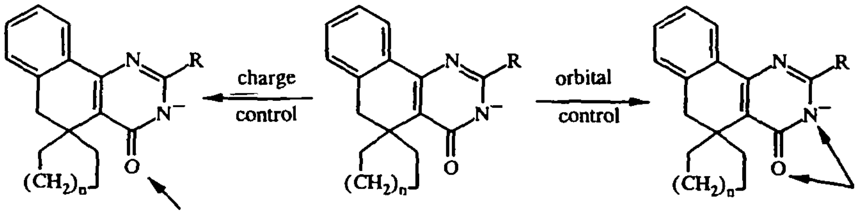


Calculation of the charge on atoms and bond orders of the molecules (IX)-(XVI) and their deprotonated analogs showed that deprotonation was accompanied by a significant increase in the size of the charge on the sulfur atoms and on $N_{(1)}$ indicating the high contribution of the corresponding structures i_3 and i_2 to the overall equilibrium of resonance structures.

Experimental alkylation of compounds (I)-(XVI) is a two stage process comprising deprotonation with alkali and then alkylation with alkyl halide (methyl iodide and ethyl iodide were used as alkylating agents). The corresponding N-methylated compounds were formed on alkylating 2-substituted 4-oxo-5,6-dihydrospiro(benzo[h]quinazoline-5,1′-cycloalkanes) (I)-(VIII) with methyl iodide in an alcohol solution of potassium hydroxide. Both N- and O-alkylation occurred on reacting 2-substituted 4-oxo-5,6-dihydrospiro(benzo[h]quinazoline-5,1′-cycloalkanes) (II), (III), (IV), (VI), (VII), and (VIII) with ethyl iodide [3, 4].

The charge on the atom was selected as the index of reactivity at the deprotonation stage. The calculations (Table 1) indicate that a positive charge is centered on the $N_{(3)}$ atom (electron-deficient center) of molecules (I)-(VIII). This leads to polarization of its bond with the hydrogen atom, leading to deprotonation in the presence of hydroxyl ion.

Theoretically the reaction may go by two pathways at the alkylation stage:



1. Charge-controlled alkylation: O-alkylation occurs (the greatest charge is centered on the oxygen atom, see Table 1).

2. Orbital-controlled alkylation: both O- and N-alkylation are equally probable since there is a large and practically identical π-orbital density on the oxygen and $N_{(3)}$ atoms (the largest π-orbital partial density in the HOMO is centered on $N_{(1)}$, however due to steric hindrance to attack by alkyl iodide, alkylation of this position is impossible).

The use of ethyl iodide, which is a milder reagent than methyl iodide, leads to orbital control as the more preferred course for the reaction and explains the formation of products of N- and O-alkylation. Methyl iodide as an alkylation agent directs the reaction along the pathway of charge control and leads to an O-alkylated compound, which is converted by rearrangement into the thermodynamically more stable N-alkylated compound.

Calculated heats of formation of alkylated compounds:

Compound	O−Me; N−Me, kcal/mole	Compound	O−Me; N−Me, kcal/mole
I	7.8; 1.3	V	6.3; −1.3
II	−4.1; −12.1	VI	−7.0; −14.4
III	35.1; 28.7	VII	38.6; 31.9
VI	31.4; 24.0	VIII	28.7; 19.7

The experimental data on the alkylation of thio derivatives (IX)-(XVI) indicate that on deprotonation a proton is removed from the $N_{(3)}$ nitrogen atom but subsequent alkylation proceeds at the sulfur atom (S-alkylation) [5, 6].

The charge on the atom (kinetic control) was selected as the index of reactivity at the stage of deprotonating thio derivatives (IX)-(XVI). The data from the calculations indicate that a significant positive charge is centered on the $N_{(3)}$ atom (electron-deficient center) in the (IX)-(XVI) molecules. This leads to polarization of the bond with its hydrogen atom leading to deprotonation in the presence of hydroxyl ion.

At the alkylation stage the π-orbital density in the HOMO (orbital control) served as the index of reactivity for molecules (IX)-(XVI). According to the calculations the greatest π-orbital partial density in the HOMO was centered on the sulfur atom (Table 2) which also leads to an S-alkylation product.

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