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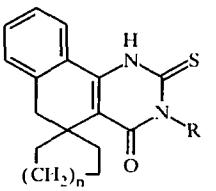
QUANTUM-CHEMICAL INVESTIGATION OF 4-OXO-2-THIOXO-SPIRO(BENZO[*h*]QUINAZOLINE-5,1'-CYCLOALKANES) IN ALKYLATION REACTIONS

K. V. Karapetyan, V. I. Terenin, A. I. Markosyan, and R. A. Kuroyan

The method of CMC was used to study the electronic and steric structure of 3-substituted 4-oxo-2-thioxo-spiro(benzo[h]quinazoline-5,1'-cycloalkanes) and the corresponding deprotonated forms, as well as their indexes of reactivity in alkylation reactions. The calculated values of charges on the atoms and of π-orbital partial densities on the HOMO and LFMO enabled a quantum-chemical explanation for the formation of S-alkylated products to be given.

The quantum-chemical method of CMC gives results closest to the experimental ones in the case of heterocyclic systems [1, 2]. The present work is a continuation of investigations of 3-substituted 4-oxo- and 4-thioxospirobenzo[*h*]quinazolines, namely 2-thioxo-4-oxospiro(benzo[h]quinazoline-5,1'-cycloalkanes) containing various substituents at the $N_{(3)}$ atom, in alkylation reactions [3].



I n = 1, R = H; II n = 1, R = Me; III n = 1, R = cyclopentyl; IV n = 1, R = cyclohexyl; V n = 1, R = cyclopentylmethyl; VI n = 1, R = cyclohexylmethyl; VII n = 1, R = Ph; VIII n = 1, R = *p*-tolyl; IX n = 1, R = *p*-anisyl; X n = 1, R = benzyl; XI n = 1, R = phenetyl; XII n = 2, R = H; XIII n = 2, R = Me; XIV n = 2, R = cyclopentyl; XV n = 2, R = cyclohexyl; XVI n = 2, R = cyclopentylmethyl; XVII n = 2, R = cyclohexylmethyl; XVIII n = 2, R = Ph; XIX n = 2, R = *p*-tolyl; XX n = 2, R = *p*-anisyl; XXI n = 2, R = benzyl, XXII n =2, R = phenetyl

The alkylation reaction of 4-oxo-2-thioxo-spiro(benzo[*h*]quinazoline-5,1'-cycloalkanes) is conducted experimentally in two stages: the addition of KOH to obtain the potassium salt, and then alkylation of this salt with an alkyl halide [3].

The charges on atoms (for the charge-controlled reactions) and π-electron partial densities (for the orbital-controlled reactions) were selected as indexes of reactivity.

The stable hydroxide ion will attack the atom carrying the highest positive charge (charge thermodynamic control). The calculated distributions of charges on the atoms are qualitatively of the same type for the molecules I-XXII. For all molecules, the lowest value of the charge on the $N_{(1)}$ nitrogen atom is characteristic (Table 1).

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TABLE 1. Data of Calculations for 3-Substituted 4-Oxo-2-thioxospiro(benzo[*h*]quinazoline-5,1'-cycloalkanes)

Molecule	Charge (π-electron population density of the atom on the HOMO)								T_{rev}, ΔH (kcal/mole)	ΔE, eV, E(HOMO) – E(LFMO)	Dipole moment, D
	$N_{(1)}$	$N_{(3)}$	S	O	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$			
1	2	3	4	5	6	7	8	9	10	11	12
I	0.196 (0.417)	0.076 (0.241)	−0.289 (0.710)	−0.338 (0.061)	−0.102 (0.017)	−0.071 (0.092)	−0.102 (0.045)	−0.080 (0.064)	12.1	−7.5	6.4
Ii	−0.244 (0.432)	0.052 (0.122)	−0.534 (0.753)	−0.472 (0.132)	−0.129 (0.001)	−0.112 (0.010)	−0.135 (0.0002)	−0.052 (0.011)	−42.8	−6.7	12.8
II	0.187 (0.339)	0.074 (0.179)	−0.303 (0.553)	−0.330 (0.029)	−0.103 (0.015)	−0.072 (0.076)	−0.102 (0.035)	−0.080 (0.055)	14.5	−7.5	5.5
IIi	−0.239 (0.434)	0.060 (0.117)	−0.531 (0.756)	−0.467 (0.139)	−0.129 (0.001)	−0.113 (0.011)	−0.135 (0.0001)	−0.052 (0.010)	−38.1	−6.7	11.2
III	0.157 (0.272)	0.053 (0.059)	−0.299 (0.206)	−0.305 (0.025)	−0.105 (0.008)	−0.074 (0.051)	−0.102 (0.025)	−0.080 (0.035)	10.2	−7.6	5.4
IIIi	−0.246 (0.444)	0.030 (0.093)	−0.536 (0.754)	−0.446 (0.126)	−0.130 (0.0005)	−0.113 (0.010)	−0.135 (0.0005)	−0.052 (0.009)	−40.7	−6.7	10.0
IV	0.157 (0.227)	0.048 (0.034)	−0.299 (0.160)	−0.309 (0.017)	−0.105 (0.006)	−0.074 (0.040)	−0.102 (0.019)	−0.080 (0.027)	5.5	−7.6	5.3
IVi	−0.249 (0.438)	0.019 (0.094)	−0.532 (0.746)	−0.446 (0.120)	−0.130 (0.0004)	−0.113 (0.010)	−0.135 (0.0005)	−0.052 (0.009)	−45.5	−6.7	9.6
V	0.187 (0.352)	0.077 (0.221)	−0.309 (0.661)	−0.334 (0.043)	−0.105 (0.011)	−0.072 (0.066)	−0.103 (0.031)	−0.081 (0.046)	−0.8	−7.5	5.3
Vi	−0.244 (0.436)	0.047 (0.100)	−0.533 (0.746)	0.461 (0.142)	−0.131 (0.002)	−0.112 (0.009)	−0.136 (0.001)	−0.051 (0.007)	−54.1	−6.7	9.0
VI	0.183 (0.335)	0.078 (0.151)	−0.307 (0.439)	−0.334 (0.070)	−0.103 (0.011)	−0.072 (0.064)	−0.102 (0.031)	−0.080 (0.045)	−6.8	−7.6	5.3
VIi	−0.239 (0.426)	0.053 (0.108)	−0.530 (0.741)	−0.466 (0.138)	−0.129 (0.001)	−0.112 (0.011)	−0.135 (0.0002)	−0.052 (0.011)	−59.8	−6.7	8.6
VII	0.143 (0.292)	0.133 (0.159)	−0.284 (0.411)	−0.291 (0.0002)	−0.106 (0.009)	−0.073 (0.054)	−0.103 (0.024)	−0.079 (0.038)	51.8	−7.5	5.0
VIIi	−0.233 (0.065)	0.139 (0.010)	−0.477 (0.073)	−0.432 (0.031)	−0.130 (0.0005)	−0.109 (0.003)	−0.134 (0.0001)	−0.049 (0.004)	0.6	−6.5	9.8

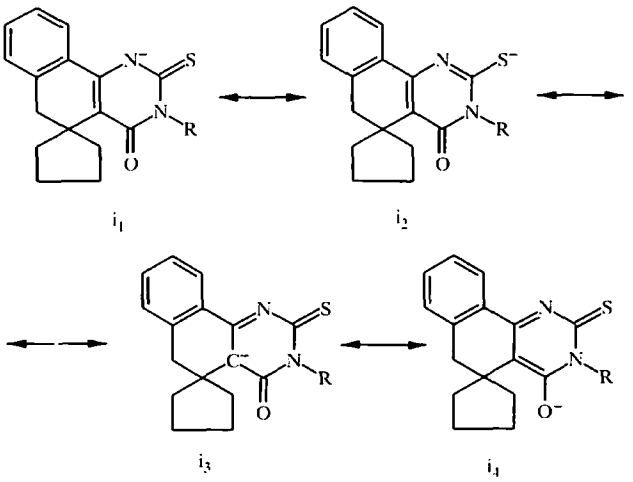
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
XV	0.156	0.047	−0.302	−0.309	−0.108	−0.073	−0.104	−0.080	−0.02	−7.6	5.6
	(0.134)	(0.020)	(0.039)	(0.001)	(0.001)	(0.018)	(0.010)	(0.011)			
XVi	−0.250	0.016	−0.532	−0.443	−0.132	−0.112	−0.136	−0.052	−50.7	−6.7	11.7
	(0.434)	(0.091)	(0.748)	(0.118)	(0.001)	(0.009)	(0.001)	(0.008)			
XVI	0.190	0.084	−0.306	−0.341	−0.108	−0.070	−0.104	−0.081	−7.2	−7.5	5.2
	(0.327)	(0.197)	(0.548)	(0.036)	(0.008)	(0.059)	(0.029)	(0.041)			
XVIi	−0.236	0.058	−0.531	0.465	−0.134	−0.110	−0.138	−0.051	−62.0	−6.7	9.0
	(0.409)	(0.111)	(0.734)	(0.124)	(0.001)	(0.009)	(0.0004)	(0.008)			
XVII	0.186	0.082	−0.302	−0.342	−0.109	−0.071	−0.105	−0.081	−13.4	−7.5	5.0
	(0.327)	(0.180)	(0.227)	(0.043)	(0.008)	(0.058)	(0.030)	(0.042)			
XVIIi	−0.238	0.057	−0.533	−0.465	−0.135	−0.109	−0.138	−0.051	−67.8	−6.7	8.8
	(0.386)	(0.106)	(0.571)	(0.121)	(0.002)	(0.008)	(0.0003)	(0.008)			
XVIII	0.184	0.209	−0.287	−0.323	−0.105	−0.070	−0.103	−0.078	54.2	−7.1	5.5
	(0.088)	(0.057)	(0.292)	(0.005)	(0.003)	(0.001)	(0.001)	(0.001)			
XVIIIi	−0.223	0.164	−0.472	−0.449	−0.129	−0.108	−0.135	−0.049	−3.5	−6.5	9.9
	(0.013)	(0.031)	(0.418)	(0.016)	(0.002)	(0.004)	(0.0001)	(0.003)			
XIX	0.185	0.216	−0.291	−0.325	−0.105	−0.070	−0.103	−0.078	44.8	−7.0	5.2
	(0.095)	(0.071)	(0.261)	(0.008)	(0.003)	(0.0005)	(0.002)	(0.002)			
XIXi	−0.223	0.165	−0.474	−0.450	−0.129	−0.108	−0.135	−0.049	−12.9	−6.5	9.1
	(0.004)	(0.037)	(0.393)	(0.016)	(0.002)	(0.004)	(0.0001)	(0.002)			
XX	0.193	0.236	−0.300	−0.334	−0.104	−0.069	−0.104	−0.078	16.5	−7.0	4.9
	(0.074)	(0.049)	(0.305)	(0.0004)	(0.004)	(0.004)	(0.0001)	(0.001)			
XXi	−0.222	0.172	−0.476	−0.449	−0.130	−0.108	−0.135	−0.049	−41.7	6.5	7.4
	(0.039)	(0.031)	(0.334)	(0.0005)	(0.002)	(0.004)	(0.0003)	(0.003)			
XXI	0.173	0.066	−0.291	−0.350	−0.104	−0.071	−0.103	−0.081	56.0	−7.0	5.3
	(0.304)	(0.181)	(0.530)	(0.027)	(0.005)	(0.040)	(0.019)	(0.029)			
XXIi	−0.173	0.236	−0.584	−0.474	−0.112	−0.109	−0.146	−0.046	6.7	−6.5	8.6
	(0.245)	(0.087)	(0.676)	(0.057)	(0.0001)	(0.001)	(0.001)	(0.001)			
XXII	0.184	0.055	−0.281	−0.386	−0.105	−0.074	−0.101	−0.088	66.8	−7.1	5.2
	(0.207)	(0.131)	(0.405)	(0.006)	(0.007)	(0.062)	(0.030)	(0.038)			
XXIIi	−0.239	0.030	−0.539	−0.472	−0.131	−0.109	−0.132	−0.061	11.3	−6.5	9.6
	(0.045)	(0.030)	(0.047)	(0.019)	(0.005)	(0.001)	(0.001)	(0.001)			

TABLE I (continued)

1	2	3	4	5	6	7	8	9	10	11	12
XV	0.156	0.047	−0.302	−0.309	−0.108	−0.073	−0.104	−0.080	−0.02	−7.6	5.6
	(0.134)	(0.020)	(0.039)	(0.001)	(0.001)	(0.018)	(0.010)	(0.011)			
XVi	−0.250	0.016	−0.532	−0.443	−0.132	−0.112	−0.136	−0.052	−50.7	−6.7	11.7
	(0.434)	(0.091)	(0.748)	(0.118)	(0.001)	(0.009)	(0.001)	(0.008)			
XVI	0.190	0.084	−0.306	−0.341	−0.108	−0.070	−0.104	−0.081	−7.2	−7.5	5.2
	(0.327)	(0.197)	(0.548)	(0.036)	(0.008)	(0.059)	(0.029)	(0.041)			
XVIi	−0.236	0.058	−0.531	0.465	−0.134	−0.110	−0.138	−0.051	−62.0	−6.7	9.0
	(0.409)	(0.111)	(0.734)	(0.124)	(0.001)	(0.009)	(0.0004)	(0.008)			
XVII	0.186	0.082	−0.302	−0.342	−0.109	−0.071	−0.105	−0.081	−13.4	−7.5	5.0
	(0.327)	(0.180)	(0.227)	(0.043)	(0.008)	(0.058)	(0.030)	(0.042)			
XVIIi	−0.238	0.057	−0.533	−0.465	−0.135	−0.109	−0.138	−0.051	−67.8	−6.7	8.8
	(0.386)	(0.106)	(0.571)	(0.121)	(0.002)	(0.008)	(0.0003)	(0.008)			
XVIII	0.184	0.209	−0.287	−0.323	−0.105	−0.070	−0.103	−0.078	54.2	−7.1	5.5
	(0.088)	(0.057)	(0.292)	(0.005)	(0.003)	(0.001)	(0.001)	(0.001)			
XVIIIi	−0.223	0.164	−0.472	−0.449	−0.129	−0.108	−0.135	−0.049	−3.5	−6.5	9.9
	(0.013)	(0.031)	(0.418)	(0.016)	(0.002)	(0.004)	(0.0001)	(0.003)			
XIX	0.185	0.216	−0.291	−0.325	−0.105	−0.070	−0.103	−0.078	44.8	−7.0	5.2
	(0.095)	(0.071)	(0.261)	(0.008)	(0.003)	(0.0005)	(0.002)	(0.002)			
XIXi	−0.223	0.165	−0.474	−0.450	−0.129	−0.108	−0.135	−0.049	−12.9	−6.5	9.1
	(0.004)	(0.037)	(0.393)	(0.016)	(0.002)	(0.004)	(0.0001)	(0.002)			
XX	0.193	0.236	−0.300	−0.334	−0.104	−0.069	−0.104	−0.078	16.5	−7.0	4.9
	(0.074)	(0.049)	(0.305)	(0.0004)	(0.004)	(0.004)	(0.0001)	(0.001)			
XXi	−0.222	0.172	−0.476	−0.449	−0.130	−0.108	−0.135	−0.049	−41.7	6.5	7.4
	(0.039)	(0.031)	(0.334)	(0.0005)	(0.002)	(0.004)	(0.0003)	(0.003)			
XXI	0.173	0.066	−0.291	−0.350	−0.104	−0.071	−0.103	−0.081	56.0	−7.0	5.3
	(0.304)	(0.181)	(0.530)	(0.027)	(0.005)	(0.040)	(0.019)	(0.029)			
XXIi	−0.173	0.236	−0.584	−0.474	−0.112	−0.109	−0.146	−0.046	6.7	−6.5	8.6
	(0.245)	(0.087)	(0.676)	(0.057)	(0.0001)	(0.001)	(0.001)	(0.001)			
XXII	0.184	0.055	−0.281	−0.386	−0.105	−0.074	−0.101	−0.088	66.8	−7.1	5.2
	(0.207)	(0.131)	(0.405)	(0.006)	(0.007)	(0.062)	(0.030)	(0.038)			
XXIIi	−0.239	0.030	−0.539	−0.472	−0.131	−0.109	−0.132	−0.061	11.3	−6.5	9.6
	(0.045)	(0.030)	(0.047)	(0.019)	(0.005)	(0.001)	(0.001)	(0.001)			

Starting from the theory of resonance, the corresponding anions of the molecules I-XXII after deprotonation with alkali may have the following resonance structures:



Calculation of the lengths and order of bonds in the corresponding anions of the molecules Ii-XXIIi showed that the highest contribution to the delocalization of the negative charge is made by the resonance structures i_2 and i_4.

Calculation of the population density of the molecular orbitals by the method of CMC for the anions of the molecules Ii-XXIIi indicates that the highest partial π-orbital density on the HOMO is centered on the sulfur atom (Table 1), so indicating its high nucleophilicity. The atoms of sulfur and oxygen have the highest, and practically the same, charge density. Therefore, the selection of the π-orbital density on the HOMO as the index of reactivity at the stage of alkylation of the ion (orbital kinetic control) leads, according to the calculations, to a single alkylation route – alkylation at the sulfur atom.

The selection of the charge on the atom as the index of reactivity at the stage of deprotonation, and of the π-orbital partial density on the HOMO at the stage of alkylation for the whole series of 4-oxo-2-thioxo-spiro(benzo[*h*]quinazoline-5,1'-cycloalkanes), corresponds completely with experimental data for the alkylation of the compounds XII, XIX, and XXI [4].

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