Chemistry of Heterocyclic Compounds, Vol. 31, No. 11, 1995

DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES.

1. QUANTUM-CHEMICAL STUDY OF DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES IN ELECTROPHILIC SUBSTITUTION REACTIONS

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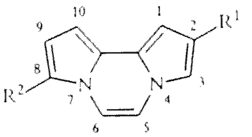
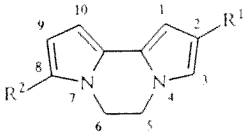
The semiempirical quantum-chemical method PM3 has been used in a study of the electronic and spatial structure of dipyrrolo[1,2-a; 2′,1′-c]pyrazines and 5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazines, and also their reactivities in electrophilic substitution reactions (protonation, acylation).

The pyrrole fragment enters into the composition of many natural compounds and biologically active substances that have become the objects of intensive theoretical investigation. One heterocyclic system that has received little attention is the dipyrrolo[1,2-a; 2′,1′-c]pyrazine system, which contains pyrrole rings with excess π-electrons and a pyrazine ring with a deficiency of π-electrons [1]. No previous quantum-chemical studies have been performed on dipyrrolo[1,2-a; 2′,1′-c]pyrazines. At the same time, quantum-chemical investigation of substitution reactions in derivatives of dipyrrolo[1,2-a; 2′,1′-c]pyrazines (I) and 5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazines (II) are of definite interest in the overall plan of comparing calculated and experimental data characterizing the reactivities of different positions of 14-electron and 12-electron (hydrogenated) systems. Theoretical analysis of the relationships that are found is an important step in explaining the selectivity of electrophilic attack in heterocyclic compounds of this type.



Ia-c



IIa-c

I, II a $R^1 = R^2 = H$; b $R^1 = Me$, $R^2 = H$; c $R^1 = R^2 = Me$

Here we are reporting on a quantum-chemical study of the electronic structure and reactivity of dipyrrolo[1,2-a; 2′,1′-c]pyrazines in electrophilic substitution reactions. As a means of investigating the electronic structure and reactivity of these compounds, we used the semiempirical PM3 method. Calculations performed by this method on a large number of compounds have shown that of all the existing semiempirical methods, this one gives results that are closest to those obtained by *ab initio* methods [2, 3]. Our initial calculations for unsubstituted dipyrrolo[1,2-a; 2′,1′-c]pyrazines showed that the molecule of Ia is practically planar. For the molecule of IIa, the $C_{(5)}$-$C_{(6)}$ bond deviates from the plane of the two pyrroles by 15°.

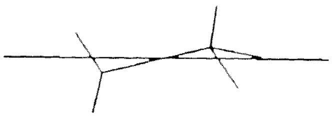


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TABLE 1. Bond Lengths, Bond Orders, and Heat of Formation of Dipyrrolo[1,2-a; 2',1'-c]pyrazines and Their Cations

Compound	Bond No	$C_{(1)}-C_{(2)}$	$C_{(2)}-C_{(3)}$	$C_{(3)}-N_{(4)}$	$N_{(4)}-C_{(5)}$	$C_{(5)}-C_{(6)}$	$C_{(6)}-N_{(7)}$	$N_{(7)}-C_{(8)}$	$C_{(8)}-C_{(9)}$	$C_{(9)}-C_{(10)}$	$C_{(10)}-C_{(11)}$	$C_{(11)}-C_{(12)}$	$C_{(1)}-C_{(12)}$	$N_{(7)}-C_{(11)}$	$N_{(4)}-C_{(12)}$	H_f, kcal
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ia	Length	1,42	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,42	1,39	1,43	1,38	1,42	1,42	74,4
	Order	1,30	1,54	1,21	1,08	1,73	1,08	1,21	1,54	1,31	1,49	1,07	1,50	1,15	1,15	
Ib	Length	1,42	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,42	1.39	1,42	1,39	1,42	1,42	65,0
	Order	1,23	1,52	1,20	1,09	1,73	1,08	1,21	1,55	1,31	1,49	1,07	1,49	1,15	1,15	
Ic	Length	1,42	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,42	1,39	1,43	1,39	1,42	1,42	55,4
	Order	1,29	1,52	1,20	1,08	1,73	1,08	1,19	1,51	1,31	1,49	1,07	1,49	1,15	1,15	
IIa	Length	1,42	1,39	1,40	1,47	1,53	1,47	1,40	1,39	1,42	1,39	1,43	1,39	1,42	1,41	60,6
	Order	1,29	1,52	1,20	1,08	0,98	1,08	1,19	1,51	1,31	1,49	1,07	1,49	1,15	1,15	
IIb	Length	1,42	1,39	1,40	1,47	1,53	1,47	1,40	1,39	1,31	1,39	1,43	1,39	1,41	1,41	63,3
	Order	1,42	1,52	1,20	1,08	0,98	1,08	1,19	1,51	1,31	1,49	1,07	1,49	1,15	1,15	
IIc	Length	1,43	1,39	1,40	1,47	1,54	1,47	1,41	1,39	1,42	1,39	1,43	1,39	1,41	1,41	67,5
	Order	1,29	1,52	1,22	0,97	0,98	0,97	1,19	1,53	1,30	1,51	1,04	1,50	1,18	1,18	
Va	Length	1,43	1,39	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	30,0
	Order	1,29	1,42	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
Vb	Length	1,42	1,40	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	11,5
	Order	1,33	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
Vc	Length	1,43	1,40	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	-120,7
	Order	1,29	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
Vd	Length	1,42	1,40	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	-130,2
	Order	1,33	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
VIa	Length	1,42	1,41	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	17,4
	Order	1,35	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
VIb	Length	1,42	1,41	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	-127,6
	Order	1,37	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
VIc	Length	1,42	1,40	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	-134,9
	Order	1,33	1,44	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
VId	Length	1,42	1,40	1,41	1,41	1,36	1,41	1,41	1,38	1,42	1,39	1,42	1,37	1,41	1,41	-332,3
	Order	1,34	1,42	1,17	1,09	1,73	1,08	1,21	1,49	1,32	1,49	1,08	1,46	1,15	1,15	
Ia	Length	1,43	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,43	1,40	1,44	1,40	1,42		257,5
1H- cation	Order	1,05	1,11	1,54	1,06	1,69	1,15	1,17	1,59	1,27	1,52	1,06	1,10	1,08		
2H- cation	Length	1,43	1,39	1,40	1,41	1,39	1,41	1,40	1,39	1,43	1,40	1,44	1,40	1,42		254,2
	Order	1,00	1,86	1,02	1,12	1,69	1,12	1,35	1,39	1,46	1,31	1,29	1,00	1,04		
3H- cation	Length	1,43	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,43	1,40	1,44	1,40	1,42		251,7
	Order	1,66	1,06	1,01	1,09	1,70	1,12	1,26	1,50	1,35	1,42	1,16	1,21	1,07		
5H- cation	Length	1,42	1,39	1,39	1,47	1,49	1,31	1,45	1,36	1,47	1,36	1,42	1,39	1,48		271,6
	Order	1,34	1,52	1,25	0,97	1,01	1,77	1,01	1,77	1,08	1,71	1,08	1,44	0,96		
IIa	Length	1,36	1,51	1,49	1,40	1,36	1,40	1,38	1,41	1,40	1,41	1,39	1,45	1,45		220,0
1H- cation	Order	1,01	1,86	1,02	0,96	0,98	0,96	1,39	1,38	1,48	1,28	1,23	1,00	1,09		
2H -cation	Length	1,43	1,39	1,40	1,41	1,36	1,41	1,40	1,39	1,43	1,40	1,44	1,40	1,42		220,9
	Order	1,02	1,03	1,73	0,96	0,98	0,97	1,24	1,53	1,33	1,46	1,06	1,73	1,13		
3H- cation	Length	1,40	1,41	1,37	1,40	1,36	1,40	1,50	1,50	1,34	1,45	1,39	1,41	1,38		213,7
	Order	1,81	1,01	0,95	0,95	0,98	0,96	1,38	1,38	1,48	1,28	1,23	1,08	1,10		
III	Length	1,36	1,51	1,49	1,40	1,36	1,40	1,38	1,41	1,40	1,41	1,39	1,45	1,45		216,5
	Order	1,76	0,99	0,96	1,12	1,70	1,11	1,34	1,40	1,45	1,32	1,26	1,10	1,05		
IV	Length	1,40	1,41	1,37	1,40	1,36	1,40	1,50	1,50	1,34	1,45	1,39	1,41	1,38		218,0
	Order	1,43	1,36	1,35	1,12	1,69	1,13	0,96	1,01	1,82	1,08	1,28	1,32	1,35		

TABLE 2. Electron Density on Atoms of Dipyrrolo[1,2-a; 2',1'-c]pyrazines

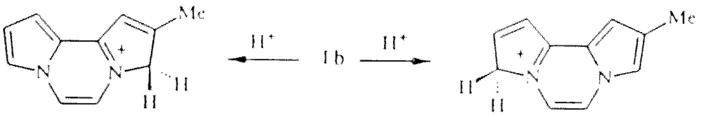
Com - pound	Atom No.	1	2	3	4	5	6	7	8	9	10	11	12
1	2	3	4	5	6	7	8	9	10	11	12	13	14
Ia	Charge on atom	0,15	0,13	0,30	0,41	0,20	0,21	0,41	0,30	0,13	0,15	0,16	0,16
	π density in HOMO	0,34	0,20	0,42	0,08	0,05	0,06	0,07	0,43	0,19	0,35	0,39	0,39
	π density in LUMO	0,05	0,23	0,22	0,04	0,57	0,57	0,04	0,22	0,23	0,06	0,25	0,24
Ib	Charge on atom	0,14	0,11	0,30	0,42	0,20	0,21	0,41	0,30	0,13	0,15	0,16	0,16
	π density in HOMO	0,26	0,26	0,42	0,15	0,01	0,11	0,02	0,42	0,15	0,38	0,36	0,39
	π density in LUMO	0,05	0,24	0,22	0,04	0,57	0,57	0,04	0,22	0,23	0,05	0,24	0,24
Ic	Charge on atom	0,14	0,11	0,31	0,42	0,21	0,21	0,42	0,27	0,13	0,14	0,17	0,16
	π density in HOMO	0,24	0,25	0,40	0,16	0,01	0,12	0,01	0,44	0,17	0,37	0,37	0,37
	π density in LUMO	0,04	0,24	0,21	0,04	0,57	0,57	0,03	0,23	0,24	0,06	0,25	0,24
IIa	Charge on atom	0,13	0,16	0,27	0,28	0,09	0,09	0,28	0,27	0,16	0,13	0,16	0,16
	π density in HOMO	0,28	0,19	0,36	0,08	0,01	0,01	0,09	0,38	0,20	0,29	0,36	0,35
	π density in LUMO	0,29	0,08	0,30	0,27	0,01	0,04	0,30	0,31	0,08	0,31	0,32	0,31
IIb	Charge on atom	0,14	0,13	0,27	0,72	0,09	0,09	0,71	0,26	0,16	0,14	0,15	0,15
	π density in HOMO	0,24	0,22	0,37	0,11	0,01	0,01	0,09	0,36	0,19	0,29	0,34	0,35
	π density in LUMO	0,29	0,08	0,30	0,26	0,01	0,01	0,30	0,31	0,08	0,30	0,32	0,30
IIc	Charge on atom	0,13	0,13	0,27	0,30	0,09	0,09	0,28	0,24	0,16	0,13	0,15	0,15
	π density in HOMO	0,25	0,21	0,36	0,11	0,01	0,01	0,07	0,38	0,22	0,29	0,36	0,34
	π density in LUMO	0,29	0,07	0,30	0,28	0,03	0,04	0,31	0,33	0,11	0,30	0,34	0,29
Va	Charge on ato.	0,16	0,05	0,37	0,47	0,21	0,21	0,43	0,30	0,13	0,14	0,18	0,14
	π density in HOMO	0,25	0,23	0,41	0,17	0,01	0,13	0,01	0,44	0,15	0,38	0,37	0,37
	π density in LUMO	0,07	0,32	0,30	0,11	0,46	0,53	0,11	0,12	0,20	0,03	0,16	0,34

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Vb	Charge on atom	0,16	0,05	0,37	0,47	0,21	0,21	0,43	0,27	0,14	0,13	0,19	0,14
	π density in HOMO	0,24	0,22	0,39	0,17	0,01	0,13	0,02	0,45	0,18	0,37	0,38	0,34
	π density in LUMO	0,08	0, 32	0,29	0,11	0,46	0,53	0,11	0,13	0,21	0,03	0,17	0,34
Vc	Charge on atom	0,16	0,03	0,40	0,48	0,23	0,18	0,41	0,29	0,13	0,13	0,18	0,14
	π density in HOMO	0,22	0,23	0,39	0,20	0,04	0,15	0,04	0,44	0,12	0,41	0,38	0,36
	π density in LUMO	0,07	0,29	0,27	0,06	0,51	0,57	0,10	0,16	0,22	0,01	0,20	0,32
Vd	Charge on atom	0,16	0,03	0,40	0,48	0,23	0,19	0,42	0,26	0,13	0,13	0,19	0,13
	π density in HOMO	0,23	0,21	0,37	0,19	0,03	0,14	0,04	0,46	0,17	0,38	0,39	0,33
	π density in LUMO	0,06	0,29	0,27	0,06	0,51	0,56	0,09	0,17	0,22	0,01	0,21	0,31
VIa	Charge on atom	0,16	0,07	0,34	0,34	0,11	0,09	0,29	0,26	0,16	0,12	0,18	0,13
	π density in HOMO	0,27	0,19	0,40	0,12	0,01	0,01	0,09	0,39	0,22	0,29	0,39	0,35
	π density in LUMO	0,18	0,24	0,34	0,33	0,02	0,02	0,23	0,24	0,03	0,27	0,22	0,35
VIb	Charge on atom	0,16	0,08	0,33	0,66	0,11	0,10	0,70	0,23	0,16	0,12	0,18	0,13
	π density in HOMO	0,23	0,16	0,33	0,11	0,01	0,01	0,07	0,38	0,22	0,27	0,37	0,29
	π density in LUMO	0,15	0,23	0,27	0,31	0,01	0,02	0,22	0,22	0,03	0,24	0,19	0,30
VIc	Charge on atom	0,15	0,05	0,36	0,33	0,11	0,09	0,28	0,25	0,16	0,12	0,18	0,11
	π density in HOMO	0,25	0,16	0,36	0,12	0,01	0,01	0,08	0,39	0,21	0,28	0,39	0,30
	π density in LUMO	0,05	0,08	0,03	0,09	0,04	0,01	0,05	0,05	0,01	0,05	0,02	0,07
VId	Charge on atom	0,13	0,04	0,34	0,34	0,11	0,10	0,30	0,22	0,10	0,22	0,06	0,16
	π density in HOMO	0,23	0,15	0,35	0,11	0,01	0,01	0,10	0,37	0,26	0,26	0,32	0,32
	π density in LUMO	0,16	0,20	0,23	0,27	0,02	0,01	0,23	0,13	0,08	0,23	0,29	0,24

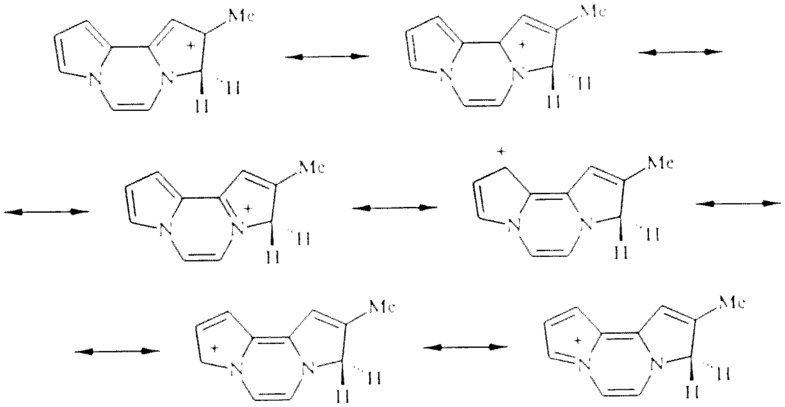
These calculations indicate that in the molecules of I and II, the α-pyrrole positions have the greatest π-electron access in the HOMO. For compounds Ia and IIa, initial attack must take place at position 3 or 8. Calculations of the heat of cation formation in the protonation of compounds Ia and IIa at positions 1, 2, and 3 show that the addition of a proton at position 3 results in the most stable 3H-cation. Compounds Ic and IIc have only one free α-pyrrole position having a high π-electron density; this should lead to preferential electrophilic attack at this position.

In compounds Ib and IIb, both α-positions of the pyrrole rings are free for electrophilic attack, and the π-orbital densities in the HOMO of positions 3 and 8 are practically identical. However, a comparison of the calculated heats of formation of the cations in protonation of compounds Ib and IIb suggests that the cations formed by electrophilic attack at position 3 are more stable than those formed by attack at position 8. For example, the heat of formation of the cation III is 216.5 kcal/mole, whereas that of cation IV is 218.0 kcal/mole. Thus, for compounds Ib and IIb we should expect preferential electrophilic attack at position 3.

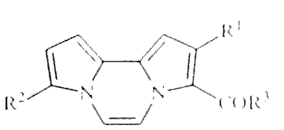


III IV

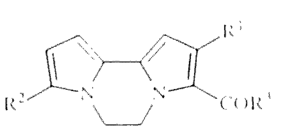
Calculations of the bond orders of the cations formed by electrophilic attack show that the positive charge is delocalized over both pyrrole rings. This is indicated by the set of resonance structures shown below, corresponding to the calculated bond orders, for example for cation III:



Thus, we have established that the initial electrophilic attack in dipyrrolo[1,2-a; 2′,1′-c]pyrazines must take place at one of the α-pyrrole positions. Hence we can assume that as a result of acetylation or trifluoroacetylation of compounds Ib,c and IIb,c, the principal products will be the monoacyl derivatives Va-d and VIa-d with the acyl substituent in position 3.



Va-d



VIa-d

V, VI a $R^1 = R^3 = CH_3$, $R^2 = H$, b $R^1 = R^2 = R^3 = CH_3$, c $R^1 = CH_3$, $R^2 = H$, $R^3 = CF_3$,
d $R^1 = R^2 = CH_3$, $R^3 = CF_3$

Under appropriate conditions, the acylation may lead to diacyl derivatives. In order to establish the positions that are active for electrophilic attack on the derivatives V and VI, we calculated π-electron partial densities in the HOMO. These calculations established that for the monoacyl derivatives Va-c and VIa-c, the greatest π-orbital density is that of the free α-position of the second pyrrole ring (position 8); this should lead to preferential formation of 3,8-diacyl derivatives.

The free positions of the pyrrole rings (positions 1, 9, 10) of the 5,6-dihydro-2,8-dimethyl-3-acyldipyrrolo[1,2-a; 2',1'-c]pyrazines VIb-d have practically identical π-orbital densities in the HOMO; this may lead to a mixture of 1,3-, 3,9-, and 3,10-diacyl derivatives. In the case of the 2,8-dimethyl-3-acyldipyrrolo[1,2-a; 2',1'-c]pyrazines Vb-d, the greatest π-orbital density in the HOMO is concentrated on the $C_{(10)}$ atom; and we may expect the formation of the diacyl derivative of the 3,10-isomer as the principal product.

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