Chemistry of Natural Compounds, Vol. 32, No. 6, 1996

QUANTUM-CHEMICAL STUDY OF THE SPIROPIPERIDINE ALKALOIDS OF *Nitraria*.

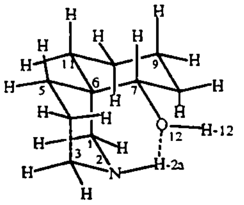
I. INTRAMOLECULAR HYDROGEN BONDS AND CHEMICAL PROPERTIES OF NITRAMINE AND ISONITRAMINE

M. A. Ashirmatov[a] and A. A. Ibragimov[b]

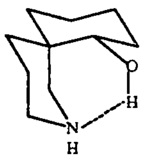
UDC 539.19

Preferential conformations have been found for nitramine and isonitramine on the basis of quantum-chemical calculations of various conformational states. The results obtained have been correlated with spectral characteristics and chemical properties.

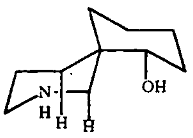
Nitramine (1-3) and isonitramine (4-6) are spiroisomers [1]. They may assume conformations with intramolecular hydrogen bonds (intraHBs) of the N—H···O type ((1) and (4)) or with intraHBs of the O—H···N type ((2) and (5)) and also without intraHBs ((3) and (6)).



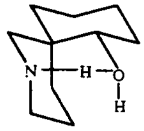
1



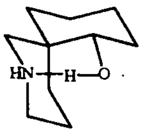
2



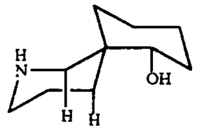
3



4



5



6

An x-ray structural analysis of crystalline salts has enabled the conformation of the cations to be determined as (3) and (6), i.e., without intraHBs [2]. However, in the liquid phase the free bases exist preferentially in conformations with intraHBs ((1) and (4), or (2) and (5)), as is shown by a shift of the absorption band of active hydrogen in IR spectra into the 3200-3235 cm^{-1} region, which is retained on dilution [1].

In order to establish the nature of the hydrogen bond and its energetic contribution to the stabilization of the molecule, to determine the charges on the atoms and the bond energies, and to correlate the results obtained with other properties of the alkaloids under investigation, we have made a quantum-chemical calculation in the MO LCAO approximation by the MINDO/3, MNDO, AM1, and PM3 methods of the conformers of nitramine (1-3) and of isonitramine (4-6). The geometric parameters

---

a) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 40 64 75. *b*) Fergana State University. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 897-902, November-December, 1996. Original article submitted May 6, 1996.

0009-3130/96/3206-0882$15.00

TABLE 1. Enthalpies of Formation (ΔH_f) of Nitramine and Isonitramine Molecules With H-Bonds and Without Them (kcal/mole)

Method	Nitramine			Isonitramine		
	O···H-N (1)	O-H···N (2)	without intraHBs (3)	O···H-N (4)	O-H···N (5)	without intraHBs (6)
MINDO/3	-56.5868	-56.5838	-53.8432	-56.3518	-56.3549	-53.8553
MNDO	-60.1284	-60.1805	-60.2232	-59.9560	-60.5606	-59.8099
AM1	-84.4482	-82.6483	-81.2276	-84.3674	-81.4112	-83.0770
PM3	-72.1504	-72.6881	-70.5453	-72.2033	-71.2404	-73.8692

TABLE 2. Energy Characteristics of Some Types of Hydrogen Bonds

Class of compounds	Type of bonds	ΔH_f, kcal/mole
Mercaptans	SH...S	1.0÷2.0
Amines	NH...N	1.0÷4.0
Amides	NH...N	2.0÷9.0
Alcohols	OH...O	3.0÷10.0
Phenols	OH...O	3.0÷8.0
Carboxylic acids	OH...O	4.0÷12.0
$H_3N...HOH$	NH...O	4.0÷9.0
$H_2O...HNH_2$	OH...N	2.0÷6.0

of the forms analyzed (**1-6**) were obtained by the full optimization of the whole geometry of the molecule. In calculation by the AMPAC program we used the PRECISE option, increasing the accuracy of self-consistency and optimization 10- to 100-fold [3].

Analysis of the figures obtained (Table 1) showed some discrepancies in the final results calculated by the various methods. The AM1 method gave results agreeing well with those obtained previously by experiment [1]. They showed that, for the molecules of both alkaloids, conformations with intraHBs of the N—H···O type ((**1**) and (**4**)) are preferential.

A more detailed analysis showed that the spiropiperidines are, in fact, described most accurately by the AM1 method. The energy of the hydrogen bond in nitramine is 3.22 and in isonitramine 1.29 kcal/mole, which agree well with literature figures for related compounds (Table 2) [4].

Table 3 gives the values of the charges calculated by the AM1 method for all 31 atoms of each structure (**1-6**) and also the carbon-13 and hydrogen-1 chemical shifts (CSs) of the signals concerned in the NMR spectra of nitramine and isonitramine. With allowance for the different states of the molecules under the conditions of NMR (solution in $CDCl_3$) and of calculation (isolated molecules) and also of the influence on CSs not only of the electron density but also of various steric interactions, a fully correct tendency is observed to an increase in screening with a rise in the negative charge, and conversely. Thus, the atoms with the lowest relative electron density — C_7, C_1, C_3, C_5, C_{11}, C_{12}, H_2, H_{1e}, H_{1a}, H_{3e}, etc. — are the most descreened and exhibit weak-field signals. Analogous results of calculations by the PM3 method (see Table 3) do not give satisfactory convergence of the results of spectroscopic and quantum-chemical investigations. This confirms our assumptions concerning the optimum nature of the use of AM1 for this class of substances.

The closeness of the link between the charges on the C and H atoms (q), on the one hand, and the chemical shifts (δ), on the other, can be evaluated objectively by calculating the coefficient of pair correlation ($r_{q\delta}$). The closer the absolute value of the correlation coefficient to unity the stronger is the linear link between q and δ.

It follows from Table 4 that the charges calculated by the AM1 method for the C atoms correlate well with the chemical shifts of these atoms. As was to be expected, no clear correlation was observed for protons (it is known that the chemical shifts of protons depend greatly on other factors: solvent and temperature). The degree of closeness of the link between charges and chemical shifts is particularly small when $r_{q\delta}$ is calculated without allowance for the hydrogen atoms of —OH and —NH groups. In addition to this, it must be mentioned the coefficients of pair correlation obtained by the AM1 method are far closer to unity than in the case of the PM3 method.

A consideration of the dynamics of the change in the charges on the atoms forming the intraHB chain (N—H—O) permits a number of important conclusions to be drawn. The electron density on the nitrogen atom falls in the sequence (**2**)(**5**)→(**3**)(**6**)→(**1**)(**4**). It is lowest in the most stable conformations (**1**) and (**4**) with intraHBs of the N—H···O type because of a displacement in the direction of the oxygen atom through the negative inductive effect of the latter (see Table 3). This correlates well with results on the reactivities of nitramine and isonitramine. Thus, they are scarcely acetylated after two days

TABLE 3. Full Charges Calculated by the AM1 Method (in electron units, e) and Chemical Shifts of (1)-(6)

Atom	Nitramine				Isonitramine			
	N-H...O (1)	O-H...N (2)	without H-bond (3)	CS, ppm	N-H...O (4)	O-H...N (5)	without H-bond (6)	CS, ppm
C-1	-0.067	-0.071	-0.071	52.0	-0.074	-0.076	-0.074	60.0
N-2	-0.271	-0.308	-0.298	-	-0.270	-0.310	-0.297	
C-3	-0.082	-0.073	-0.074	46.7	-0.083	-0.075	-0.075	47.3
C-4	-0.192	-0.163	-0.154	23.2	-0.191	-0.163	-0.154	23.1
C-5	-0.142	-0.143	-0.153	37.4	-0.136	-0.139	-0.150	28.7
C-6	-0.075	-0.073	-0.031	36.1	-0.076	-0.075	-0.070	36.2
C-7	0.042	0.049	0.033	77.0	0.041	0.055	0.031	79.8
C-8	-0.192	-0.190	-0.189	32.0	-0.191	-0.156	-0.187	29.8
C-9	-0.151	-0.153	-0.152	23.9	-0.152	-0.156	-0.152	24.3
C-10	-0.158	-0.158	-0.157	21.1	-0.158	-0.156	-0.159	20.4
C-11	-0.150	-0.152	-0.149	36.3	-0.150	-0.150	-0.145	36.3
O-12	-0.335	-0.328	-0.330	-	-0.333	-0.335	-0.325	-
H-1e	0.089	0.090	0.087	3.34	0.086	0.087	0.089	2.88
H-1a	0.088	0.050	0.072	2.37	0.089	0.050	0.067	2.44
H-2	0.160	0.157	0.154	3.98	0.159	0.159	0.157	3.87
H-3e	0.087	0.088	0.084	2.95	0.087	0.088	0.087	2.92
H-3a	0.084	0.043	0.046	2.58	0.084	0.045	0.045	2.54
H-4a	0.100	0.115	0.087	-	0.100	0.111	0.092	-
H-4e	0.079	0.080	0.080	-	0.079	0.080	0.080	-
H-5e	0.076	0.085	0.077	0.9-2.1	0.079	0.090	0.08[illegible]	2.14
H-5a	0.077	0.073	0.098	-	0.076	0.073	0.073	-
H-7a	0.070	0.105	0.072	3.48	0.069	0.064	0.114	3.57
H-8e	0.076	0.093	0.075	-	0.076	0.094	0.092	-
H-8a	0.095	0.082	0.094	-	0.096	0.093	0.079	-
H-9a	0.079	0.081	0.078	-	0.080	0.079	0.081	-
H-9e	0.083	0.081	0.080	-	0.082	0.082	0.081	-
H-10a	0.085	0.079	0.086	-	0.084	0.083	0.078	-
H-10e	0.082	0.080	0.080	-	0.081	0.079	0.081	-
H-11e	0.086	0.081	0.104	-	0.086	0.079	0.081	-
H-11a	0.080	0.083	0.073	-	0.080	0.080	0.100	-
H-12	0.199	0.217	0.198	3.98	0.199	0.222	0.196	3.87

TABLE 4. Coefficient of Pair Correlation $r_{q\delta}$ between the Charges on the Atoms and the Chemical Shifts of Compounds (1)-(6)

Method	Atom	1	2	3	4	5	6
AM1	C	0.914	0.909	0.832	0.912	0.931	0.910
PM3	C	0.832	0.802	0.778	0.816	0.799	0.800

in acetic anhydride, which is connected with a lowering of the basicity of the nitrogen atom. Under analogous conditions, the related alkaloid nitraramine, for example, which has no intraHBs, readily gives a N-acetyl derivative [5]. On the addition of pyridine to the reaction medium, nitramine and isonitramine give N-acetyl derivatives, while on heating in the presence of *p*-toluenesulfonic acid they form N,O-diacetyl derivatives [2]. Displacement of the electron density in the direction of the oxygen through the covalent N—H bond is obviously more favorable than through the N···H hydrogen bond (2) as has sometimes been stated [6].

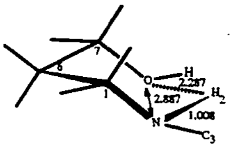
An analysis of torsional angles shows that the six-membered ring formed by the intraHB in conformations (1) and (4) is close to an ideal chair. The covalent N—H bond participating in the formation of the hydrogen bond (conformations (1) and (4)) is lengthened by an average of 0.004 Å (the length of the N—H bond is 1.004 Å for (3) and (6) and 1.008 for (1) and (4)), while the analogous O—H bond is lengthened by only 0.001 Å (the length of the O—H bond is 0.964 Å for (1), (3), (4) and (6), and 0.965 Å for substances (2) and (5)). The O···H hydrogen bond ((1) and (4)) is shorter by ~0.120, on average, than the N···H hydrogen bond, which is due to the smaller distance between the heteroatoms in the preferential conformations (1) and (4) (~2.9 Å) than in conformations (2) and (5) (~3.07 Å). In the conformations without intraHBs ((3) and (6)) the distance between the heteroatoms averages 4.15 Å. It must be mentioned that in these conformations the N—H bond preferentially assumes the equatorial orientation, as is shown by the corresponding dihedral angles. However, the gain in energy through the formation of an intraHB obviously exceeded its loss as a consequence of the axial reorientation of the N—H bond in the piperidine ring. Thus, as shown above, the total gain in energy of the conformational transition (3) → (1) amounts to 3.22 kcal/mole (see Table 1, AM1).

A number of concrete conclusions also follow from calculations of the energies of individual bonds of the nitrarine and isonitrarine conformers. Thus, because of the formation of an intraHB and the lengthening of the covalent N—H bond caused

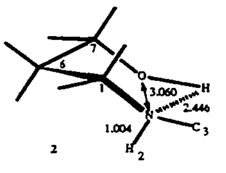
TABLE 5. Energies of Covalent Bonds of Compounds (1)-(6) Calculated by the AM1 Method using the AMPAC Program (eV)

Bond	Nitramine			Isonitramine		
	1	2	3	4	5	6
C_1-N_2	14.900	14.856	14.815	14.903	14.862	14.851
N_2-C_3	14.735	14.810	14.823	14.717	14.799	14.832
C_3-C_4	13.808	13.984	13.977	13.824	13.984	13.979
C_4-C_5	14.080	14.111	14.106	14.072	14.103	14.084
C_5-C_6	13.731	13.809	13.823	13.909	13.920	13.916
C_6-C_7	13.727	13.636	13.640	13.716	13.617	13.574
C_1-C_6	13.756	13.523	13.757	13.638	13.421	13.640
C_7-C_8	13.974	13.957	13.987	13.980	13.995	14.001
C_8-C_9	14.078	14.084	14.065	14.061	14.119	14.070
C_9-C_{10}	14.052	14.051	14.053	14.047	14.048	14.048
C_{10}-C_{11}	14.101	14.097	14.096	14.095	14.100	14.087
C_{11}-C_6	13.784	13.760	13.925	13.781	13.752	13.885
C_7-O_{12}	14.176	14.550	14.177	14.192	14.456	14.356
N_2-H_2	12.997	13.189	13.162	12.993	13.199	13.165
O_{12}-H_{12}	13.141	13.072	13.144	13.136	13.102	13.080
$N_2 \cdots\cdots O_{12}$	0.357	0.461	-	0.345	0.460	-
$O_{12} \cdots H_2$	0.425	-	-	0.412	-	-
$N_2 \cdots H_{12}$	-	0.464	-	-	0.491	-

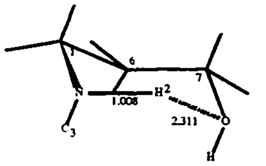
by it, in conformations (**1**) and (**4**) the energy of this bond falls in comparison with its value in conformations (**2**) and (**5**) by an average of 0.2 eV (see Table 5). The analogous decrease in the energy of the O—H bond in (**2**) and (**5**) as compared with (**1**) and (**4**), respectively, averages only 0.05 eV.



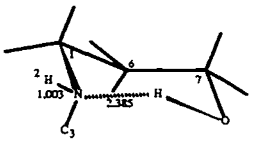
1



2



4



5

Analysis of the results on the skeletal bonds shows that, as was to be expected, the spiro bonds (C_6—C_1, C_6—C_5, C_6—C_7, C_6—C_{11}) and, in particular, those of them that are located in the *β*-position to heteroatoms (C_6—C_1 and C_6—C_7) are the least strong. Then follow the other bonds in *β*-positions to heteroatoms: C_3—C_4 and C_7—C_8. Conformational differences are scarcely reflected in the energies of the skeletal bonds. It must be mentioned that the strongest peaks of fragment ions in the mass spectra of nitramine and isonitramine, with *m/z* 123, 122, 96, 84, etc., are due to the cleavage of just the above-mentioned least strong spiro bonds.

REFERENCES

1. A. A. Ibragimov, in: Results of an Investigation of Alkaloid-bearing Plants [in Russian], Tashkent (1993), p. 105.
2. A. A. Ibragimov, Z. Osmanov, B. Tashkhodzhaev, N. D. Abdullaev, M. R. Yagudaev, and S. Yu. Yunusov, Khim. Prir. Soedin., **623** (1981).
3. AMPAC: QPCE program 506.
4. P. Schuster, G. Zundel, C. Sandorfy, The Hydrogen Bond. Recent Developments in Theory and Experiments, North-Holland, Amsterdam (1976).
5. B. Tashkhodzhaev, A. A. Ibragimov, and S. Yu. Yunusov, Khim. Prir. Soedin., **692** (1985).
6. General Organic Chemistry [in Russian], Vol. 3, Khimiya, Moscow (1978), p. 736.