Nitration in the Imidazo[1,2-*a*]pyrazine Series. Experimental and Computational Results

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Nitration was carried out on a series of imidazo[1,2-*a*]pyrazine derivatives. The reactivities of diversely substituted derivatives and of all positions of substitution were analysed and experimental results compared with ^{13}C-nmr data and semi empirical calculations (AM1). Although the unsubstituted heterocycle is highly resistant to nitration, electron-donating groups such as alkoxy or alkylamino on position 8 enhance the reactivity of the imidazo[1,2-*a*]pyrazine derivatives towards electrophilic substitution and, more specifically, nitration. The ^{13}C-nmr experiments, electronic distributions and Molecular Electrostatic Potential isodensity surfaces calculated on the neutral forms are in good agreement with experimental results indicating position 3 is the most reactive position towards nitration.

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Introduction.

The imidazo[1,2-*a*]pyrazine series displays many pharmacological potentialities and has been reported to exhibit uterine relaxing, cardiac-stimulating or antiulcer activities [1-3]. 8-(Alkylamino) derivatives have been shown to be potent antibronchospastic agents [4] and the pharmacology of 6-bromo-8-(methylamino)imidazo[1,2-*a*]pyrazine-2-carbonitrile (SCA40) has been recently studied extensively [5-11].

The 2- and 3-substituted imidazo[1,2-*a*]pyrazines were obtained after direct cyclisation or electrophilic substitution [4]. The imidazo[1,2-*a*]pyrazine heterocycle is highly deactivated towards electrophiles. Hydroxymethylation leads to much higher yields when applied to the imidazo[1,2-*a*]pyrimidine than to the imidazo[1,2-*a*]pyrazine series [12]. Bromination of unsubstituted imidazo[1,2-*a*]-pyrazine with bromine in glacial acetic acid afforded the 3,5-dibromoimidazo[1,2-*a*]pyrazine in 16% yield, whereas with *N*-bromosuccinimide the 3-bromo derivative was obtained in better yield (58%) [13]. The 3-bromo-, 5-bromo and 3,5-dibromoimidazo[1,2-*a*]pyrazines were synthesized with bromine in ethanol with 5%, 81% and 5% yields, respectively [1]. While nitration occurs easily on the imidazo[1,2-*a*]pyridine heterocycle [14,15], all our investigations to attach a nitro group on the unsubstituted imidazo[1,2-*a*]pyrazine ring have failed regardless of the nitration conditions. Nitration has been described in many major reviews [16-21] and can be considered as the most frequently studied of all electrophilic aromatic substitutions. Its study as a standard reaction is likely to provide the most information on the reactivity and the orientation of electrophilic substitution in the imidazo[1,2-*a*]pyrazine series. Experimental results are compared with ^{13}C-nmr data and theoretical values from semi-empirical quantum calculations.

Results and Discussion.

Among all methods for the nitration of aromatic compounds [22,23], nitric acid in sulfuric acid is surely the most useful nitrating system [24].

The imidazo[1,2-*a*]pyrazine derivatives **1** to **8** were stirred in a mixture of nitric acid (d = 1.38)/98.2% sulfuric acid at 0° for 1 hour and at room temperature for 2 hours. No nitration products were formed with **1** and **4**. In these cases, starting materials were recovered. For compounds **5** to **8**, the reaction conditions led to a separable mixture of unchanged material and a mononitrated imidazo-[1,2-*a*]pyrazine derivative. The reaction was also performed at 50° and 100° following the same procedure. Raising the temperature to 50° did not significantly modify the results of the reaction. Total degradation of starting material took place at 100°.

Assignments of the different signals of the ^{1}H-nmr and ^{13}C-nmr spectra were made according to proton-proton, carbon-proton correlations and previous data [25]. For **7**, the ^{1}H-nmr spectrum showed two doublets at δ 7.47 (H2) and 7.80 (H3) (J = 1 Hz) characteristic of a coupling effect H2-H3 [25] and a singlet at δ 7.97 (H5). The ^{1}H-nmr spectrum of its nitro derivative showed only two singlets at δ 7.57 and 8.43. This data (no coupling effect between the protons) excludes position 5 as the substitution position. Furthermore,

NOE experiments and ^{13}C-nmr were performed on both compounds. For **7**, irradiation of H2 had a strong effect on H3 and no effect on H5. Large effects were observed on H2 and H5 when irradiation occured on H3. Irradiation of H5 showed no effect on H2 but a strong effect on H3. For the nitro derivative, irradiation of both protons did not lead to any response. The ^{13}C-nmr spectrum of the parent compound **7** showed three primary carbons at δ 108.7 (C5), 114.6 (C3) and 132.2 (C2) (Table 2). The ^{13}C-nmr spectrum of the nitro compound exhibited two primary carbons at δ 119.2 and 133.6. If C2 was the nitration position, its chemical shift at low field would have been highly deshielded, which was not the case. Similar results were obtained with all the imidazo[1,2-*a*]pyrazine derivatives **5-8**. Thus, NOE experiments and ^{13}C-nmr data lead to unambiguous assignment of the nitration position to position 3.

In conclusion, nitric acid (d = 1.38) in sulfuric acid proved to be a suitable reagent. It leads to regioselective mononitration on position 3 of imidazo[1,2-*a*]pyrazines.

Comparison of the Reactivity of Imidazo[1,2-*a*]pyrazine Derivatives Towards Electrophilic Substitution.

Ab initio and semi-empirical calculations have been reported for benzene or its substituted derivatives [26,27], heterocycles such as imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-dioxide and dithieno[3,4-*b*:3',4'-*d*]pyridine [28,29] and on larger molecular systems, for instance, fused heterocycles such as 7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole, or pyrrolo[1,2-*a*]quinoxalines [30,31].

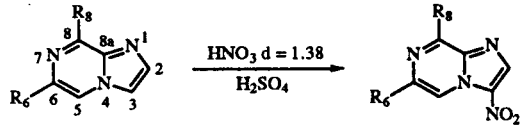
In the present work, 3D molecular structures have been generated using both Molecular Mechanics [32] and MOPAC 6.0-AM1 semi-empirical calculations.

The determination of the Highest Occupied Molecular Orbital (HOMO) energy for all compounds leads to a definite separation of three groups of derivatives (Table 1). The first one with an electron withdrawing substituent on position 8 such as a bromine atom, the other ones with electron donating substituents such as alkoxy and alkylamino groups. The presence of an electron donating group on position 8 increases the energy level of the HOMO while an electron withdrawing group decreases it when compared to unsubstituted imidazo[1,2-*a*]pyrazine. 8-Alkoxy-6-bromoimidazo[1,2-*a*]pyrazines **5**, **6** and 8-(alkylamino)-6-bromoimidazo[1,2-*a*]pyrazines **7**, **8** exhibit an energy level of their HOMO higher than that of 6,8-dibromoimidazo[1,2-*a*]pyrazine **4** and the unsubstituted imidazo[1,2-*a*]pyrazine (**1**). Such compounds **5-8** are more prone to electrophilic attacks. These results are in full agreement with the experimental observations and confirm that the HOMO energy provides a good tool to predict the reactivity of the series towards electrophilic substitution.

Comparison of the Reactivity of the Imidazo[1,2-*a*]-pyrazine Positions Towards Electrophilic Substitution.

Table 1

Nitration of Imidazo[1,2-*a*]pyrazines. Yields and HOMO Values of the Starting Materials



1-8

Compound	R_6	R_8	Yields (%)	HOMO[a] (eV)
1	H	H	No reaction	- 9.156
2	H	OCH_3	30	- 8.892
3	H	$NHCH_3$	50	- 8.343
4	Br	Br	No reaction	- 9.423
5	Br	OCH_3	30	- 9.068
6	Br	OC_2H_5	35	- 9.028
7	Br	$NHCH_3$	65	- 8.459
8	Br	NHC_2H_5	55	- 8.656

[a] Calculated by AM1.

The ^{13}C-nmr chemicals shifts of compounds **1** to **8** are reported in Table 2. Assignment of the ^{13}C-nmr spectra was achieved according to previously published data [25], and carbon-proton correlations. This data enables us to study the relationship between the electronic character

Table 2

Carbon NMR Shifts (ppm)

Compound	Solvent	C2	C3	C5	C6	C8	C8a
1	$CDCl_3$	134.8	118.6	113.1	128.6	143.0	139.9
1	$(CD_3)_2SO$	135.1	120.3	114.6	128.8	143.0	140.0
2 [a]	$(CD_3)_2SO$	133.1	115.6	115.9	125.3	153.9	132.6
3 [a]	$(CD_3)_2SO$	131.2	109.8	115.1	127.9	149.4	132.8
4	$CDCl_3$	133.8	119.4	116.0	120.2	136.9	138.3
5	$CDCl_3$	134.4	115.0	114.2	119.5	153.1	132.5
6	$CDCl_3$	134.2	114.9	113.9	119.7	152.7	132.4
7	$CDCl_3$	132.2	114.6	108.7	123.2	148.3	131.6
8	$CDCl_3$	132.1	114.6	108.7	123.0	147.5	132.0

[a] Compounds **2** and **3** were insoluble in deuteriochloroform.

(donating or withdrawing) of the group on position 8 and the reactivity towards electrophiles of 8-substituted imidazo[1,2-*a*]pyrazine derivatives. In comparison with **1**, the introduction of an electron donating group on C8 in compounds **2** and **3** has a shielding effect on C3, the effective nitration reaction position, and a deshielding effect on C5. Compound **4**, the 6,8-dibromoimidazo-[1,2-*a*]pyrazine (with two electron withdrawing groups) has both C3 and C5 deshielded, which may explain the absence of reactivity of this compound towards nitration. In compounds **5** to **8**, C3 and C5 are shielded. The introduction on position 8 of an electron donating group such as an alkoxy group in **5** and **6** or an alkylamino group in **7** and **8** increases the electronic density on these positions and enhances the reactivity towards electrophiles. For all compounds **1** to **8**, C3 and C5 are assigned at lower magnetic field than the other carbons.

The C3 and C5 positions appear as the most reactive positions towards electrophiles because of the increase of the electronic density on these carbons. However, for 6-bromo derivatives **5-8**, C5 resonance appears always at a lower field than C3. This might lead to the incorrect conclusion that C5 could be the most reactive position towards nitration.

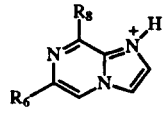
Theoretical studies such as theoretical electronic, HOMO distributions and Molecular Electrostatic Potential isodensity surfaces [33] were performed on all positions of the imidazo[1,2-*a*]pyrazine heterocycle in order to better understand the observed regiochemistry of the nitration process.

The reactivity of 7,12-dihydropyrido[3,2-*b*:5,4-*b'*]diindole towards the NO_2+ electrophile in acidic media has been investigated by Trudell *et al.* [30] who calculated the net atomic charges densities for the protonated species as well as for the free base. Recently, theoretical calculations (charge sensitivity and Molecular Electrostatic Potential) were performed on 2-aminopyridine to predict the most reactive position for electrophilic attack [34]. In the case of the nitration reaction, in low acidity medium, the electrophilic substitution occurs on the free base. In high acidity medium (98.2% sulfuric acid), protonation occurs first on the exocyclic nitrogen atom and then, on the annular nitrogen atom. Nitration takes place with the participation of both protonated structures, the monocation and dication forms.

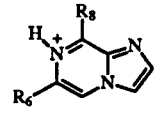
In our study, since the nitration reaction is carried out in a mixture of concentrated nitric and sulfuric acids, imidazo[1,2-*a*]pyrazine derivatives are mostly in their protonated forms. The heats of formation of the different protonated forms, on N(1), named forms **A**, N(7), named forms **B** and, for the 8-(alkylamino)imidazo[1,2-*a*]pyrazine derivatives, on the exocyclic N(8) nitrogen atom, were calculated to discriminate the preferential protonation site (Table 3). The protonation forms on the exocyclic nitrogen atom for compounds **3**, **7** and **8** can be excluded because of the much

Table 3

Energies (heat of formation) Calculated (AM1) for the Protonated Forms (Kcal.mole^{-1}).



(1-8) A



(1-8) B

Compound	Forms A	Forms B	Δ (EA-EB)
1	242.95	250.56	- 7.61
2	195.86	204.12	- 8.26
3	242.20	239.09	+3.11
4	261.36	270.87	- 9.51
5	211.97	213.90	- 1.93
6	205.15	213.45	- 8.30
7	251.58	248.46	+3.12
8	244.36	240.79	+3.57

Table 4

Net Atomic Charges (AM1) of the Protonated A and B Forms

Compound	C-2	C-3	C-5	C-6	C-8	C-8a
1 A	- 0.0277	- 0.1215	- 0.0636	- 0.0688	- 0.0235	+0.0199
1 B	- 0.0912	- 0.0720	- 0.0390	- 0.0807	+0.1333	- 0.1279
2 A	- 0.0225	- 0.1316	- 0.1200	- 0.0256	+0.1783	- 0.0357
2 B	- 0.0227	- 0.1317	- 0.1200	- 0.0252	+0.1784	- 0.0297
3 A	- 0.0276	- 0.1405	- 0.1638	+0.0014	+0.2100	- 0.0380
3 B	- 0.1253	- 0.0789	- 0.0651	- 0.0567	+0.3283	- 0.1447
4 A	- 0.0369	- 0.1318	- 0.0361	- 0.3705	- 0.3289	+0.0568
4 B	- 0.0935	- 0.1048	- 0.0190	- 0.3922	- 0.1788	- 0.1141
5 A	- 0.0334	- 0.1338	- 0.0997	- 0.3139	+0.1740	+0.0096
5 B	- 0.1208	- 0.0813	- 0.0357	- 0.3577	+0.3198	- 0.1250
6 A	- 0.0349	- 0.1346	-0.1038	- 0.3121	+0.1822	+0.0064
6 B	- 0.1222	- 0.0826	- 0.0376	- 0.3584	+0.3283	- 0.1276
7 A	- 0.0288	- 0.1490	- 0.1411	- 0.2912	+0.1955	- 0.0327
7 B	- 0.1258	- 0.0905	- 0.0567	- 0.3427	+0.3151	- 0.1360
8 A	- 0.0373	- 0.1355	- 0.0765	- 0.3329	+0.1190	- 0.0765
8 B	- 0.1270	- 0.0919	- 0.1038	- 0.3430	+0.3200	- 0.1332

Table 5

Net Atomic Charges (AM1) of the Neutral Forms

Compound	C-2	C-3	C-5	C-6	C-8	C-8a
1	- 0.1312	- 0.1884	- 0.0933	- 0.1208	- 0.0035	- 0.0788
2	- 0.1366	- 0.1843	- 0.1500	- 0.0723	+0.1938	- 0.1130
3	- 0.1469	- 0.1891	- 0.1858	- 0.0465	+0.2208	- 0.1065
4	- 0.1418	- 0.2175	- 0.1184	- 0.4307	- 0.3351	- 0.0517
5	- 0.1518	- 0.1972	- 0.1475	- 0.3840	+0.1784	- 0.0725
6	- 0.1526	- 0.1975	- 0.1499	- 0.3831	+0.1833	- 0.0743
7	- 0.1512	- 0.2080	- 0.1928	- 0.3592	+0.2041	- 0.1017
8	- 0.1482	- 0.2066	- 0.1692	- 0.3734	+0.1675	- 0.0845

higher values of their heats of formation, *i.e.*, 256.10, 264.88 and 256.98 Kcal.mole^{-1}, respectively. The differences between the heats of formation calculated for the two forms **A** and **B** for imidazo[1,2-*a*]pyrazine derivatives **1-8** individually are lower than 10 Kcal.mole^{-1}. Such values are not large enough to discriminate between the two protonated sites. This leads to the conclusion that in high acidic medium (98.2% sulfuric acid), nitration might occur on both forms **A** and **B** of the imidazo[1,2-*a*]pyrazines. Accordingly, electronic distribution was calculated for all protonated species **1-8, A/B** and for the neutral forms **1-8**. The main electronic characteristics of the derivatives are shown in Tables 4-7. The net atomic charge densities are reported in Tables 4 and 5 and the charges calculated from the Mulliken population analysis in Tables 6 and 7. The charges densities generated from the net charges calculation or from the

Table 6

Charges Calculated from the Mulliken Population Analysis (AM1) on the Protonated A and B Forms

Compound	C-2	C-3	C-5	C-6	C-8	C-8a
1 A	- 0.0724	- 0.1620	- 0.1071	- 0.1143	- 0.0505	+0.0584
1 B	- 0.1404	- 0.1149	- 0.0738	- 0.1218	- 0.1010	- 0.0918
2 A	- 0.0669	- 0.1716	- 0.1615	- 0.0698	+0.2373	+0.0139
2 B	- 0.0672	- 0.1717	- 0.1615	- 0.0695	+0.2374	+0.0145
3 A	- 0.0716	- 0.1799	- 0.2028	- 0.0396	+0.2745	+0.0102
3 B	- 0.1726	- 0.1211	- 0.0980	- 0.0948	+0.3896	- 0.0941
4 A	- 0.0810	- 0.1722	- 0.0811	- 0.4334	- 0.3730	+0.0924
4 B	- 0.1415	- 0.1469	- 0.0577	- 0.4510	- 0.2177	- 0.0831
5 A	- 0.0776	- 0.1739	- 0.1430	- 0.3749	+0.2331	+0.0571
5 B	- 0.1694	- 0.1243	- 0.0742	- 0.4148	+0.3726	- 0.0738
6 A	- 0.0790	- 0.1746	- 0.1469	- 0.3733	+0.2417	+0.0536
6 B	- 0.1705	- 0.1253	- 0.0760	- 0.4158	+0.3819	- 0.0767
7 A	- 0.0723	- 0.1884	- 0.1821	- 0.3498	+0.2611	+0.0144
7 B	- 0.1728	- 0.1326	- 0.0944	- 0.3997	+0.3766	- 0.0860
8 A	- 0.0816	- 0.1758	- 0.1203	- 0.3940	+0.1750	+0.0741
8 B	- 0.1740	- 0.1340	- 0.1469	- 0.4003	+0.3811	- 0.0832

Mulliken population analysis vary in the same order. However, on both forms **A** and **B** of the protonated species, electron densities do not give any correct ordering and can not be considered as predictive parameters. Interestingly, in all cases, electron densities calculated on the free bases give carbon 3 as the most reactive position towards electrophiles, in agreement with experimental results.

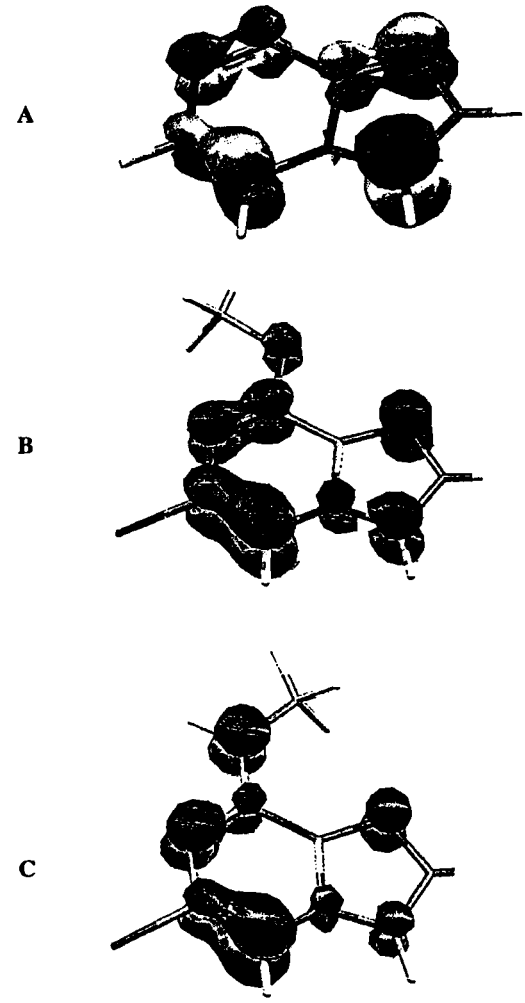
Table 7

Charges Calculated from the Mulliken Population Analysis (AM1) on the Neutral Forms

Compound	C-2	C-3	C-5	C-6	C-8	C-8a
1	- 0.1752	- 0.2250	- 0.1296	- 0.1598	- 0.0332	- 0.0465
2	- 0.1798	- 0.2208	- 0.1856	- 0.1106	+0.2447	- 0.0758
3	- 0.1897	- 0.2250	- 0.2196	- 0.0820	+0.2789	- 0.0658
4	- 0.1836	- 0.2524	- 0.1524	- 0.4437	- 0.3350	- 0.0229
5	- 0.1953	- 0.2333	- 0.1821	- 0.3952	+0.2274	- 0.0297
6	- 0.1960	- 0.2336	- 0.1842	- 0.3945	+0.2325	- 0.0318
7	- 0.1931	- 0.2433	- 0.2262	- 0.3691	+0.2635	- 0.0613
8	- 0.1905	- 0.2420	- 0.2034	- 0.3834	+0.2210	- 0.0440

The localization of both the HOMO as well as Molecular Electrostatic Potential isodensity surfaces have been studied for all imidazo[1,2-*a*]pyrazine derivatives. For simplification, only results obtained for the unsubstituted **1**, the 8-methoxy **5** and the 8-(methylamino) **7** compounds are shown. The study of the localization of the HOMO (Schemes 1 A-C) shows a competition between

Scheme 1. High Occupied Molecular Orbital (HOMO) distribution calculated by AM1 on the neutral from of **1**, **A**, **5**, **B** and **7**, **C**.



the two positions 3 and 5. For all imidazo[1,2-*a*]pyrazine derivatives, the HOMO is never localized on position 2. This data excludes position 2 as a reactive position towards electrophilic substitution. Such a result confirms previous work which indicated position 3 and 5 as the only ones to be able to eventually undergo electrophilic substitution [35]. The Molecular Electrostatic Potential has been used with considerable success to interpret and predict molecular behaviour [26,36]. Aromatic compounds have extensive regions of negative potential above and below the aromatic ring, to which a positively charged species can be attracted. This electrostatic potential which is created in the space around a molecule by its nuclei and electrons is expressed by the formula [37]:

$$V(\vec{r}) = \sum_A \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r})\,d\vec{r}'}{|\vec{r}' - \vec{r}|} \qquad (1)$$

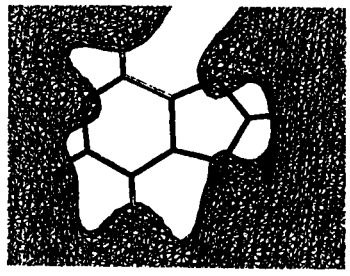
The first term on the right-hand side of eq (1) represents the contribution of the nuclei, which is positive, Z_A is the charge on nucleus A, located at $\vec{R}_A$. The second term gives the potential due to the electrons, which is negative. $\rho(\vec{r}')$ is the electronic density of the molecule at any point $\vec{r}'$, which is obtained from the molecular wave function. Thus, a region in which the Molecular Electrostatic Potential is negative is one in which the effects of the electrons predominate and to which an electrophile, such as NO_2+, would be attracted. Thus, Molecular Electrostatic Potential's values can be key factors in the regioselectivity of the reaction control of the long distance interactions during the approach of the nitronium ion reactant. In 2-aminopyridine, Molecular Electrostatic Potential studies were applied to predict the most sensitive centers for electrophilic attack [34]. In recent work [38], Langenaecker *et al.* concluded that Molecular Electrostatic Potential is the best reactivity indicator for a comparison of reactivity.

Molecular Electrostatic Potential plots were prepared for the neutral forms of all derivatives **1-8** in a surface parallel to the surface ring at a distance of 4Å. Actually, in the presence of counter ions, calculated values for both neutral and protonated **A** and **B** forms remain similar. The representations obtained for compounds **1**, **5** and **7** are visualized on Schemes 2, where hatched regions correspond to negative potentials (- 0.1 eV). For **1** and **7**, only position 3 penetrates into the potential surface. For **5**, no carbon atom enters this surface, however, C3 is much nearer than C5. It is clear from this study of Molecular Electrostatic Potential plots obtained for all imidazo[1,2-*a*]pyrazines **1-8** that carbon 3 is the preferred reaction site for electrophilic attack, again in full agreement with the observed reactivity.

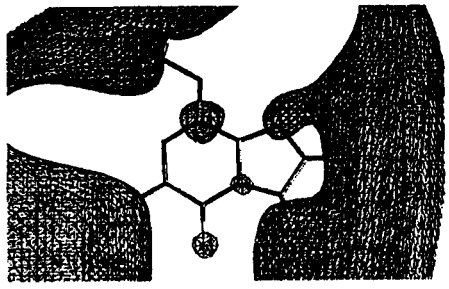
In conclusion, electron-donating groups such as alkoxy or alkylamino on position 8 highly enhance the reactivity of the imidazo[1,2-*a*]pyrazine heterocycle towards electrophilic susbtitution and variations of the calculated HOMO energy values are in accord with those of the mononitration yields. Electronic distributions and Molecular Electrostatic Potential isodensity surfaces generated from the neutral forms confirm experimental results that show position 3 is the most reactive position towards nitration.

Scheme 2. Molecular Electrostatic Potential isodensity surfaces calculated (AM1) in a surface parallel to the surface ring at a distance of 4 Å and corresponding to -0.1 eV on the neutral form of **1**, **A**, **5**, **B** and **7**, **C**.

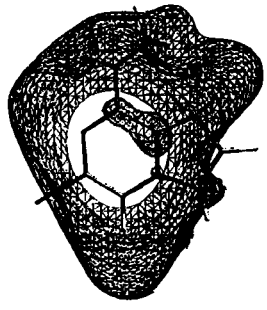
A



B



C



EXPERIMENTAL

General Details.

All melting points are uncorrected and were determined on a Köfler hot plate. Purity of the compounds was checked by thin-layer chromatography on silica gel (230-240 mesh from Merck). The ^{1}H nmr spectra were recorded on a Brucker AC 100. Chemical shifts are expressed relative to internal tetramethylsilane

in deuteriochloroform. Mass spectrometry was carried out on a LKB 2091 spectrometer at 70 eV [(θ_{source}): 180°].

Starting Materials.

All compounds **1-8** were synthesized as previously described [4].

Theoretical Calculations.

All calculations were performed on a HP 730 cluster of work stations. All visualisations were performed on a SGI R 10000 Impact work station.

Using the Molecular Advanced Design Software [32] we have generated the refined cartesian coordinates of all neutral and protonated species. We have studied the electron distribution by a semi-empirical method (MOPAC 6.0 with AM1 hamiltonien) [32].

The Molecular Electrostatic Potential study was made by the method [33] which allows a bi- or tridimensional visualisation.

General Nitration Procedure.

The imidazo[1,2-*a*]pyrazine derivative (2.2 mmoles) was dissolved in cold (-15°) 98.2% sulfuric acid (3.5 ml) and nitric acid (0.35 ml, d = 1.38) was added dropwise with stirring. The solution was allowed to stand for 1 hour at 0° and 2 hours at room temperature. Then, the resulting mixture was poured onto ice, neutralized with sodium carbonate and extracted with dichloromethane. After drying with sodium sulfate 98%, the extracts were evaporated and the solid residue was purified by column chromatography on silica gel eluted with dichloromethane. In all cases, we obtained only two products, the unreacted material and a mononitro compound.

8-Methoxy-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 30% yield, mp 148-150°; ^{1}H nmr (deuteriochloroform): δ 4.19 (s, 3H), 7.76 (d, 1 H, J = 4.8 Hz), 8.68 (s, 1 H), 8.71 (d, 1 H, J = 4.8 Hz); ms: m/z 194 (M^+, 100).

Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.29; H, 3.12; N, 28.87. Found: C, 43.05; H, 3.24; N, 28.61.

8-(Methylamino)-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 50% yield, mp 166-168°; ^{1}H nmr (deuteriochloroform): δ 3.28 (d, 3H, J = 5 Hz), 7.63 (d, 1 H, J = 4.8 Hz), 8.69 (s, 1 H), 8.83 (d, 1 H, J = 4.8 Hz); ms: m/z 193 (M^+, 100).

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.51; H, 3.65; N, 36.27. Found: C, 43.49; H, 3.55; N, 36.42.

6-Bromo-8-methoxy-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 30% yield, mp 190-192°; ^{1}H nmr (deuteriochloroform): δ 4.27 (s, 3 H), 7.78 (s, 1 H), 8.29 (s, 1 H); ms: m/z 272/274 (M^+, 100).

Anal. Calcd. for $C_7H_5BrN_4O_3$: C, 30.89; H, 1.85; N, 20.60. Found: C, 31.02; H, 1.92; N, 20.54.

6-Bromo-8-ethoxy-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 35% yield, mp 130-132°; ^{1}H nmr (deuteriochloroform): δ 1.46 (t, 3 H, J = 7 Hz), 4.56 (q, 2 H, J = 7 Hz), 7.88 (s, 1 H), 9.22 (s, 1 H); ms: m/z 286/288 (M^+, 100).

Anal. Calcd. for $C_8H_7BrN_4O_3$: C, 33.57; H, 1.85; N, 19.59. Found: C, 33.43; H, 1.82; N, 19.61.

6-Bromo-8-(methylamino)-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 65% yield, mp 231-233°; ^{1}H nmr (deuteriochloroform): δ 3.11 (d, 3H, J = 5 Hz), 7.57. (s, 1 H), 8.45 (s, 1 H); ms: m/z 271/273 (M^+, 100).

Anal. Calcd. for $C_7H_6BrN_5O_2$: C, 31.00; H, 2.47; N, 25.84. Found: C, 31.27; H, 2.56; N, 25.50.

6-Bromo-8-(ethylamino)-3-nitroimidazo[1,2-*a*]pyrazine.

This compound was obtained in 55% yield, mp 223-225°; ^{1}H nmr (deuteriochloroform): δ 1.34 (t, 3 H, J = 7 Hz), 3.75 (m, 2 H, J = 7 Hz), 7.56 (s, 1 H), 8.43 (s, 1 H); ms: m/z 285/287 (M^+, 100).

Anal. Calcd. for $C_8H_8BrN_5O_2$: C, 33.68; H, 2.23; N, 25.84. Found: C, 33.52; H, 2.19; N, 25.72.

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