Conformational equilibria and barriers to rotation in some novel nitroso derivatives of indolizines and 3- and 5-azaindolizines – an NMR and molecular modeling study†

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Conformational equilibria in novel C-nitroso derivatives of indolizines and 3- and 5-azaindolizines have been studied by NMR. ^{13}C chemical shifts of the carbon *alpha* to the nitroso group confirmed that these compounds are present in solution as monomers. The conformers arising from restricted rotation about the C–NO bond in monomers were identified by the chemical shifts of the carbon *beta* to the nitroso group. Barriers to rotation in these compounds were unusually high, particularly for substituents in position 3 of indolizine. Ethyl 2-(methylamino)-1-nitrosoindolizine-3-carboxylate displayed conformers arising from the restricted rotation about the C–COOR bond. Molecular modelling demonstrated that in 1-nitrosoindolizines, the position of the conformational equilibrium is due to steric effects, while for 3-nitrosoindolizines electronic effects prevail.

Introduction

In connection with the synthesis of a series of heterocyclic derivatives, we had occasion to prepare some C-nitroso-heterocycles, namely indolizines **1–4**, pyrrolo[1,2-*b*]pyridazine **5** and 3-nitroso-pyrazolo[1,5-*a*]pyridine **6** (Fig. 1), as intermediates.

The NMR spectra of some of these compounds, **1–4** and **5**, displayed in certain conditions two sets of signals, characteristic for two compounds in exchange. In principle, these sets of signals could arise from either of two isomeric azodioxy dimers (Fig. 2) or include one or both of the two rotamers arising from restricted rotation about the C–NO bond (Fig. 3).

Spectroscopic methods can differentiate monomers from dimers. Monomers are green-blue, due to an n–π^* transition around 750 nm, while dimers are colorless.[1] The N=O stretching frequency in the IR spectra of nitrosobenzenes is at 1485–1515 cm^{-1} in the monomer, 1250–1300 cm^{-1} in the *E*-dimer, while the *Z*-dimer has two bands in the region 1350–1400 cm^{-1}.[2-4] Monomers and dimers are also characterized by the ^{13}C chemical shift of the carbon bearing the nitroso group, the substituent chemical shift (SCS) on C_{ipso} in nitrosobenzenes being *ca.* 25–30 ppm downfield in the monomers than in the dimers.[2,5-7]

Monomer *syn* and *anti* rotamers are distinguished by the ^{13}C chemical shifts of the carbons *gamma* to the oxygen. The carbon *syn* to the oxygen would be shielded by 25–35 ppm compared to the one *anti*,[8,9] due to the '*gamma* effect'.[10,11]

The monomer–dimer ratio depends on conditions and on structural features. Dimers are favored in solid state or at lower

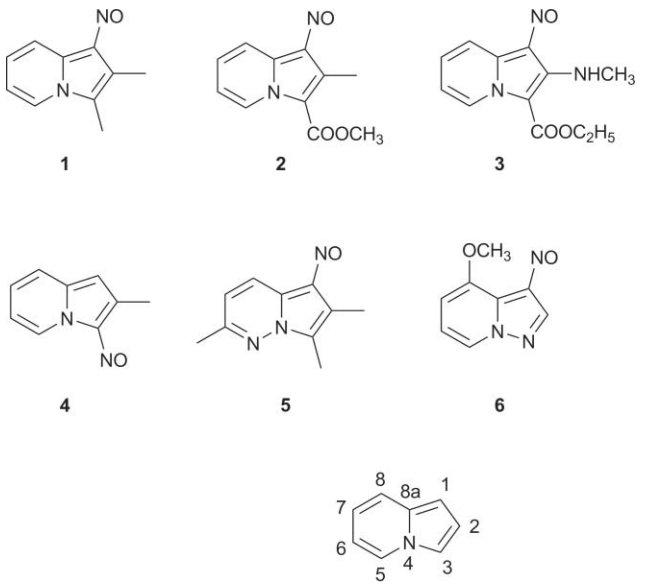

Fig. 1 C-nitroso derivatives of indolizines and 3- and 5-azaindolizines taken into study.

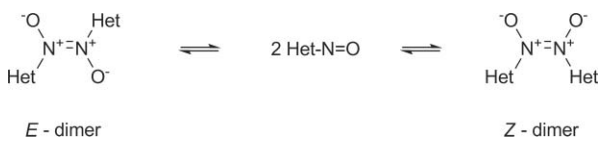

Fig. 2 Monomer–dimer equilibria in heteroaromatic nitroso compounds.

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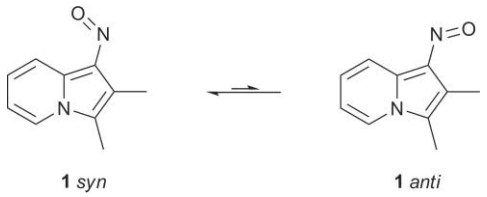


Fig. 3 Rotamers equilibrium in **1**.

temperatures in solution. A high double bond character of the C–NO bond favors the monomer.

Electron-donating substituents in the *para* position in nitrosobenzenes stabilize the monomer: 4-alkyl- or 4-dialkylaminonitrosobenzenes exist as monomers in all conditions; 4-methoxynitrosobenzene is thought to dimerize to a very small extent in concentrated solutions. Nitrosobenzene itself is an equilibrium mixture of the monomer and the two dimers in solution, in which the monomer predominates. 2-Nitrosopyridines display the same equilibrium, but here dominates the dimer.[4] Methyl or chlorine substituents in both of the 2 and 6 positions in nitrosobenzenes tilt the equilibrium from monomers towards the *E*-dimers, presumably by hindering the coplanarity of the nitroso group and the benzene ring. Larger substituents destabilize the dimer. The interplay of steric and electronic factors similarly affects the barrier to rotation about the C–NO bond; $\Delta G^{\#}$ values are good predictors for the tendency of nitroso compounds to dimerize.[7]

Although aromatic nitroso compounds have been known since the early days of organic chemistry, heterocyclic nitroso compounds are relatively rare. A Beilstein search disclosed 7 1-nitrosoindolizines similar to **1–3**, and also 47 3-nitrosoindolizines similar to **4**, but no report on the conformation of these compounds was found, nor were any ^{13}C NMR data uncovered. A search for the 3-nitroso-pyrrole substructure of **1–3** produced 118 hits, and 85 hits were found for the 2-nitrosopyrrole substructure of **4**. The single conformational study found, was theoretical and dealt with the conformation of the parent compounds, 2- and 3-nitrosopyrrole.[12]

We found no 5-nitrosopyrrolo[1,2-*b*]pyridazine, of type **5**. There are 14 3-nitrosopyrazolo[1,5-*a*]pyridines like **6**, out of which only one has ^{13}C NMR data.[13] There are 393 4-nitrosopyrazoles (they have been known for more than 100 years), but only a single conformational study.[9,14]

1,3,5-Trisubstituted-4-nitrosopyrazoles are mixtures of *syn* and *anti* rotamers; with identical substituents in positions 3 and 5, the dominant rotamer had the nitroso oxygen *anti* to N1. NMR and X-ray data confirmed that the shielding anisotropy of the nitroso group in 4-nitrosopyrazoles is similar to that in nitrosobenzenes.[9]

Nitroso derivatives of electron-rich heterocycles are not expected to dimerize, however the dimer of 3,5-dimethyl-4-nitrosopyrazole was recently prepared in solid state. Upon heating its ethanol solution, this dimer dissociates into monomer.[15] We found no other dimers of nitrosopyrroles, nitrosopyrazoles, or nitrosoimidazoles.

The lack of data on the dimerization and conformational equilibria of nitroso derivatives of indolizines, pyrrolo[1,2-*b*]pyridazine and pyrazolo[1,5-*a*]pyridines (and the paucity of data on related heterocycles) prompted us to study compounds **1–6**.

Results and disscussion

The syntheses of C-nitrosoheterocycles **1–6** and details of the NMR spectroscopy are described in the Supplementary Material.†

NMR spectroscopy

The ^{1}H and ^{13}C chemical shifts in the isomers of these compounds were assigned based on the ^{1}H–^{13}C correlations seen in the gHMBC and gHMQC spectra, and are given in Tables 1 and 2. For the purpose of consistency, the same position numbering as in indolizine (Fig. 1) was used for all of the compounds.

2,3-Dimethyl-1-nitrosoindolizine (1)

Compound **1** displayed in the proton spectrum in acetone-*d6* at −65 °C the signals for two isomers, the molar fraction of the major being 0.62. Of the two methyl protons of the major isomer, at 2.74 and 2.45 ppm, the former displays cross-peaks with three aromatic carbons at 154.5, 126.7 and 123.4 ppm, therefore it is the methyl in position 2. The latter two of these carbons also couple with 2.45, and are in positions 2 and 3, leaving 154.5 for position 1. The carbon at 123.4 couples with the doublet at 8.37, therefore it is in position 3, and 8.37 is the proton in position 5. 8.37 is on 125.0 and it couples with 119.7 and 135.4. The latter carries the triplet at 7.83, therefore they are in positions 8a and 7, respectively. The remaining signals of the major, the doublet at 8.25 and the triplet at 7.36 have been assigned to positions 8 and 6, correspondingly. The signals in the minor have been assigned with confidence in a similar way.

The ^{13}C chemical shifts of C1 indicate that both isomers of **1** are monomers. In the related 3,5-dimethyl-4-nitrosopyrazole the chemical shift of C4 is 161.0 in the monomer[14] (SCS = 56.2 ppm) and 132.6 ppm in the dimer[15] (SCS = 27.8 ppm) The chemical shift of C1 in indolizine being 99.5 ppm,[16] the calculated values for 1-nitrosoindolizine are 155.7 in the monomer and 127.3 in the dimer. The chemical shifts of C1 in the two isomers of **1** are 154.3 and 154.5, clearly indicating that they are both monomers, evidently rotamers about the C1–NO bond in the monomer (Fig. 3). We call them *syn* and *anti* referring to the orientation of the nitroso oxygen relative to N4.

The rotamers of **1** have been identified on the basis of the chemical shifts of C2 and C8a. The chemical shift differences between isomers, 17.3 ppm in position 2 and 23.3 ppm in position 8a, are similar to those seen for rotamers of 1,3,5-trimethyl-4-nitrosopyrazole, for which an NMR and X-ray study demonstrated that the carbon *gamma* and *syn* to the oxygen is shielded.[9]

In the major isomer of **1** in acetone-*d6* at −65 °C, C8a is at 119.7 ppm (Table 2), while in the minor is at 143.0, therefore in the major the nitroso oxygen and the indolizine nitrogen are *syn*. Chemical shifts of C2 in the two isomers agree with this assignment. Nitroso dimers do not display this type of isomerism.[5]

The proton chemical shifts (Table 1) in general agree with earlier studies[7,17] which found large differences, up to 3 ppm, between the protons *syn* and *anti* to the oxygen in the nitroso group, the former being more shielded. The only exception is compound **4**, in which H5 is more shielded in the *anti* conformer.

Table 1 ^{1}H chemical shifts in compounds **1–9**

Compd.	Position						
	1	2	3	5	6	7	8
1 *syn*[a]	—	2.74[b]	2.45[b]	8.37	7.36	7.83	8.25
1 *anti*[a]	—	2.14[b]	2.36[b]	8.45	7.37	7.78	8.56
2 *syn*[c]	—	3.16[b]	3.98[b]	9.70	7.47	7.95	8.33
2 *anti*[c]	—	2.41[b]	3.92[b]	9.68	7.47	7.95	8.87
2 *syn*[d]	—	3.21[b]	3.40[b]	9.29	5.94	6.55	8.24
2 *anti*[d]	—	2.55[b]	3.26[b]	9.29	5.94	6.55	8.49
3 *syn* **a**[d]	—	3.28[b]	1.03[b]	8.29	6.12	6.69	8.67
		8.28[e]	4.07[f]				
3 *syn* **b**[d]	—	3.40[b]	1.06[b]	9.48	6.10	6.65	8.63
		6.86[e]	4.12[f]				
3 *syn* **a**[a]	—	3.55[b]	1.40[b]	9.21	7.4	7.80	8.52
		8.39[e]	4.38[f]				
3 *syn* **b**[a]	—	3.48[b]	1.34[b]	9.71	7.46	7.84	8.53
		7.87[e]	4.39[f]				
4 *syn*[g]	5.84	2.72[b]	—	10.07	6.14	6.60	6.65
4 *anti*[g]	5.70	2.22[b]	—	9.21	6.10	6.62	6.65
5 *syn*[d]	—	2.85[b]	2.01[b]	—	1.87[b]	5.87	7.93
5 *anti*[d]	—	2.22[b]	1.89[b]	—	1.95[b]	5.87	8.36
5 *syn*[h]	—	2.77[b]	2.31[b]	—	2.46[b]	7.36	7.95
5 *anti*[h]	—	2.04[b]	2.22[b]	—	2.55[b]	7.42	8.75
6 *anti*[a]	—	7.76	—	8.69	7.47	7.65	4.25[b]
6 *anti*[i]	—	7.72	—	8.58	7.31	7.53	4.14[b]
7[h]	6.28	2.23[b]	2.39[b]	—	2.39[b]	6.41	7.67
8[i]	6.57	7.87	—	8.23	6.77	6.58	3.92[b]
9[j]	6.24	2.33[b]	7.10	7.80	6.37	6.58	7.25

[a] In acetone-*d6* at –65 °C. [b] Methyl. [c] In acetone-*d6* at 0 °C. [d] In toluene-*d8* at –65 °C. [e] NH. [f] Methylene. [g] In toluene-*d8* at 25 °C. [h] In DMSO-*d6* at 25 °C. [i] In DMSO-*d6* at 70 °C. [j] In chloroform-*d* at 25 °C.

2,6,7-Trimethyl-5-nitrosopyrrolo[1,2-b]pyridazine (5)

Compound **5** displayed in the proton spectrum in DMSO-*d6* at 25 °C the signals for two isomers in equal amounts. In acetone-*d6* at –65 °C, the molar fraction of the major isomer was 0.58. The assignment of ^{1}H and ^{13}C chemical shifts in compound **5** followed the same procedure as for **1**, up to the point where the lack of a proton in position 5 made the discrimination between C2 and C3 impossible. The *syn* and *anti* rotamers were identified by the chemical shifts in position 8, and then C2 and C5 were assigned based on the chemical shifts trends seen in **1**. The chemical shift differences between the rotamers of **5**, 19.3 ppm in position 2 and 24.5 ppm in position 8a, are very similar to the ones found in **1**. The chemical shifts of the methyl carbons in positions 2 and 3 are practically the same in compounds **1** and **5**.

Methyl 2-methyl-1-nitrosoindolizine-3-carboxylate (2)

Proton spectra of compound **2** were recorded in 5 °C increments in acetone-*d6* in the interval –65 to 45 °C and in toluene-*d8* in the interval –65 to 75 °C. In both solvents, at –65 °C, there were two isomers in the mixture, the molar fraction of the major being 0.95. As the temperature increased, the signals of the minor which did not overlap the signals for the same position in the major broadened and then disappeared. The signals for the same position in the major broadened then became sharp again. ^{13}C chemical shifts were measured for the major isomer only, due to limited solubility and dynamic range, in acetone-*d6* at 0 °C and in toluene-*d8* at –65 °C.

Of the two doublets in **2**, only one coupled in the gHMBC spectrum with a quaternary carbon (C8a), and was assigned as H5. H5 also coupled with an aromatic carbon bearing a proton, which identified C7 and H7. The remaining doublet and triplet were assigned to H8 and H6, correspondingly. The methyl protons at 3.98 ppm, coupled with only one carbon which had the chemical shift of an ester, therefore this is the methoxy methyl. The methyl protons at 3.16 ppm coupled with three carbons, at 154.7, 140.9 and 114.8 ppm. None of these carbons displayed any cross-peak with H5 or H8, and they had to be assigned based on chemical shift values.

The chemical shift of C8 in the major conformer of **2** is 3.2 ppm higher than that in **1** *syn*, and 22.1 ppm lower than in **1** *anti*, therefore the major conformer of **2** is *syn*. 154.7 is basically identical to the chemical shift of C1 in **1** *syn*, and was assigned as such. The methoxycarbonyl group is expected to produce shielding of C3 and deshielding of C2 in **2** as compared to **1**, so 140.9 was assigned to C2 and 114.8 to C3.

Conjugation of the carboxyl group with the electron-donor heterocycle could raise barriers for the rotation about the C3–COOMe bond enough to observe two distinct rotamers. Since the ^{13}C chemical shifts in the minor could not be measured, the question arises if the two rotamers observed are due to restricted rotation about the C1–NO bond, or about the C3–COOMe bond. Proton chemical shift differences between rotamers, in positions 5 and 8, demonstrate that they are the *syn* and *anti* orientations of the nitroso group. The difference in position 8, 0.54 ppm, is comparable with that found for the *syn–anti* pair of **1**, 0.31 ppm. The difference in position 5 is 0.02 ppm for **2**, and 0.08 ppm for **1**. The similarity of the chemical shifts of H5 in both isomers of **2** with that in **3B** (see below) indicates that in both isomers of **2** the carbonyl oxygen and the indolizine nitrogen are *syn*.

Table 2 ^{13}C chemical shifts in compounds **1–9**

Compd.	Position 1	2	3	5	6	7	8	8a	Other
1 *syn*[a]	154.5	126.7	123.4	125.0	118.4	135.4	118.2	119.7	8.7 (CH_3 in pos. 2); 8.6 (CH_3 in pos. 3)
1 *anti*[a]	154.3	109.4	125.0	126.2	117.0	129.8	115.9	143.0	10.9 (CH_3 in pos. 2); 7.6 (CH_3 in pos. 3)
2 *syn*[b]	154.7	140.9	114.8	128.5	119.4	136.7	117.8	122.9	10.9 (CH_3 in pos. 2); 51.9 (CH_3O); 162.5 (C=O)
2 *syn*[c]	154.9	141.1	113.8	127.4	117.6	134.8	118.0	122.5	11.7 (CH_3 in pos. 2); 51.1 (CH_3O); 162.5 (C=O)
3 *syn* **a**[c]	150.6	151.9	99.7	128.1	118.2	133.7	117.3	123.5	34.1 (CH_3 in pos. 2); 14.6 (CH_3 in pos. 3); 60.1 (CH_2O); 162.0 (C=O)
3 *syn* **b**[c]	150.8	149.2	99.4	127.5	118.6	134.2	116.9	124.4	34.5 (CH_3 in pos. 2); 14.9 (CH_3 in pos. 3); 59.8 (CH_2O); 161.3 (C=O)
3 *syn* **a**[a]	*nm*[d]	*nm*	*nm*	129.6	120.3	135.5	116.8	*nm*	34.3 (CH_3 in pos. 2); 14.3 (CH_3 in pos. 3); 60.5 (CH_2O); 161.4 (C=O)
3 *syn* **b**[a]	*nm*	*nm*	*nm*	128.3	120.3	135.6	116.8	*nm*	34.9 (CH_3 in pos. 2); 14.8 (CH_3 in pos. 3); 59.8 (CH_2O); 161.4 (C=O)
4 *syn*[e]	107.3	141.6	153.5	125.0	117.4	130.8	117.0	136.3	11.7 (CH_3 in pos. 2)
4 *anti*[e]	107.5	118.1	159.2	121.8	114.3	129.1	117.8	138.0	13.8 (CH_3 in pos. 2)
5 *syn*[c]	153.1	126.4[f]	125.5[f]	—	153.4	123.7	126.4	110.8	9.0 (CH_3 in pos. 2); 8.5 (CH_3 in pos. 3); 21.2 (CH_3 in pos. 6)
5 *anti*[c]	152.8	106.7	127.4	—	152.8	119.5	124.2	135.3	11.0 (CH_3 in pos. 2); 7.6 (CH_3 in pos. 3); 21.2 (CH_3 in pos. 6)
5 *syn*[g]	152.3	125.8	125.8	—	154.7	125.8	125.8	113.3	8.5 (CH_3 in pos. 2); 8.3 (CH_3 in pos. 3); 21.3 (CH_3 in pos. 6)
5 *anti*[g]	151.9	106.2	128.0	—	154.5	121.7	124.1	135.5	10.2 (CH_3 in pos. 2); 7.4 (CH_3 in pos. 3): 21.3 (CH_3 in pos. 6)
6[a]	158.0	124.5	—	123.2	117.0	111.2	153.1	135.1	57.6 (CH_3O in pos. 8)
6[h]	158.3	126.3	—	123.8	117.4	112.5	153.2	134.7	57.7 (CH_3O in pos. 8)
7[g]	100.0	120.6	122.4	—	149.4	110.0	126.4	124.3	12.4 (CH_3 in pos. 2); 9.6 (CH_3 in pos. 3); 22.3 (CH_3 in pos. 6)
SCS *syn*[i]	*52.3*	*5.2*	*3.4*	—	*5.3*	*15.8*	*–0.6*	*–11*	
SCS *anti*[j]	*51.9*	*–14.4*	*5.6*	—	*5.1*	*11.7*	*–2.3*	*11.2*	
8[h]	95.4	141.2	—	122.3	112.5	100.7	151.2	135.2	56.5 (CH_3O in pos. 8)
SCS[k]	*62.9*	*–14.9*	—	*1.5*	*4.9*	*11.8*	*2*	*–0.5*	
9[l]	100.1	125.1	111.4	125.1	109.7	116.8	118.5	133.1	12.8 (CH_3 in pos. 2)
SCS *syn*[m]	*7.2*	*16.5*	*42.1*	*–0.1*	*7.7*	*14*	*–1.5*	*3.2*	
SCS *anti*[n]	*7.4*	*–7*	*47.8*	*–3.3*	*4.6*	*12.3*	*–0.7*	*4.9*	

[a] In acetone-*d6* at –65 °C. [b] In acetone-*d6* at 0 °C. [c] In toluene-*d8* at –65 °C. [d] Not measured. [e] In toluene-*d8* at 25 °C. [f] Interchangeable. [g] In DMSO-*d6* at 25 °C. [h] In DMSO-*d6* at 70 °C. [i] δ(**5** *syn*) – δ(**7**). [j] δ(**5** *anti*) – δ(**7**). [k] δ(**6**) – δ(**8**). [l] In chloroform-*d* at 25 °C. [m] δ(**4** *syn*) – δ(**9**). [n] δ(**4** *anti*) – δ(**9**).

Ethyl 2-(methylamino)-1-nitrosoindolizine-3-carboxylate (3)

Compound **3** displayed in the proton spectrum in toluene-*d8* at –65 °C the signals for two isomers; the molar fraction of the major was 0.52. The methyl doublet in the major, at 3.28, coupled with a quaternary carbon at 151.9, assigned as C2. The NH quartet coupled with two carbons, at 150.6 and 99.7 ppm, which were assigned as C1 and C3 respectively, based on their chemical shifts. C3 coupled with the doublet at 8.29, which was assigned as H5. H5 coupled with a quaternary carbon at 123.5, assigned as C8a, and with a carbon at 133.7, which caries the triplet at 6.69, assigned to position 7. The remaining triplet, at 6.12, and doublet, at 8.67, were assigned to H6 and H8, correspondingly. The assignment of the chemical shifts in the minor parallels the one in the major.

The chemical shift of C8a indicates that in both of the isomers of **3** the indolizine nitrogen and the nitroso oxygen are *syn*. This is confirmed by the chemical shift of H8 which is basically the same for the two isomers. Large chemical shifts differences between isomers are seen for the NH protons in position 2 and for H5. The isomers of **3** are two of the four rotamers arising from the restricted rotation about the C2–N and C3–COOEt bonds (Fig. 4).

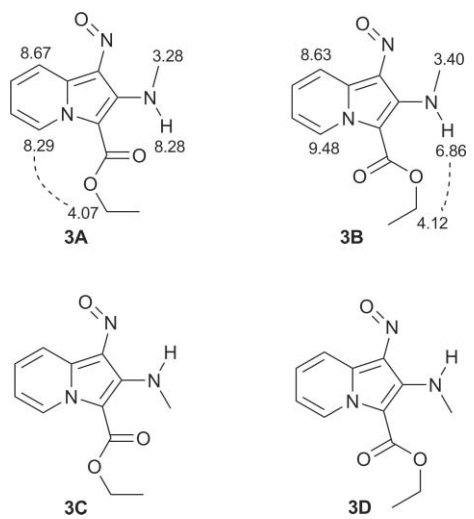


Fig. 4 Possible conformations for **3**, relevant proton chemical shifts and nOes.

The chemical shift of the NH proton in the major, 8.28 ppm, suggests a hydrogen bond with the carbonyl group, as in **3A**. This is confirmed by the nOe between the CH_2O protons and H5.

The chemical shifts of H5 in the major (8.29 ppm) and in the minor (9.48 ppm) indicate that they have different orientations of the ethoxycarbonyl group; of **3B** and **3D**, the former agrees with the nOe between the NH and the CH_2O protons, seen in the minor (Fig. 5). To our knowledge, this is the first report of observation by NMR of rotamers arising from restricted rotation about the C–COOR bond in pyrrole carboxylates. Such rotamers of 2- and 3-pyrrole carboxylates have been demonstrated by IR spectroscopy.[18,19]

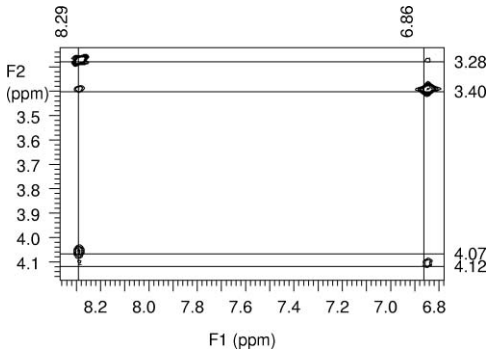


Fig. 5 Expansion of the NOESY spectrum of **3**.

The intramolecular hydrogen bond in **3A** is confirmed by the shift of the molar fraction of the isomer with the deshielded NH from 0.52 to 0.35 when spectra were taken in acetone-*d6* at –65 °C. The hydrogen-bond acceptor solvent competes with the carbonyl group for the hydrogen bond donor, the NH. The chemical shift of the NH in **3A** in toluene-*d8* (8.28 ppm) is close to the one in acetone-*d6* (8.39 ppm), as it is determined mostly by the strength of the hydrogen bond. The chemical shift of the NH in **3B** in toluene-*d8* is 6.86 ppm, while in acetone-*d6* is 7.87 ppm, because of the hydrogen bonding with the solvent.

4-Methoxy-3-nitrosopyrazolo[1,5-*a*]pyridine (6)

Coupling with the methoxy protons in **6** identifies C8. The triplet at 7.47 is H6, and the singlet at 7.76 is H2. The remaining doublets, at 8.69 and 7.65 ppm, have been assigned to positions 5 and 7 correspondingly, based on the chemical shifts of the carbons that carry them. Both of these protons couple with a quaternary carbon at 135.1, which was assigned to position 8a. C8a also couples with H2. The remaining quaternary carbon which couples with H2 is C1.

A single set of signals was detected in the proton spectrum of **6**, both in DMSO-*d6* at 70 °C and in acetone-*d6* at –65 °C, however, in a series of spectra in acetone-*d6* in which the temperature was increased from –65 °C to 45 °C in steps of 5 °C, the signal of H2 broadened between –45 °C and –15 °C, then sharpened again between –15 °C and 10 °C. This indicates that at temperatures above –45 °C a minor conformer is present in exchange with the major, and that the exchange becomes fast on the NMR time scale at temperatures above 10 °C. Comparison of the ^{13}C chemical shifts of **6** between acetone-*d6* at –65 °C and DMSO-*d6* at 70 °C indicates that the composition of the rotameric mixture is about the same. The largest chemical shift difference is in position 2, *ca.* 2 ppm, which amounts to 10% of the minor at 70 °C, considering that the chemical shift difference in position 2 is *ca.* 20 ppm between the *syn* and *anti* rotamers.

The major rotamer of **6** was identified by the SCSs for the nitroso group, inferred from the parent compounds of **5** and **6**, **7** and **8**, correspondingly (Fig. 6).

7 **8**

Fig. 6 Parent compounds of **5** and **6**.

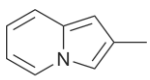
While **7** was available pure, **8** occurred as a 10% impurity in the sample of **6**. Limited solubility in acetone at –65 °C precluded the measurement of the ^{13}C chemical shifts for **8** in these conditions, therefore they were measured in DMSO-*d6* at 70 °C, where the major rotamer of **6** was in exchange with *ca.* 10% of the minor. The SCS in position 2 indicates that the major rotamer of **6** is *anti*. The SCS in position 8a however, is neutral. This is due perhaps to the influence of the conformational equilibrium of the methoxy group on the chemical shift of C8a; this equilibrium is not the same in **6** and in **8**. This may also be the explanation why the SCS in position 1 is 11 ppm larger than expected.

2-Methyl-3-nitrosoindolizine (4)

The proton spectrum of **4** in toluene-*d8* at 25 °C displayed two sets of signals, the molar fraction of the major isomer being 0.92. The barrier to rotation was quite high, since selective irradiation for 10 s did not display the interconversion of isomers at room temperature, but did at 80 °C.

The methyl protons at 2.72 ppm couple with three carbons, at 107.3, 141.6 and 153.5. The former carries the proton at 5.84 ppm and was assigned to position 1. The latter couples with the proton at 10.07 ppm, therefore they were assigned as C3 and H5. C8a and C7 were identified by their coupling with H5.

The rotamers of **4** were identified by the SCSs for the nitroso group, inferred from **9**, the parent compound of **4** (Fig. 7). The ^{13}C SCS in position 2, 16.5 ppm, indicates that the major rotamer of **4** is *syn*. The chemical shift of N4 is also 17 ppm lower in **4** as compared to **9**, as expected for the *syn* conformer.



9

Fig. 7 Parent compound of **4**.

^{15}N chemical shifts

The ^{15}N chemical shifts, given in Table 3, were measured in ^{1}H-^{15}N CIGAR-gHMBC spectra acquired with a pulse sequence optimized for ^{15}N.[20] Unfortunately, the chemical shifts for the nitroso group could not be determined, because these compounds do not have any protons within two or three bonds from the nitroso nitrogen.

Table 3 ^{15}N chemical shifts in compounds **1–7** and **9**

Compd.	Position 4	Other
1 *syn*[a]	200.0	
1 *anti*[a]	200.6	
2 *syn*[b]	195.2	
3[b]	194.0	75.9 ($NHCH_3$)
4 *syn*[c]	174.4	
5 *syn*[a]	230.1	302.7 (N5)
5 *anti*[a]	230.4	300.8 (N5)
6 *anti*[b]	242.9	289.1 (N3)
7[a]	221.6	295.8 (N5)
9[d]	191.3	

[a] In DMSO-*d6* at 25 °C. [b] In DMSO-*d6* at 70 °C. [c] In toluene-*d8* at 25 °C. [d] In chloroform-*d* at 25 °C.

Barriers to rotation

The barriers to rotation were measured by variable temperature NMR in toluene-*d8*. The exchange rates were determined by line-shape simulation in gNMR.[21] The free enthalpies of activation at 25 °C ($\Delta G^{\#}_{298}$) for the process *syn* → *anti* in compounds **1**, **2**, **4** and **5** have been calculated from the enthalpy and entropy of activation and are 16.6, 15.6, 24.0 and 15.7 kcal mol^{-1}, correspondingly. These values are significantly larger than those found in nitrosobenzene (8.2 kcal mol^{-1}), 4-methoxynitrosobenene (9.8 kcal mol^{-1}) and 4-dimethylaminonitrosobenzene (12.6 kcal mol^{-1}).[22] It was demonstrated that in 4-substituted-nitrosobenzenes the barrier to rotation increases with the p-donor capability of the substituent.[22] Smaller values for compounds **2** and **5**, compared to **1**, are due to a less electron-donating pyrrole moiety in the former two.

The barrier for the process **3B** → **3A**, in toluene-*d8* is 14.4 kcal mol^{-1}, significantly larger than the barrier for the carboxylate rotation in methyl benzoate, 5.0 kcal mol^{-1},[23] methyl 4-methylamino-3-nitrobenzoate, 6.3 kcal mol^{-1},[24] methyl 8-isopropyl-1-naphthoate, 8.9 kcal mol^{-1},[25] ethyl 7-ethyloxepine-2-carboxylate, 6–8 kcal mol^{-1},[26] or methyl 2-dimethylamino-3-nitrothiophene-1-carboxylate, 7.7 kcal mol^{-1}.[24]

Molecular modelling

Calculations were performed using the *MM+* and the *ab initio* methods, as implemented in the HyperChem program.[27] *Ab initio* calculations for compounds **1** and **3** were run in Gaussian 03.[28] First, a conformational search was run using the *MM+* method, retaining all conformations within 10 kcal mol^{-1} from the minimum. The energy of these conformers was also calculated with the a*b initio* method with the 6-31 g(d,p) basis set.

The eight conformations for compound **1** are depicted in Fig. 8, and their energies are given in Table 4. The calculated molar fraction of the *syn* conformer is 0.55 by *MM+* and 0.43 by *ab initio*, *vs*. 0.62 experimental.

Both methods indicate that the conformations in which a hydrogen of the methyl group in position 3 is facing H5 are the least stable and don't have much weight in the conformer population. In the significant conformations, the methyl groups are either geared (**1a** and **1a′**) or face-to-face (**1b** and **1b′**). In the geared conformations, a hydrogen of the methyl group in position 2 is facing the NO group and it is sterically more demanding than H8. Both methods found **1a** more stable than **1a′**. In the face-to-face arrangement of the methyl groups, the methyl in position 2 presents its back to the NO group, and it is sterically less demanding than H8. Both methods found **1b′** more stable than **1b**. Assuming no interaction between the lone pair on the nitroso nitrogen and the methyl in position 2, the face-to-face arrangement of the methyls is less stable than the geared one (**1b-1a**) by 0.66 kcal mol^{-1} in MM+ and by 0.18 kcal mol^{-1} in *ab initio*. The difference between the *syn* and *anti* orientations of the nitroso group is 0.35 kcal mol^{-1} (MM+) or 0.78 kcal mol^{-1} (*ab initio*) for geared methyls (**1a′-1a**) and –0.39 kcal mol^{-1} (MM+) or –0.29 kcal mol^{-1} (*ab initio*) for the face-to-face arrangement (**1b′-1b**). In conclusion, the conformational preferences of **1** are dominated by steric effects; the strongest is the interaction between the methyl group in position 3 and H5, which leaves the former with a hydrogen facing the methyl group in position 2. The energy difference for the interaction of the two methyl groups in the face-to-face or geared conformations is comparable to the energy difference of the two orientations of the nitroso group.

Table 4 Calculated energy differences (kcal mol^{-1}) and molar fractions, at –65 °C, for conformers of **1**

Conformer	*MM+*	*x*	*Ab initio*	*x*
1a	0.00	0.43	0.47	0.17
1b	0.66	0.09	0.29	0.26
1c	1.47	0.01	2.69	0.00
1d	1.35	0.02	2.79	0.00
1a′	0.35	0.18	1.25	0.03
1b′	0.27	0.22	0.00	0.53
1c′	0.93	0.05	2.20	0.00
1d′	2.62	0.00	3.35	0.00

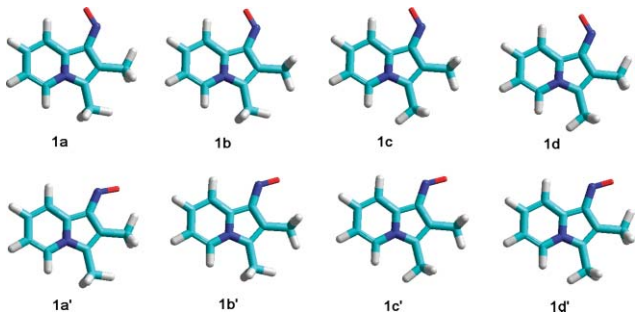


Fig. 8 Conformers of **1**.

A conformation search with MM+ found three conformers for compound **5** (Fig. 9). Their energies are given in Table 5. The calculated molar fraction of the *syn* conformer is 0.68, *vs*. 0.58 experimental.

The conformational preferences of **5** are very similar to those of **1**. Compound **5** however misses conformations in which the methyl

Table 5 Calculated energy differences (kcal mol^{-1}) and molar fractions, at –65 °C, for conformers of **5**

Conformer	*MM+*	*x*	*Ab initio*	*x*
5a	0.00	0.53	0.08	0.43
5b	0.22	0.31	0.97	0.05
5c	0.52	0.15	0.00	0.52

Table 6 Calculated energy differences (kcal mol^{-1}) and molar fractions, at −65 °C, for conformers of **2**

Conformer	*MM+*	*x*	*Ab initio*	*x*
2a	0.00	0.78	0.00	0.99
2b	0.60	0.18	2.04	0.01
2c	1.41	0.03	2.82	0
2d	1.94	0.01	4.66	0

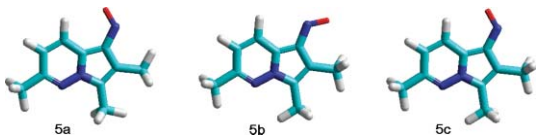


Fig. 9 Conformers of **5**.

groups are face-to-face, because there is no need to minimize the interaction between the methyl in position 3 and H5.

Compounds **1** and **5**, which have different heterocycles but the same substituents in positions 2 and 3, display similar conformational equilibria, indicating that, in these cases, steric interactions of the methyl groups are more important than the electronic interactions between the nitroso group and the heterocyclic frame.

A conformation search with *MM+* found four conformers for compound **2** (Fig. 10). Their energies are given in Table 6. The calculated molar fraction of the *syn* conformer is 0.81 by *MM+* and 0.99 by *ab initio*, *vs*. 0.95 experimental.

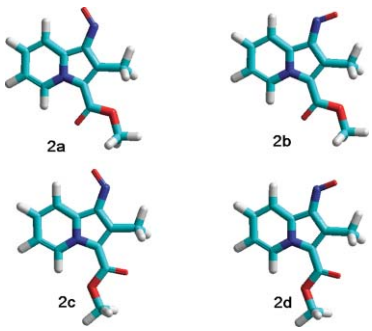


Fig. 10 Conformers of **2**.

For compound **2** also, the conformational preference can be explained by steric effects. The carboxyl group in the plane of the heterocycle forces the methyl in position 2 to have a hydrogen pointing towards the nitroso group in all of the conformers. As seen in **1** and **5**, for this conformation of the methyl group, the *syn* conformer of the nitroso group is more stable.

The molar fraction of the *syn* conformers in the equilibrium of **3** was 0.91 by *MM+* and 1.00 by *ab initio* (Fig. 11 and Table 7). The *anti* conformers in *MM+* had the NMe group out of the plane of the heterocycle and the method does not account for the electronic destabilization of these conformers. Conformers of type **3A** in Fig. 4, **3d–f** in Fig. 11, represent a fraction of 0.14 by *MM+* and 0.20 by *ab initio*, compared with 0.35 observed in acetone-*d6*.

The coplanarity of the carboxyl group and the heterocycle precludes conformations **3C** and **3D** in Fig. 4, in which there is a strong repulsion between the methyl in position 2 and the carboxyl in position 3. In the accessible conformations of the methylamino group, the NH bond is in the plane of the heterocycle, with the hydrogen pointing towards the carboxyl. The methyl group

Table 7 Calculated energy differences (kcal mol^{-1}) and molar fractions, at −65 °C, for conformers of **3**

Conformer	*MM+*	*x*	*Ab initio*	*x*
3a	0.00	0.34	0.00	0.47
3b	0.20	0.21	0.43	0.16
3c	0.20	0.21	0.43	0.16
3d	0.71	0.06	0.58	0.12
3e	0.88	0.04	0.97	0.04
3f	0.88	0.04	0.97	0.04
3a′	0.93	0.04	5.14	0.00
3b′	1.21	0.02	5.20	0.00
3c′	1.21	0.02	5.20	0.00
3d′	1.56	0.01	5.34	0.00
3e′	1.77	0.00	5.59	0.00
3f′	1.77	0.00	5.59	0.00

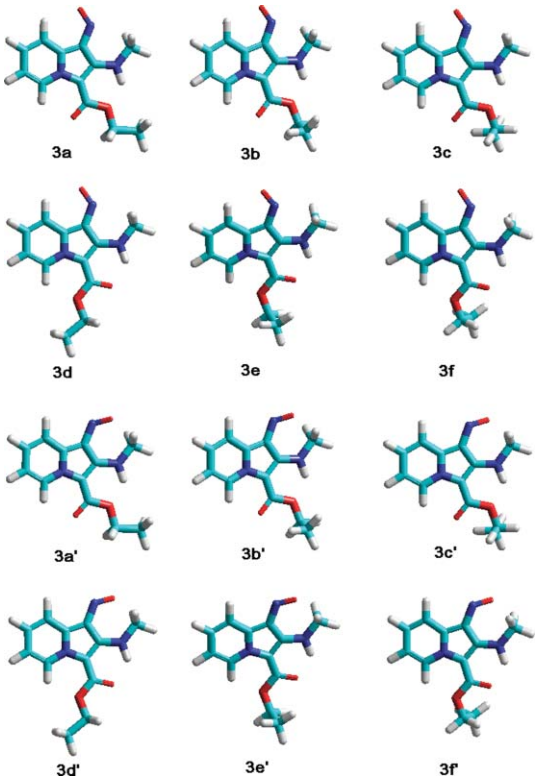


Fig. 11 Conformers of **3**.

pointing towards the nitroso is much bulkier than the hydrogen in **2**, therefore the *anti* orientation of the nitroso is not possible any more. The NH group in **3** appears to the carboxyl group bulkier than the methyl group in **2**, and comparable to H5, making the two orientations of the carboxyl of comparable energies. In addition, conformations of type **3A** in Fig. 4, **3d–f** in Fig. 11, are stabilized by the hydrogen bond between the NH and the C=O.

The energies of the conformers of **6**, calculated with *MM+* (Fig. 12 and Table 8) reproduce very well the fraction of the *syn* conformer found by NMR, 0.00 at −65 °C and 0.10 at 70 °C.

The methoxy group appears to the nitroso larger than H2 and the *anti* isomer is favored by *ca*. 2 kcal mol^{-1}.

MM+ calculations (Fig. 13 and Table 9) predict that **4** would be 82% *anti*, as would be expected from the pattern of steric interactions seen in **1**, **2** and **5**. However, ^{13}C chemical shifts in position 2 indicate that **4** is 92% *syn*. This resembles the

Table 8 Calculated energy differences (kcal mol^{-1}) and molar fractions, at −65 °C, for conformers of **6**

Conformer	*MM+*	*x*	*Ab initio*	*x*
6a	0.00	0.79	0.00	0.72
6b	0.84	0.10	0.68	0.14
6c	0.84	0.10	0.68	0.14
6d	2.01	0.01	3.32	0.00
6e	2.70	0.00	3.10	0.00
6f	2.70	0.00	3.10	0.00

Table 9 Calculated energy differences (kcal mol^{-1}) and molar fractions, at 25 °C, for conformers of **4**

Conformer	*MM+*	*x*	*Ab initio*	*x*
4a	0.00	0.82	1.15	0.18
4b	1.21	0.11	0.00	0.82
4c	1.43	0.07	Converged to **4b**	

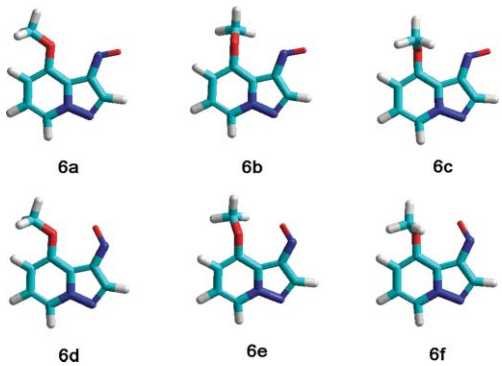


Fig. 12 Conformers of **6**.

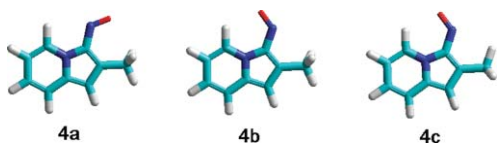


Fig. 13 Conformers of **4**.

preference for the *syn* orientation of the carbonyl group of 2-carboxy- and 2-formylpyrroles to the nitrogen (methylated or not), which was explained by an electrostatic attraction between the positive nitrogen and the negative carbonyl oxygen.[19] *Ab initio* calculations reflect the observed equilibrium better, and predict 82% *syn* conformer at 25 °C. This is the only case in this study in which the two methods produced a different order of the energy of the conformers.

In order to evaluate the size of the electronic effects, in particular the difference between conjugation of the nitroso or carbonyl group and the double bond on the pyrrole moiety in the *s-cis* and *s-trans* geometry, we considered model compounds in Fig. 14, for which the ground states and Natural Bond Orbital Analysis (NBO) have been calculated at HF/6-31g(d,p) and B3LYP/6-31g(d,p) level respectively.

The *s-trans* geometry was found to be the lowest energy one for all of the compounds **10–12** (Table 10). Comparison with calculations in *MM+* indicated that this stabilization is mostly steric in the case of **10** and **11**, and mostly electronic in the case of **12**. The explanation for this came from the NBO analysis

Table 10 Calculated energy differences (kcal mol^{-1}) for conformers of model compounds **10–12**

	HF/6-31g(d,p)		*MM+*	
Compound	*trans*	*cis*	*trans*	*cis*
10	0.00	0.69	0.00	0.92
11	0.00	1.13	0.00	1.40
12	0.00	3.14	0.00	–0.86

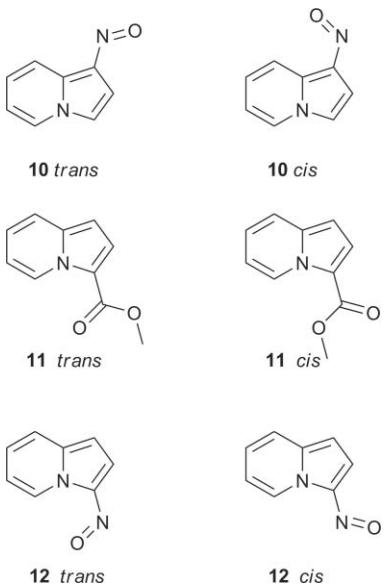


Fig. 14 Model compounds for the *s-cis vs. s-trans* conjugation.

which indicated that the extra stabilization in the *s-trans* geometry coming from the donor–acceptor interaction between the π orbital of the pyrrole double bond and the π* orbital of the nitroso or carbonyl group, Δ*E* (*trans–cis*), is significantly larger in **12** than in **10** or **11** (Table 11).

Barriers for rotation about the C–NO bond or the C–COOMe bond in model compounds **10–12**, calculated with the HF/6-31g(d,p) method, are 15.1, 14.4 and 17.6 kcal mol^{-1}, respectively. The barrier in **10** compares well with the barriers in **1** and **2**, 16.6 and 15.6 kcal mol^{-1} respectively. The calculated barrier in **11** is identical to that found in **3**, 14.4 kcal mol^{-1}. The barrier in **12** is smaller than the barrier found for **4**, 17.6 *vs.* 24 kcal mol^{-1}, but the value reflects the experimental trend.

The large barriers in the indolizine system can be explained by the partial double bond character of the C–X=O bond (X is N or C) and the increased aromaticity of the pyridine ring in the ground state. Results of the NBO analysis for the ground state and the highest energy point on the rotation pathway are presented in Tables 12 and 13.

Table 11 Calculated stabilization energy and Δ*E* (*trans–cis*) (kcal mol^{-1}) for the donor–acceptor interaction of interest in model compounds **10–12**

Compound	Donor (π)	Acceptor (π*)	*trans*	*cis*	Δ*E*
10	C1=C8a	N=O	29.94	27.49	2.45
11	C2=C3	C=O	27.77	26.59	1.18
12	C2=C3	N=O	38.4	30.69	7.71

Table 12 Distances (Å) for some bonds at the lowest (0°) and highest point of the rotation (90°) in model compounds **10–12**

	Compd.					
	10		**11**		**12**	
Distance	0°	90°	0°	90°	0°	90°
C–XO	1.384	1.443	1.453	1.493	1.36	1.442
N4–C8a	1.369	1.384	1.375	1.386	1.371	1.387
N4–C5	1.369	1.376	1.373	1.383	1.351	1.378
N4–C3	1.386	1.364	1.386	1.368	1.393	1.365

Table 13 Electron donor–acceptor interactions and N4 occupancy at the lowest (0°) and highest point of the rotation (90°) in model compounds **10–12**

	Compd.					
	10		**11**		**12**	
Donor → acceptor	0°	90°	0°	90°	0°	90°
N4 → C8a=C1	40.0	35.0	40.1	34.9	42.0	34.6
N4 → C5=C6	34.9	33.9	36.0	34.4	35.0	33.4
N4 → C2=C3	25.6	33.3	29.2	33.6	29.4	34.2
C8a=C1 → N=O	29.9	1.6	—	—	—	—
C2=C3 → X=O	—	—	27.8	4.5	38.4	3.2
Nitrogen occupancy	1.480	1.495	1.479	1.491	1.478	1.506

In the transition state, the length of the C–XO bond is larger than in the ground state, due to the loss of the partial double bond character. The length of the N4–C8a and N4–C5 bonds also increases, due to some loss of the aromaticity of the pyridine ring. The N4–C3 bond is shorter in the transition state, suggesting a higher donation from the lone pair into the C2=C3 bond.

Data in Table 13 demonstrate a large decrease in the donation to the X=O bond in the transition state in compounds **10–12**, and particularly in the latter, which correlates well with the increase in the C–XO bond distance, which loses its double bond character in the transition state. The N4 lone pair donation decreases in the transition state, while its occupancy increases.

Conclusions

^{13}C substituent chemical shifts (SCS) in the *alpha* position to the nitroso group identified compounds **1–6** as monomers, as expected for nitroso derivatives of electron-rich heterocycles.

The SCS in the *beta* position to the nitroso group identified the *syn* and *anti* rotamers of the monomers. Compounds **1** and **5** displayed both rotamers in comparable amounts, **2** and **4** were mostly *syn*, and **6** was mostly *anti*. Compound **3** had two rotamers in comparable amounts, but they were both *syn*, and they were due to restricted rotation of the carboxyl group.

Molecular modelling provided the interpretation for the conformational preferences of the monomers. Both *MM*+ and *ab initio* with the 6-31 g(d,p) basis set calculations gave the same order of stability for conformers, except for the case of **4**. This is because in all of the compounds but **4**, steric interactions prevail over electronic ones. The extra stabilization coming from better delocalization in the *s-trans* geometry of the endocyclic double bond and the N=O bond is significantly larger in 3-nitrosoindolizines than in 1-nitrosoindolizines, and this is the determining factor in the conformational equilibrium of **4**.

In 1-nitrosoindolizines, steric interactions were found to prevail over the electronic interactions between the nitroso group and the heterocycle. The *syn* and *anti* orientations of the nitroso group flanked by a *peri* hydrogen (H8) and a freely rotating methyl in position 2 are of comparable energies. This is the case for compounds **1** and **5**. In compound **2**, the methyl in position 2 has a hydrogen pointing towards the nitroso, and the *syn* conformation prevails. The methyl is forced in this conformation by the carboxyl group in position 3, which has to be in the plane of the heterocycle. The carboxyl group has the carbonyl facing H5, which appears larger than the methyl. In compound **3**, both the carboxyl and the methylamino group are in the plane of the heterocycle. The methylamino group has the methyl pointing towards the nitroso, and **3** is entirely *syn*. The methylamino group in **3** appears to the carboxyl group larger than the methyl group in **2**, and the two orientations of the carboxyl group in **3** are of comparable energies.

Barriers to rotation about the C–NO bond were larger than in other C-nitroso compounds, and more so for 3-nitrosoindolizines than for 1-nitrosoindolizines. The barrier to rotation about the C–COOR bond in **3** is also exceptionally large. Molecular modeling demonstrated that this is because the stabilization of the *s-trans* geometry coming from the donor–acceptor interaction between the π orbital of the pyrrole double bond and the π* orbital of the nitroso or carbonyl group is significantly larger when these substituents are in position 3, than when they are in position 1.

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