Rotation about the N^2–N^3 bond in 3,3-dimethyl-1-(isoxazol-3-yl)-triazenes

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The rotational barrier around the N^2–N^3 bond of a series of 3,3-dimethyl-1-(isoxazol-3-yl)triazenes was evaluated by means of NMR line shape analysis. The results obtained were compared to ^{15}N chemical shift measurements and semi-empirical quantum mechanical calculations. An increase of N^2–N^3 bond order, possibly due to an electron withdrawing effect of the isoxazole ring, was noted in our compounds.

Introduction

We have recently reported the synthesis of 3,3-dialkyl-1-(isoxazol-3-yl)triazenes as well as their mass spectrometric characterization in the frame of an investigation of the antimetastatic action of these compounds.[1–3] It is known that the N^2–N^3 bond of the triazene group has a partial double bond character, with considerable delocalization of electron charge density on N^1, as represented by the two resonance forms shown in Fig. 1.

Any contribution to the ground state of the mesomeric 1,3-dipolar form II, which has a double bond between N^2 and N^3, results in a high free energy barrier for internal rotation around this bond, as observed for several triazenes by NMR.[4–7] The activation energy observed for some 3,3-dialkyltriazenes has been correlated with N^2–N^3 bond order obtained from semi-empirical molecular orbital theory calculations.[8] Moreover, the height of the energy barrier has been evaluated by MO calculations.[9,10] Finally the N=N vibrational frequencies and fragmentation patterns observed in the mass spectra of the 1-aryl-3,3-dialkyltriazenes have been correlated with their structure.[11] Since the influence on the rotational energy barrier of a series of heterocycles linked to N^1 has not been considered, we report in this paper the results of our NMR measurements on some representative isoxazol-3-yltriazenes (**1**–**6**, see Fig. 2). Two types of parameters have been used in the present investigation. Firstly the ^1H resonances of the methyl groups on N^3 and their line shape as a function of temperature have been analysed to determine the barrier to rotation around the N^2–N^3 bond. Secondly the ^{15}N chemical shift of the triazene group has been measured in order to correlate it with the electronic structure of the triazene functional group. Data sets coming from these NMR experiments have been eventually compared with theoretical calculations.

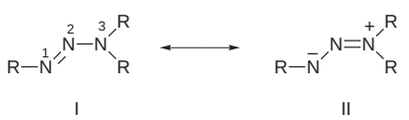

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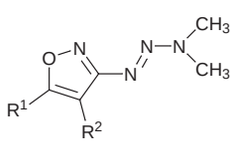
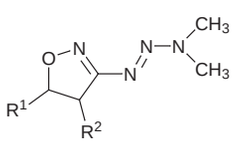
Fig. 1



1,3–6



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Compound	R^1	R^2
1	CH_3	H
2	CH_3	H
3	CH_3	COOEt
4	Ph	COOEt
5	CH_3	Br
6	CH_3	NO_2

Fig. 2

Experimental

Materials

Compounds **1**, **3**, **4**, **6**[1] and **2**[3] were prepared as previously described. 3,3-Dimethyl-1-(4-bromo-5-methylisoxazol-3-yl)triazene **5** was prepared as follows: 3,3-dimethyl-1-(5-methylisoxazol-3-yl)triazene[1] (1 g, 6.5 mmol) was dissolved in 13 mL of dichloromethane; NBS (1.279 g, 7.2 mmol) was added and the mixture was stirred at room temperature until the starting material disappeared on TLC analysis (5 h). Water was added, the mixture was stirred for 15 min and then extracted with EtOAc. The organic phase was dried over sodium sulfate and evaporated to yield crude material from which pure **5** (1.32 g, 88%) was obtained as a colourless oil by flash column chromatography (cyclohexane–EtOAc 7:3 as eluent) (Found: C, 30.99; H, 3.86; N, 23.88. $C_6H_9BrN_4O$ requires C, 30.92; H, 3.89; N, 24.04%); *m*/*z* 232 (M^+, 33%), 190 ($M^+ - N(CH_3)_2$, 100%); ν_{max}/cm^{-1} 1610.

Spectrometry

^1H NMR spectra were measured using a Bruker AC200 Fourier transform spectrometer equipped with a cryomagnet. The samples, dissolved (0.05 M) in 1,1,2,2-tetrachloroethane-d_2, were contained in 5 mm tubes. The temperature of the probehead, controlled by a Bruker accessory B-VT 1000, was checked with an ethylene glycol standard. Each sample was allowed to thermostat in the probehead for 20 minutes before measurement of the spectrum. The lineshape was analysed using the WINNMR and WINKUBO Bruker software programs for personal computers. The root mean square deviation between calculated and observed lineshape was on average 0.005, but in any case was always less than 0.01. The activation

Table 1 Coalescence temperatures and activation parameters of isoxazol-3-yltriazenes

Compound	R^1	R^2	T_c/K	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
1	Me	H	348	68.8 ± 1.5	−0.1 ± 1.4
2	Me	H	351	70.1 ± 1.8	0.0 ± 2.0
3	Me	COOEt	360	73.7 ± 0.8	0.0 ± 1.8
4	Ph	COOEt	365	71.4 ± 1.2	0.0 ± 1.2
5	Me	Br	372	72.0 ± 0.8	−0.1 ± 1.7
6	Me	NO_2	390	77.8 ± 1.4	−0.1 ± 1.2

Table 2 Bond order and activation free energy in triazenes R–N=N–NMe_2

R	Bond order/pm N^1–N^2	Bond order/pm N^2–N^3	ΔG^{*}/kJ mol^{-1}	Ref.
n-Butyl	1.888	1.050	43.9	5
Benzyl	1.886	1.052	44.8	5
Phenyl	1.840	1.064	57.7	5
p-Carboxyphenyl	1.821	1.088	55.9	8
p-Methoxyphenyl	1.844	1.057	53.1	4
p-Methylphenyl	1.840	1.061	54.4	4
p-Chlorophenyl	1.834	1.070	58.2	4
p-Nitrophenyl	1.797	1.100	65.7	4
4-Carboxamidoimidazol-5-yl	1.802	1.091	60.8	7
5-Methylisoxazol-3-yl	1.800	1.108	68.8	this work
5-Methyl-4,5-dihydroisoxazol-3-yl	1.814	1.099	70.1	this work
4-Nitro-5-methylisoxazol-3-yl	1.788	1.135	77.8	this work
4-Carboxy-5-methylisoxazol-3-yl	1.782	1.124	73.7	this work
4-Bromo-5-methylisoxazol-3-yl	1.786	1.120	72.0	this work

parameters were obtained using the Eyring equation with least-squares adjustment on both variables.

The ΔT for bandshape analysis was of the order of 90 K, stepped in 15 measurement temperatures. The rms deviation of the Eyring plot was in any case better than 0.01.

^{15}N NMR spectra were measured at 50.7 MHz using a Bruker AMX 500 spectrometer. The samples, dissolved (0.1 M) in $CDCl_3$, were contained in 10 mm tubes. The pulse program was INVGATE, with pulse width 8.5 μs, relaxation delay 5 s, number of scans 16 K.

Semi-empirical molecular orbital calculations were carried out using Hyperchem software (PM3 parametrization, geometry optimized with steepest descent algorithm).

Results and discussion

The activation parameters obtained for the N^2–N^3 bond rotation in the six examined compounds are reported in Table 1.

It is apparent that, in comparison with the values reported for 3,3-dialkyl-1-(phenyl-substituted)triazenes,[4,6] whose N^3 signals have a coalescence point at low temperature [the only exception being 3,3-dimethyl-1-(4-nitrophenyl)triazene],[4] the activation enthalpy of our isoxazolyltriazenes is rather large, resulting in high coalescence temperatures, ranging up to 117 °C for compound **6**. This observation suggests that the isoxazole ring relative to the phenyl ring enhances the mesomeric effect and favours the 1,3-dipolar structure. Interestingly, the result is also observed with the non-aromatic ring of dihydroisoxazole **2**.

Secondly in any case the activation entropy is consistently small, being not larger than the experimental error. This result shows that the rotation process is not associated with considerable entropy changes between the transition state and the ground state, and is in agreement with an intramolecular mechanism for the process.

Finally the barrier of activation appears to be very sensitive to the substitution pattern in the isoxazole ring, *i.e.* the electronic structure. In order to consider this aspect from a more general point of view a survey of activation free energy $\Delta G^{\ddagger}$ for a set of 1-substituted-3,3-dimethyltriazenes is given in Table 2 together with the calculated order of the N^1–N^2 and N^2–N^3 bonds.

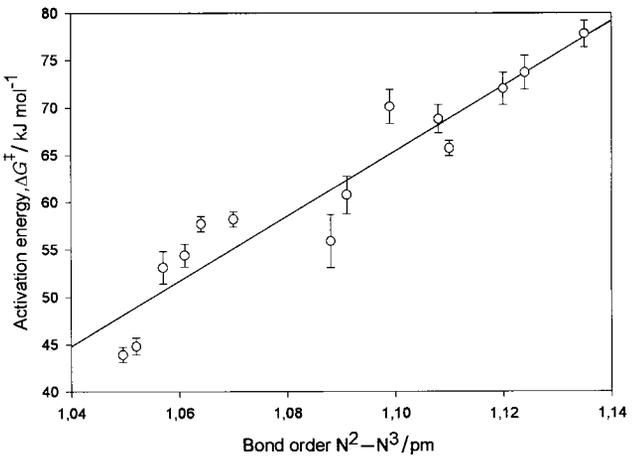

Fig. 3 Barrier to rotational *versus* bond order.

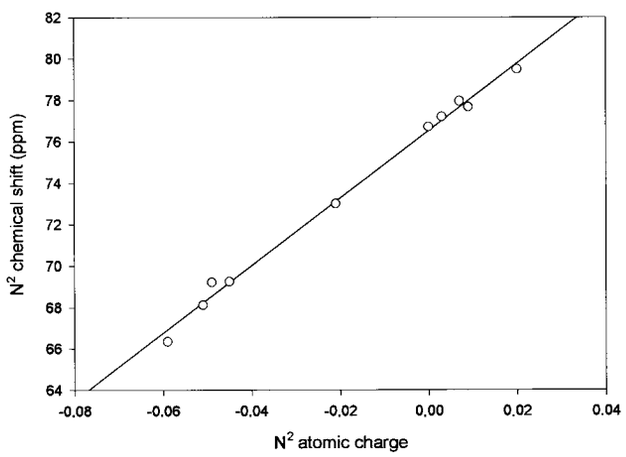

Fig. 4 N^2 chemical shift *versus* atomic charge.

Inspection of the data shows that the rotation of the NMe_2 moiety is related to the bond order: an increase in bond order results in raising the height of the energy barrier for rotation. Indeed by plotting $\Delta G^{\ddagger}$ as a function of the N^2–N^3 bond order a linear correlation is obtained with a correlation coefficient $r = 0.95$, as reproduced in Fig. 3. Experimental points corresponding to the isoxazolyltriazenes are in the upper right region of the plot, showing that the effect of the heterocycle is to increase the bond order, or alternatively, in resonance theory language, to increase the contribution of the 1,3-dipolar form II. This feature is enhanced by strongly electron-withdrawing substituents located in the isoxazole ring, such as a nitro group. The latter corresponds to the largest bond order in the set and therefore to the highest measured barrier height of 78 kJ mol^{-1}. The latter effect echoes a trend, already described in the literature for some aryltriazenes, in which the *para*-NO_2 derivative has the largest bond order, with $\Delta G^{\ddagger} = 65.7$ kJ mol^{-1}. In contrast to the isoxazolyl triazenes, the alkyltriazenes appear in the lower barrier region of the plot, corresponding to a decrease in the contribution from the 1,3-dipolar form and to a less restricted rotation accordingly.

The increase in N^2–N^3 bond order reported in Table 2 is always associated with a corresponding decrease in the N^1–N^2 bond order. This is in agreement with a progressively larger contribution of the 1,3-dipolar mesomeric form. The electron charge redistribution toward the substituent at N^1 is monitored by the atomic charges calculated by the molecular orbital

Table 3 ^{15}N chemical shifts and atomic charges in the triazene group

R	Atomic net charge		^{15}N chemical shift		Ref.
	N^2	N^3	N^2	N^3	
Phenyl	−0.049	−0.011	69.22	−224.23	5
p-Methylphenyl	−0.051	−0.012	68.12	−226.29	5
p-Methoxyphenyl	−0.059	−0.013	66.35	−228.16	5
p-Nitrophenyl	−0.021	0.010	73.01	−210.64	5
p-Chlorophenyl	−0.045	0.008	69.25	−221.83	5
5-Methylisoxazol-3-yl	0.003	0.003	77.21	−216.09	this work
4-Carboxy-5-methylisoxazol-3-yl	0.009	0.012	77.69	−211.54	this work
4-Bromo-5-methylisoxazol-3-yl	0.007	0.010	77.97	−210.52	this work
4-Nitro-5-methylisoxazol-3-yl	0.020	0.018	79.50	−204.77	this work
5-Methyl-4,5-dihydroisoxazol-3-yl	0.000	−0.003	76.72	−216.22	this work

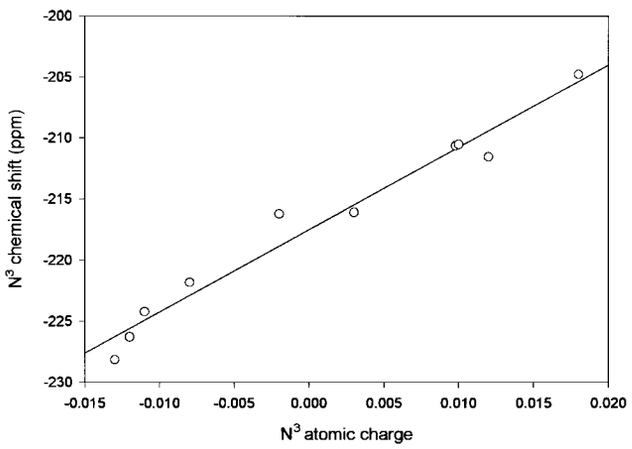

Fig. 5 N^3 chemical shift *versus* atomic charge.

technique and collected in Table 3. An experimental test for the reported values for the N^2 and N^3 atoms is given by their ^{15}N NMR chemical shifts, also included in Table 3. The variation of the ^{15}N chemical shifts with substitution has been previously described[12] in the literature for a series of 1-aryl-3,3-dialkyltriazenes, which show good correlations between the chemical shifts and the electronic properties as measured by the σ substitution coefficient for the *meta* and *para* substituents in the aryl group. In the present work a direct correlation has been obtained between chemical shift and MO atomic charge, as shown in the plots of Figs. 4 and 5.

Conclusions

The results described in the present paper show that the triazenyl group has an electronic structure which is strongly affected by the nature of the substituent attached to N^1. In particular electron-withdrawing substituents favour the 1,3-dipolar mesomeric form of the triazene. This effect is associated with an increase in the bond order and an electronic charge shift from atoms N^3 and N^2 toward the substituent. These two structural features can be detected by NMR spectroscopy: the N^2–N^3 bond order increase is correlated with a restricted rotation of the dialkylamino NR_2 group, *i.e.* with a higher energy barrier as measured by lineshape analysis of the ^1H NMR resonances, while the charge drain is correlated with a deshielding of nuclei N^2 and N^3, *i.e.* with a ^{15}N chemical shift toward high frequency. In this context the isoxazole ring appears to be a powerful electron-withdrawing substituent showing both a high energy barrier of rotation and deshielding of atoms N^2 and N^3.

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