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ARTICLE *in* MAGNETIC RESONANCE IN CHEMISTRY · JULY 2005

Impact Factor: 1.18 · DOI: 10.1002/mrc.1592 · Source: PubMed

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Magn. Reson. Chem. 2005; **43**: 563–566
Published online 29 April 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mrc.1592

Tautomerism and ^{1}H, ^{13}C and ^{15}N NMR spectral assignments of some nitro derivatives of malonic acid diamide

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Received 10 January 2005; Revised 27 February 2005; Accepted 7 March 2005

Because of its reactivity, malonic acid diamide (1) was initially identified as an alternative precursor for the development of a new class of high-density insensitive energetic materials possessing low sensitivity to thermal decomposition and detonation by impact. Nitration of 1 was studied under different conditions and led to three different tautomeric forms (2–4) of nitromalonic acid diamine. Using stronger oxidation conditions the oxadiazole 5 was generated in one step. We report the full ^{1}H, ^{13}C and ^{15}N NMR structural characterization of these compounds in DMSO together with thermal, infrared, mass spectrometric and x-ray analysis. Experimental data obtained for 4 are compatible with an enol-imine form. Our interpretation is consistent with calculated ^{1}H and ^{13}C NMR spectra (ACD).

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; energetic compounds; malonic acid diamide; nitration; imine; oxadiazole; furoxan

INTRODUCTION

The synthesis and structural characterization of new insensitive energetic compounds with high density and improved energetic properties have been the focus of recent studies in our laboratories. The most significant properties or characteristics of high-performance energetic materials are the molecular composition, heat of formation, solid-state density and microstructure. Recently, our research efforts were concentrated on the synthesis and structural characterization of energetic compounds bearing both amino and nitro substituents. Having in mind the above observations and in continuation of this work, we studied the nitration of malonic acid diamide (**1**) (Scheme 1) which was initially identified as an alternative precursor for the development of a new class of insensitive energetic materials, because of its inherent thermal stability. Reported structural investigations on nitromalonamide dealt with x-ray and neutron diffraction[1–3] measurements performed on a single crystal at ambient or very low temperature and showed the presence of a single tautomer corresponding to structure **3**, the enol form. These studies evidenced a very short intramolecular hydrogen bond leading to a nearly symmetrical planar structure with a slightly asymmetric position of the acidic hydrogen between the two oxygen atoms. This structure and especially the strength and nature of the nitrogen bond were studied by theoretical *ab initio* and semi-empirical calculations.[2–5] In this paper, we report the detailed ^{1}H, ^{13}C and ^{15}N NMR structural characterization of three tautomeric forms of nitromalonic acid diamide **2** (diketo), **3** (enol) and **4** (enol-imine) forms and also the oxadiazole **5** (furoxan-3,4-dicarboxamide) obtained using different oxidation conditions (Scheme 1).

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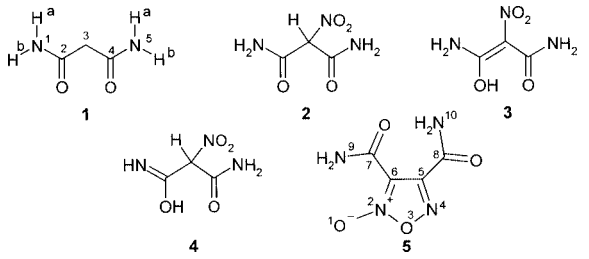
RESULTS AND DISCUSSION

All experimental chemical shifts extracted from the ^{1}H, ^{13}C and ^{15}N NMR spectra of molecules **1**–**5** are given in Table 1. Chemical shifts of the tautomers **2**–**4** calculated with the ACD program are also given for protons (except exchangeable protons, which are generally dependent on solvent effects) and all carbons. The data concerning starting material **1** in DMSO are similar to already published results[6,7] and are given for comparison. They are compatible with a diketo form in a blocked conformation. The two different NH proton signals of the two protons of both amide groups (H^a and H^b; see Scheme 1) were assigned by the observation in the NOESY experiment showing a positive NOE contact only between H^a and H-3 and not with H^b. In addition, a negative exchange peak between H^a and H^b was observed.

Tautomers 2 and 3

Previous investigations on single crystals of nitromalonamide performed by x-ray and neutron diffraction[1–3] measurements and theoretical calculations[2–5] showed the existence of a single tautomer corresponding to structure **3**, the enol form. The present NMR measurements on nitromalonamide in DMSO solution show two separate sets of signals compatible with a mixture of both tautomers **3** and **2** (diketo). The relative concentrations as determined from ^{1}H NMR spectra are 55 and 45%, respectively. ^{1}H and ^{13}C chemical shifts assignments of the mixture were established on the basis of TOCSY, HMQC and COLOC experiments. The unique line observed at δ 170.3 ppm for the two carbon atoms



Scheme 1. Structures of malonic acid diamide (**1**) and its nitro derivatives.

of the carbonyl and enol function of structure **3** agree well with the mean calculated value for both carbons (Table 1). This is consistent with the existence of an almost symmetrical structure with the acid proton equally spaced between the two oxygen atoms (as in the solid state) or alternatively with a rapid equilibrium between the two enolic forms of **3** which makes positions 2 and 4 chemically equivalent.

^{15}N chemical shifts of the nitro group and the amide group for both structures were unambiguously assigned on the basis of quantitative ^{15}N NMR measurements (measured integrations $I_{NH_2}/I_{NO_2} = 2$ for both sets of signals and the same proportions as in the ^{1}H NMR spectrum) and ^{1}H-coupled spectra [couplings $^1J(^{15}N,^1H) = 88.4$ and 89.6 Hz for **2** and **3**, respectively]. As for the carbon and the protons, a unique line is observed for both amide groups of structure **3**.

Tautomer 4

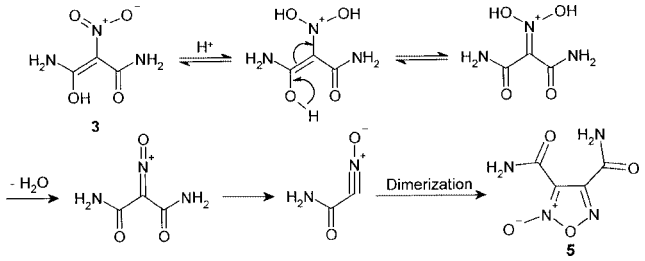
NMR and differential scanning calorimetric (DSC) measurements obviously established that the nitration conditions we used led to the formation of another compound with different thermal properties but the same weight as **2** and **3**, confirmed by chemical ionization mass spectrometry (CI-MS). This third isomer of nitromalonamide could be the nitrated enol-imine form shown as structure **4**. To our knowledge, experimental evidence for such a structure has not been reported until now. Our interpretation is supported by the following observations. (i) The ^{1}H NMR spectrum contains a single line strongly deshielded at δ 6.13 ppm integrating for one proton which corresponds to an aliphatic proton. (ii) Two sets of signals characteristic of exchangeable protons are detected, both integrating for two hydrogen atoms: the first one exhibits two single lines around 7.9 ppm characteristic of an amide group (a situation similar to that for malonamide), the second is a broad line at δ 10.17 ppm assigned to exchangeable acid protons, N*H* (imine) and/or O*H* (enol). (iii) The presence of a strongly deshielded aliphatic ^{13}C signal at δ 91.4 ppm and two non-equivalent carbonyl signals around δ 161 ppm observed in the ^{13}C NMR spectrum confirms the non-symmetric structure of the tautomer **4**. (iv) Both experimental ^{1}H and ^{13}C chemical shifts are consistent with ACD-calculated spectra. (v) Two signals bearing the same integration are observed in the ^{15}N NMR spectrum of **4**: the nitro and the amino groups at δ −8.0 and −270.1 ppm, respectively. The coupling constant $^1J(^{15}N,^1H) = 88$ Hz was directly measured in the ^{1}H-coupled ^{15}N NMR spectrum. The absence of a signal for the nitrogen atom N-1 is certainly a consequence of the broadening effect due to proton exchange between imine, enol and probably residual water protons as revealed in the ^{1}H NMR spectrum. This is a common situation encountered

Table 1. Chemical shifts, δ (ppm), of compounds **1**–**5** in DMSO, referenced to TMS for ^{1}H and ^{13}C and to CH_3NO_2 for ^{15}N (for details, see Experimental)[a]

	1	**2**	**3**	**4**	**5**
H-1a	7.46	7.93	9.27	10.17	—
H-1b	7.04	7.76	8.92	—	—
H-3a,b	2.96	5.92 (5.4)	—	6.13 (5.6)	—
H-5a	7.46	7.93	9.27	7.98	—
H-5b	7.04	7.76	8.92	7.83	—
2-OH	—	—	3.46[b]	10.17	—
H-9,10	—	—	—	—	8.73, 8.43
					8.37, 8.32
C-2	169.4	161.6 (164.4)	170.3 (194.5)	161.3 (166.3)	—
C-3	43.2	90.5 (97.0)	106.3 (104.1)	91.4 (85.4)	—
C-4	169.4	161.6 (164.4)	170.3 (156.8)	160.7 (165.1)	—
C-5	—	—	—	—	151.5
C-6	—	—	—	—	110.1
C-7,8	—	—	—	—	159.8, 158.0
N-1	—	−269.7	−270.2	—	—
N-2	—	—	—	—	−4.7
3-NO_2	—	−6.3	−14.3	−8.0	—
N-4	—	—	—	—	−18.5
N-5	—	−269.7	−270.2	−270.1	—
N-9,10	—	—	—	—	−267.1, −268.7

[a] Values in parentheses were calculated with the ACD program.

[b] OH-exchange peak with residual water.



Scheme 2. Tentative reaction mechanism for the formation of the oxadiazole derivative **5**.

in ^{15}N NMR spectroscopy when an intermediate regime governs the exchange process.

When tautomer **4** was subjected to radiocrystallographic analysis, structure **3** emerged. However, recrystallization of the sample in 2-propanol was necessary prior to that analysis during which **4** could convert to **3**. Although **4** could not be detected by x-ray measurements, this experiment confirms that **4** is an isomer of **3**. In addition, NMR measurements of a DMSO solution of structure **4** repeated after a few weeks at ambient temperature show the presence of structure **2** together with the formation of degradation products.

Oxadiazole 5

We have already seen that the nature of the oxidation products depends on the concentration of the nitric acid used. Therefore, we investigated the nitration of **1** under more acidic conditions. In an attempt to convert the malonamide **1** into dinitro compounds, **1** was treated at 10–12 °C with N_2O_4-fortified (15%) nitric acid; none of the desired product was obtained but instead the oxadiazole **5** was produced.

We suggest that this method involves the production of nitrile oxide from the nitro-containing precursor **3**. It is known that nitrile oxide dimerizes unless intercepted by a dipolarophile and thus produces 3,4-disubstituted-1,2,5-oxadiazole-2-oxides (Scheme 2).[8–11] This compound has been reported before but its synthesis is usually more complex and involves very toxic reactives.[11–13]

Extensive quantitative ^1H, ^{13}C and ^{15}N NMR spectroscopy clearly showed the presence of two inequivalent amino groups (four proton lines and two nitrogen lines) and carbonyl groups (two carbon lines) as shown in Table 1. Two other signals detected in the ^{13}C NMR spectrum at δ 110.1 and 151.5 ppm are characteristic of the furoxan carbon atoms C-6 and C-5, respectively.[14–17] The structure is confirmed by the two lines of equal integration detected in the ^{15}N NMR quantitative spectrum at δ −4.7 and −18.5 ppm, which are compatible with nitrogen N-2 and N-4 respectively.[18]

CONCLUSION

We investigated the nitration of malonic acid diamide, providing a safe and efficient method for the production of derivatives which are suitable for designing new energetic materials. We showed that the nature, thermal stability and structure of the reaction products depend strongly on the composition of the nitric acid used. Three different tautomers of nitromalonic acid diamide, namely diamide, enol and enol-imine forms, and a furoxan structure were identified from the full ^1H, ^{13}C and ^{15}N NMR data. The experimental results presented in this paper can be the basis of further investigations of the relative structural stability and equilibrium between tautomers as studied by NMR spectroscopy using different solvents and varying temperatures.

EXPERIMENTAL

Compounds

*Mixture of 2-nitromalonamide (**2**) and 3-amino-3-hydroxy-2-nitroacrylamide (**3**).*[1–4] To an ice-cooled solution of malonic acid diamide (**1**) (2 g, 0.019 mol) in acetic acid (15 ml), 99% nitric acid (3 ml) was added dropwise. During the addition, the temperature was kept at 15–20 °C using an ice-bath. The mixture was stirred for an additional hour with continued cooling and then filtered. The product was washed with a mixture of ice and water. The product was dried under reduced pressure and gave 2.42 g (86%) of a mixture of **2** and **3**. DSC: 177 °C (single sharp exothermic peak). IR (neat): ν = 3390, 3280, 1494, 1286, 1145, 1039, 786 cm^{-1}. CI-MS: m/z (%) 148 (100) [M + 1]. $C_3H_5N_3O_4$ (147.09): calcd C 24.49, H 3.43, N 28.57, O 43.61; found C 24.53, H 3.45, N 28.46, O 43.05%.

*2-Carbamoyl-2-nitroacetimidic acid (**4**).* Malonic acid diamide (**1**) (2 g, 0.019 mol) was added over a 5 min period in small portions with constant agitation to 12 ml of 99% nitric acid. During the addition, the temperature increased up to 50 °C. After complete addition of malonamide, the acid solution was quickly poured on to crushed ice, and the product was separated quickly by filtration and washed with cold water. The air-dried product **4** weighed 0.840 g (30%). DSC: 135 °C (single sharp exothermic peak). IR (neat): ν = 3208, 1657, 1589, 1416, 1352, 1269, 1035, 917, 715 cm^{-1}. CI-MS: m/z (%) 148 (100) [M + 1]. For x-ray measurements the product was dissolved in 2-propanol at reflux and slowly recrystallized during 4 days at ambient temperature to produce several monocrystals.

*1,2,5-Oxadiazole-3,4-dicarboxamide-2-oxide (**5**).*[19,20] Malonic acid diamide (**1**) (2 g, 0.019 mol) was added over a 1 min period in small portions with constant agitation to 12 ml of N_2O_4-fortified (15%) nitric acid. During the addition, the temperature was kept at 10–15 °C by cooling with an ice-bath. After complete addition of **1**, the mixture was stirred for 5 min with continued cooling. Then the acid solution was poured on to crushed ice and the furoxan was separated by filtration and washed with cold water. The product was dried under reduced pressure, giving 1.31 g (40%) of **5**. DSC: 260–262 °C (single sharp exothermic peak). IR (neat): ν = 3403, 3215, 3095, 1690, 1556, 1460, 1395, 1325, 1024, 749 cm^{-1}. CI-MS: m/z (%) 173 (100) [M + 1], 157 (8), 129 (8), 89 (11), 71 (15), 61 (24).

Measurements and NMR spectra

The malonamide was purchased in the highest purity commercially available and was used without further

purification. DSC analyses were recorded with a Mettler DSC 822 apparatus by heating a few milligrams of sample at 10 °C min^{-1} in the presence of static air. IR spectra were recorded on a Perkin-Elmer Universal ATR sampling accessory. Mass spectra were recorded on a HP 5973 mass spectrometer at the University of Pharmacy of Tours, France.

All NMR measurements were performed at room temperature on Bruker Avance 200, Avance 300 WB and Avance 400 WB spectrometers. Solutions with concentrations in the range 50–100 mg ml^{-1} in $(CD_3)_2SO$ were prepared for analysis. Experiments were carried out at 200 and 400 MHz for ^1H, 50 and 100 MHz for ^{13}C and 30 and 40 MHz for ^{15}N using a standard Bruker 5 mm QNP probe for ^1H and ^{13}C measurements and an H-X Broadband probe for 10 mm sample tubes for ^{15}N measurements. ^1H and ^{13}C chemical shifts were calibrated according to the DMSO solvent signal used as a secondary internal reference (^1H δ 2.5 ppm, ^{13}C δ 39.5 ppm, with respect to TMS, δ 0 ppm). The ^{15}N signal of a 90% formamide solution in DMSO (δ −268 ppm, with respect to CH_3NO_2, δ 0 ppm) was used as an external secondary reference for ^{15}N chemical shifts.

Excitation pulses of 8 μs (90° flip angle) and relaxation delays of 10 s were applied for recording ^1H spectra. The data point size was 32K for a resolution of 0.12 Hz per point (spectral width 4000 Hz). Depending on the spectrometer, excitation pulses in the range 6.5–7 μs (90° flip angle) and a recycle time of 10 s were used for direct ^{13}C measurements. For direct ^{15}N measurements, short pulses of about 7 μs (30° flip angle) and a long recycle time (>30 s) were used. The following parameters were used for ^{13}C and ^{15}N: data points size = 65K, resolution = 0.46 and 0.24 Hz per point for ^{13}C and 0.42 or 0.12 Hz per point for ^{15}N. When necessary, T_1 (^{15}N), the nitrogen-15 longitudinal relaxation time, was reduced to a value between 1 and 2 s by adding calibrated amount of paramagnetic relaxation agent [chromium(III) penta-2,4-dionate]. The induced paramagnetic relaxation time was controlled by measuring the aliphatic proton linewidth in the ^1H NMR spectrum. For ^1H-decoupled experiments, a ^1H radiofrequency field was applied only during the acquisition time, which was reduced to as short as reasonable (2 s for ^{13}C and 1 s for ^{15}N). This procedure almost eliminates any NOE effect, which can cause a dramatic loss of ^{15}N signal owing to its negative gyromagnetic ratio. Under such conditions, quantitative ^1H-coupled or decoupled ^{13}C and ^{15}N NMR spectra could be acquired with sufficiently high sensitivity. Typical scan numbers were in the range 100–500 and 5000–15 000 for ^{13}C and ^{15}N, respectively.

Conventional 2D (NOESY, TOCSY, COLOC, HMQC) correlation sequences were carried out. The NOESY and the TOCSY experiments were performed using mixing times of 0.2 s and 1.67 ms, respectively. The delay used in the COLOC experiment was set to $1/2J = 40$ ms in such a way that correlations involving J couplings higher than (or around) 12.5 Hz could be observed.

For the 2D experiments the following parameters were used: data points size (F_2/F_1): 2K/512 for NOESY and HMQC, 1K/512 for TOCSY and 4K/512 for COLOC; and resolution (F_2/F_1): 1.95/14.16 Hz for NOESY, 1.95/39.3 Hz for HMQC, 2.35/4.69 Hz for TOCSY and 4.92/12.5 Hz for COLOC.

All calculated ^1H and ^{13}C NMR data were obtained using the ACD predictor commercial program (V. 4.08) from Advanced Chemistry Development.

Acknowledgements

The authors thank Dr H. Allouchi for helpful technical assistance.

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