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Synthesis, characterization, and structure of a new *N*-nitrosamine of cyclam (1,4,8,11-tetraazacyclotetradecane)

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Abstract—A novel *N*-nitrosamine of cyclam has been synthesized. The N–N bond lengths values, as determined from the X-ray crystal structure, fall in the 1.318(2) and 1.320(2) Å range, smaller than the ones expected for the N–N single bond. The N–NO bond angles are in the 115.0(1)° and 114.8(1)° range. The νNO, νNN, and δN–NO vibrational modes were observed in the infrared spectrum at 1454, 1139, and 555 cm^{-1}, respectively. The photolysis of the cyclam$(NO)_4$ compound gives rise to the nitrosyl release through an heterolytic cleavage of the N–NO bonds, as indicated by the appearance of the νNO^+ band at 2228 cm^{-1} at the expense of decreasing the νNO, νNN, and δN–NO bands.

It has been reported that cyclam (1,4,8,11-tetraazacyclotetradecane) has slight activity against HIV-1 (IC_{50}, 399 μM) and HIV-2 (IC_{50}, 150 μM),[1] whereas a series of cyclam derivatives possess greatly increased anti-HIV activity.[2] For example, the HIV-1 and HIV-2 IC_{50} values for the *N*-(4-methylbenzyl)cyclam derivative are 1.4 and 1.1 μM, respectively.[1] Also, the incorporation of NO in the composition of many molecules is of interest to study the chemical and enzymatic mechanisms of NO release and the pharmacological aspects and biomedical applications of these compounds.[3] Assuming that these *N*-nitroso compounds belong to a class of NO donors by transferring nitrosyl homolytically or heterolytically to another species,[4] we have performed the nitrosylation reaction of the cyclam species aiming to study the reactivity of a new *N*-nitrosamine system toward the release of nitric oxide species. The *N*-nitrosamines are generally considered as carcinogens,[5] although the literature report the vasorelaxant activity with concomitant stimulation of soluble guanylyl cyclase (sGCs) for some of them.[6,7]

We report here the synthesis, characterization and X-ray structure of a new *N*-nitrosamine of cyclam, as well as a preliminary photoreactivity study toward NO release.

The *N*-(tetranitrosamine)cyclam compound, cyclam$(NO)_4$, was prepared by the reaction of the nitrosating agent (HNO_2) with cyclam in aqueous solution.[8] The elemental analysis data are consistent with the chemical formulation $C_{10}N_8H_{20}O_4$. Recrystallization of cyclam$(NO)_4$ from water solution yielded pale yellow crystals suitable for single crystal X-ray analysis.[9] An ORTEP view of the structure[10] is shown in Figure 1.

The N–N bond lengths values fall in the 1.318(2) and 1.320(2) Å range, similar to those observed for nitrosamines in which the NNO moieties are linked to sp^3-hybridized carbon atoms.[11–13] These lengths are smaller than the ones expected for the N–N simple bond[12,13] (1.42 Å), as could be expected due to the contribution of the resonant forms showed in Scheme 1.

The N–O bond lengths fall in the 1.244(2) and 1.246(2) Å range. The N–NO bonds angles are 115.0(1)° and 114.8(1)° and the four CNN angles fall in the 114.2(1)°–122.5(1)° range. These findings are all

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Keywords: *N*-Nitrosamine; Cyclam; Photoreactivity; NO release.

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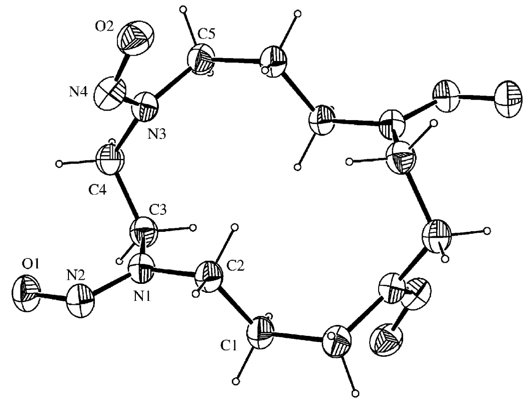
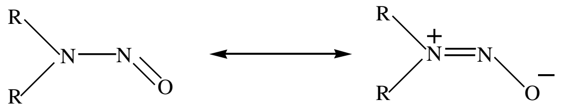


Figure 1. ORTEP-3 projection of the cyclam(NO)$_4$ compound.



Scheme 1. Resonant forms of N–NO bonds of *N*-nitrosamines.

consistent with those reported in the literature for *N*-nitrosamines compounds.[11–13]

The infrared spectrum (IR) of cyclam(NO)$_4$ displays two characteristic bands at 1454 and 1139 cm^{-1} assigned to the νNO and νNN modes, respectively. The peaks of νN–H observed in the range 3400–3190 cm^{-1} in the spectrum of the cyclam starting material disappear in the spectrum of cyclam(NO)$_4$. The bent deformation mode of the N–N–O bonds is observed at 588 cm^{-1} in the spectrum of the free N_2O, under nitrogen atmosphere.[14] In the same conditions this peak is observed at 555 cm^{-1} for cyclam(NO)$_4$. In agreement with the formulation proposed here, this peak is not observed in the spectrum of the cyclam macrocyclic compound.

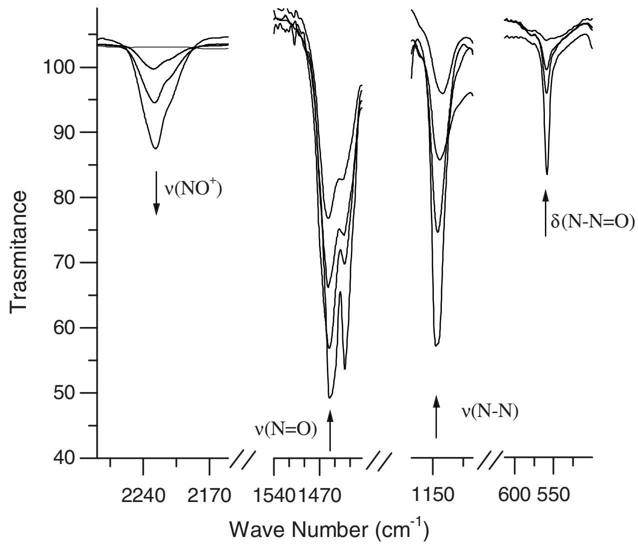


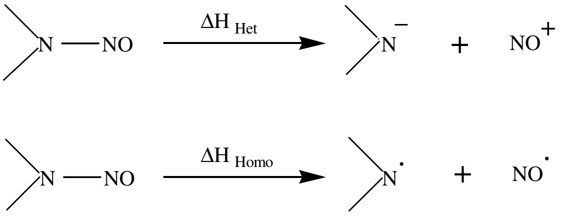
Figure 2. Infrared spectra of the cyclam(NO)$_4$ compound dispersed in KBr as function of the irradiation process under white light.

Upon white light photolysis of the title compound dispersed in KBr, the infrared spectra (Fig. 2) showed the decrease of the νNO, νNN, and δN–NO bands at the expense of the appearance of a new band at 2228 cm^{-1}, assigned to νNO^+ stretching mode.[15] This indicates that the cyclam(NO)$_4$ compound under white light photolysis conditions behaves as a nitrosyl donor through an heterolytic cleavage of N–NO bond, contrary to that is generally observed for most *N*-nitrosamines.[16,17] It has been reported that the homolytic cleavage of N–NO bonds is thermodynamically more favorable than the heterolytic cleavage by 23.6–44.9 kcal/mol,[4,16] suggesting that the N–NO bonds would much favor generating $NO^{\bullet}$ rather than NO^+ (Scheme 2).

As generally observed for *N*-nitrosamines,[18] the electronic spectrum of the cyclam(NO)$_4$ compound in dichloromethane showed two absorptions at 365 nm ($\varepsilon = 2.76 \times 10^2$ M^{-1} cm^{-1}) and 238 nm ($\varepsilon = 2.33 \times 10^4$ M^{-1} cm^{-1}), corresponding to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively.

The mass spectrum[19] of cyclam(NO)$_4$ is displayed in Figure 3. The molecular ion is observed at *m*/*z* 317 as expected for the proposed structure of the compound. Although the molecular ion of cyclam(NO)$_4$ gives a mass of 317 we found in the APCI mode four additional peaks at *m*/*z* 286, 257, 226, and 197. A subsequent loss of one, two, three, and four NO molecules, would account for the observation of these peaks. The series of steps that involve stepwise loss of NO from the original species is presented in Scheme 3.

The data collected in this work suggest that the cyclam(NO)$_4$ is a potential NO-donor compound under white light photolysis conditions.



Scheme 2. Homolytic and heterolytic cleavage modes for N–NO bond.

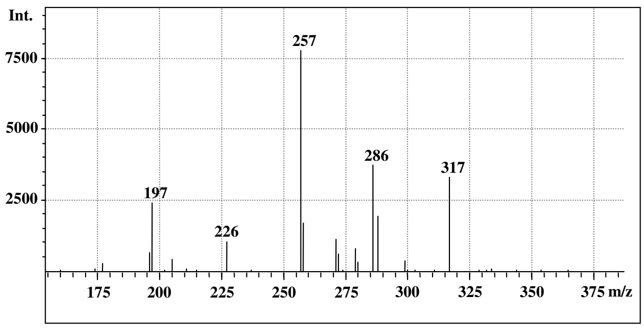
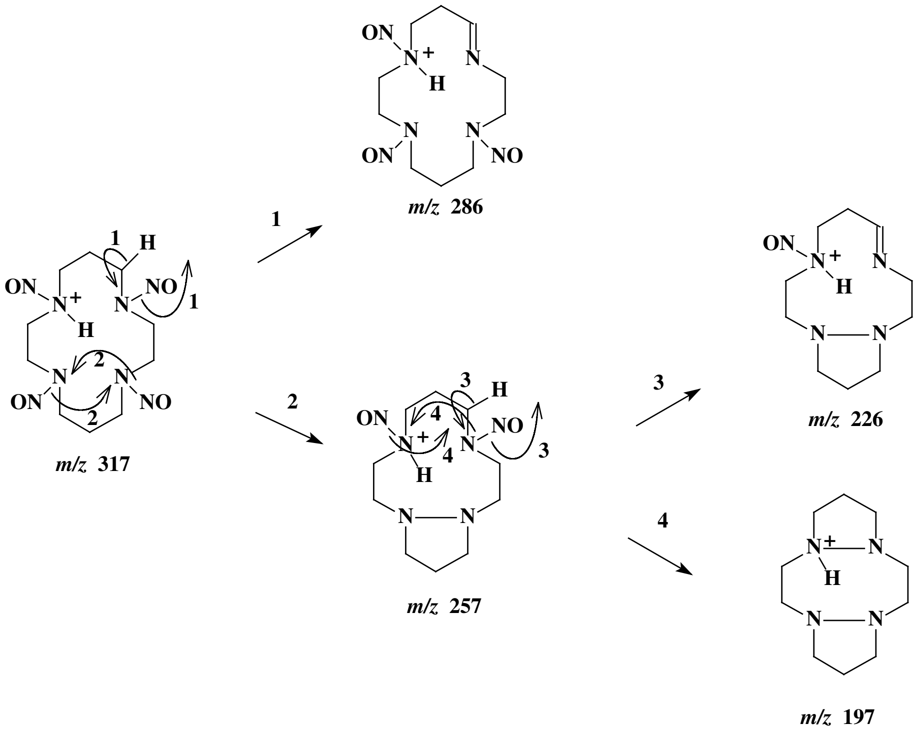


Figure 3. Mass spectrum of the cyclam(NO)$_4$ compound.



Scheme 3. Pictorial steps for the stepwise loss of NO from the cyclam$(NO)_4$ compound.

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8. Typical procedure: 100 mg (50 mmol) of 1,4,8,11-tetraazacyclotetradecane (cyclam) were dissolved in 30.0 mL of distilled water. A NO flow (produced by the reaction of $NaNO_2$ salt with H_2SO_4) was bubbled through this solution during 4 h, when it was observed the precipitation of a yellow crystalline solid. The crystals were collected by filtration, washed with cold water, and dried under vacuum. Elemental analysis: Cald C: 37.97; H: 6.37; N: 35.42. Found. C: 37.69; H: 6.34; N: 35.26.
9. X-ray data for the cyclam$(NO)_4$: X-ray data were collected at 120 K on a NONIUS KAPPA-CCD diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SHELS-97). Refinement was done by full-matrix least-squares procedures on F^2 using SHELX-97. All non-hydrogen atoms were refined anisotropically. $C_5H_{10}N_4O_2$, MW = 158.17, colorless crystal of size: $0.20 \times 0.04 \times 0.02$ mm^3, crystal system: Monoclinic, space group: $P2_1/c$, cell parameters: $a = 9.0624(4)$ Å, $b = 7.4402(4)$ Å, $c = 11.4115(7)$ Å, $\beta = 109.503(2)°$, $V = 725.29(7)$ Å^3, $Z = 4$, $Dc = 1.449$ mg/m^3, $T = 120(2)$ K, μ(Mo Kα) = 0.114 mm^{-1}, $F_{000} = 336$. Total number of l.s. parameters = 100, $R1 = 0.0418$ for 1034 $I > 2\sigma(I)$ and 0.0525 for all 1262 data. $WR2 = 0.1159$, GOF = 1.049 for all data. Crystallographic data (excluding structure factors) for cyclam$(NO)_4$ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 249972. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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19. LCMS analyses were conducted using isocratic elution (acetonitrile/water, 90:20 v/v) with a Shimadzu C18 column (250×2.0 mm, 4.6 μm). The experiments were carried out on a Shimadzu LCMS-2010 equipment. The measurements were performed in positive mode by scanning between *m/z* 50 and 400 using an APCI interface and SIM technique.