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Synthesis, characterization and X-ray structural determination of a stable dication derived from symmetrical *ortho*-aminophenyl diamine and 2-pyridinecarboxaldehyde

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ABSTRACT

N,*N*′-Bis(2-aminophenyl)-1,2-ethanediamine is synthesized from 1,2-diaminoethane and 1-chloro-2-nitrobenzene in the presence of sodium carbonate and the product reduced by zinc dust and ammonium chloride. A novel stable dication is synthesized by reaction of *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine and 2-pyridinecarboxaldehyde in the presence of manganese chloride in methanol. The X-ray structural analysis shows formation of the dication.

Introduction

Protozoal parasitic diseases continue to pose serious public health problems in developing parts of the world. One such disease is leishmaniasis, a disease in humans caused by several species of the Leishmania parasite. These unicellular organisms are related to trypanosomes, the pathogenic parasites responsible for sleeping sickness in Africa and Chagas' disease in South America. In recent years, the coexistence of human immunodeficiency virus and Leishmania species causing visceral disease has resulted in several hundred cases of dually infected individuals.[1] By current estimates, leishmaniasis affects people in 88 countries, with 350 million at risk of contracting the disease and approximately 2 million new cases each year (www.who.int/emc/diseases/leish/leisdis1.html). The devastating impact of this disease is exemplified by the epidemic of visceral leishmaniasis that occurred in the 1990s in the Sudan.[2] Dicationic compounds based on aromatic rings have shown impressive antimicrobial activity against a variety of organisms.[3–5] Dicationic molecules showing improved efficacy and reduced toxicity compared to pentamidine have been reported in animal models of pneumocystosis and cryptosporidiosis.[6–8] Many of these compounds also possess excellent activity against Leishmania parasites. The antileishmanial activity of several such dicationic molecules was reported in 1990.[9] Since, many new dications have been synthesized and improved assay systems have been developed for testing of candidate drugs against amastigote-like parasites.[10–13] Based on this, herein, we report the synthesis and characterization of the dication **3** derived from *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine **2** and 2-pyridinecarboxaldehyde. The diamine, **2**, was synthesized by reaction of 1,2-diaminoethane with 1-chloro-2-nitrobenzene in the presence of sodium carbonate and reduction of the resulting product **1** using dust zinc and ammonium chloride.

The dication was prepared by reaction of *N*,*N*′-bis(2-aminophenyl)-1,2-ethandiamine **2** and 2-pyridinecarboxaldehyde in the presence of $MnCl_2$. Next, sodium perchlorate was added to stabilize the product (Scheme 1). The absence of bands characteristic of the carbonyl and primary amine groups of the starting materials in the infrared spectrum, and also the absence of a Schiff-base ν(C=N) vibration and the presence of perchlorate vibrations were evidence of formation of the dication. The reaction was almost quantitative and produced a pale yellow solid which was stable in air and soluble in common organic solvents. The structure of the dication **3** was confirmed by elemental analysis, IR, and X-ray diffraction. The IR spectrum shows a strong band at 1591 cm^{-1} assignable to the pyridine-ring vibrations. In solution or solid state, dications are stabilized by counterions, by interaction with solvent molecules,[14] and/or by appropriate ligands.[15,16] Large polyatomic dications can also be stabilized by appropriate substituents that are able to accommodate the positive charge. Our dication is stabilized by perchlorate ions. Absorptions attributable to ionic perchlorate were found at approximately 1097 and 738 cm^{-1}. A single crystal of **3** was prepared, and X-ray crystallography clearly showed that a dication had been synthesized.[17] Selected bond lengths and bond angles are listed in Table 1. An ORTEP representation of the crystal structure is shown in Figure 1 together with the numbering scheme adopted. The X-ray crystal structure confirms the presence of two well-separated perchlorate anions which are both well ordered, with expected Cl–O bond lengths and O–Cl–O angles. The structure has two planar five-membered imidazolium rings. This is in accordance with delocalization of the free electrons of nitro-

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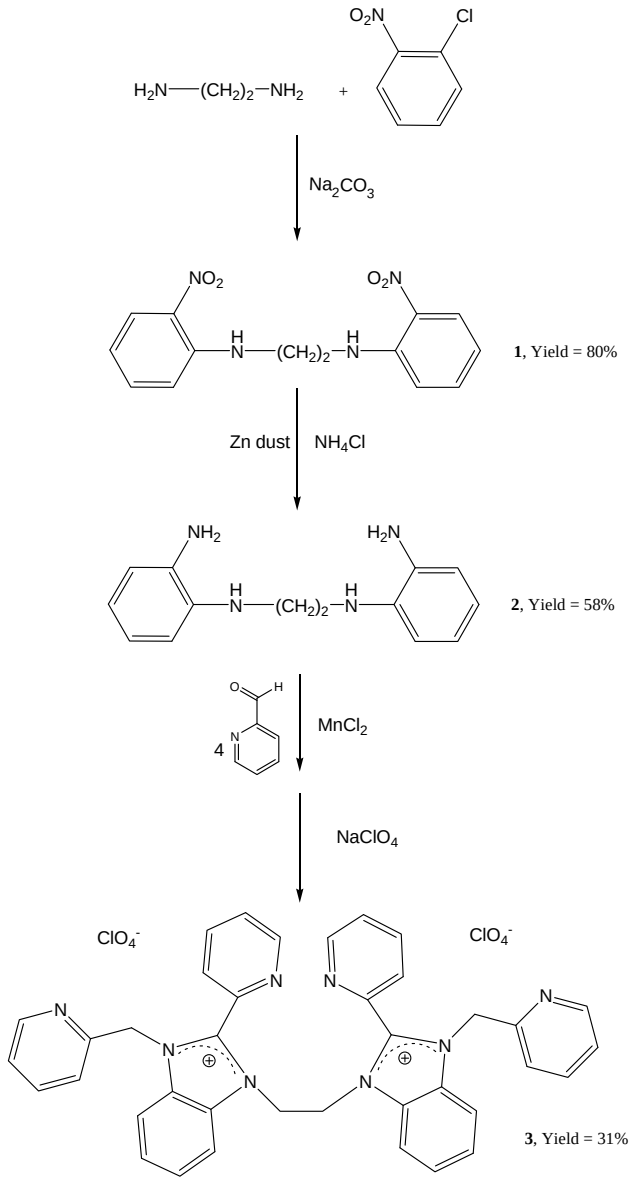

Scheme 1. Synthetic route for the preparation of *N*,*N*′-bis(2-nitrophenyl)-1,2-ethanediamine, *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine and the dication **3**.

Table 1
Selected bond lengths (Å) and bond angles (°) for the dication **3**

Bond length		Bond angle	
C(7)–C(12)	1.380(4)	N(2)–C(33)–N(3)	109.0(2)
N(3)–C(12)	1.385(4)	N(2)–C(33)–C(34)	124.4(3)
N(2)–C(7)	1.391(4)	N(3)–C(33)–C(34)	126.6(3)
N(2)–C(33)	1.343(4)	C(33)–N(2)–C(6)	126.9(2)
N(3)–C(33)	1.348(4)	C(7)–N(2)–C(6)	123.7(2)
N(2)–C(6)	1.473(4)	C(33)–N(2)–C(7)	108.5(2)
N(3)–C(13)	1.459(4)	C(8)–C(7)–N(2)	131.0(3)
C(33)–C(34)	1.468(4)	C(12)–C(7)–C(8)	122.1(3)
Bond angle		C(12)–C(7)–N(2)	106.9(3)
C(33)–N(3)–C(12)	108.5(2)	C(7)–C(12)–N(3)	107.1(3)
C(33)–N(3)–C(13)	127.9(2)	C(7)–C(12)–C(11)	122.2(3)
C(12)–N(3)–C(13)	123.6(2)	N(3)–C(12)–C(11)	130.7(3)

gen between the N–C–N atoms in the heterocyclic ring. The C–N bond lengths in the ring are different. The N(2)–C(33) and N(3)–C(33) bond distances are shorter, 1.343(4) Å and 1.348(4) Å, respectively, while the N(2)–C(7) and N(3)–C(12) bond distances

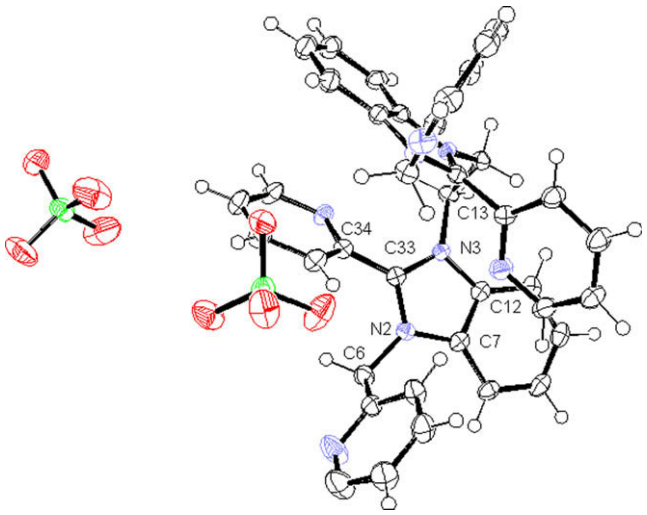

Figure 1. ORTEP drawing of the molecular structure of the dication **3**.

are greater, 1.391(4) Å and 1.385(4) Å, respectively. In the heterocyclic ring, the N(2)–C(7)–C(12) and C(7)–C(12)–N(3) angles are small, 106.9(3)° and 107.1(3)°, respectively, while the C(7)–N(2)–C(33) and N(2)–C(33)–N(3) angles are larger, 108.5(2)° and 109.0(2)°, respectively. Also, these distances and angles confirm the delocalization of the positive charge on the N–C–N atoms.

In conclusion, we have shown that an aromatic nitro compound (*N*,*N*′-bis(2-nitrophenyl)-1,2-ethanediamine) can be reduced in high yield to the corresponding diamine (*N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine) using zinc dust and NH_4Cl, and have reported the first synthesis and characterization of a dication from reaction of this diamine and 2-pyridinecarboxaldehyde in the presence of manganese chloride. The dication has been characterized by X-ray diffraction measurements.

Synthesis of *N*,*N*′-bis(2-nitrophenyl)-1,2-ethanediamine

1,2-Diaminoethane (0.6 g, 10 mmol), 1-chloro-2-nitrobenzene (3.15 g, 20 mmol), and sodium carbonate (2.12 g, 20 mmol) were mixed in a round-bottomed flask, and then fused at 170 °C for 3 h. The resulting solid was washed with 2:1 H_2O/EtOH. Yield: (80%), IR (KBr, cm^{-1}): 3378 ν(NH), 3105 ν(CH), 2951 $\nu(CH_2)$ and 1572 and 1360 $\nu(NO_2)$, ^1H NMR δ_H (300 MHz, $CDCl_3$, ppm) 3.39 (t, 4H, CH_2–CH_2), 6.66 (m, 4H, Ar), 7.37(t, 2H, Ar), 7.91 (d, 2H, Ar), 7.37 (t, 2H, NH). Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.93; H, 4.52; N, 18.28%. Melting point: 98 °C.

Synthesis of *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine

A mixture of *N*,*N*′-bis(2-nitrophenyl)-1,2-ethanediamine (3 g, 10 mmol), ammonium chloride (2.1 g, 40 mmol), and water 10 mL in ethanol 100 mL was heated to boiling, and then zinc dust (2 g, 30 mmol) was added. After 4 h, the solution turned pale green and was filtered, and then more water was added and the solution was adjusted to pH 11 with NaOH to yield *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine as a brown solid. Yield: (58%), IR (KBr, cm^{-1}): 3499 and 3452 $\nu(NH_2)$; 3336 ν(NH); ^1H NMR δ_H (300 MHz, $CDCl_3$, ppm): 3.33 (br, 10H, CH_2–CH_2 and NH), 6.64 (m, 8H, Ar); ^{13}C NMR δ_C (300 MHz, $CDCl_3$, ppm): 40.0, 135.9, 134.7, 120.1, 118.0, 113.4, 109.1. Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.46; N, 23.12. Found: C, 69.12; H, 7.14; N, 23.41. Melting point: 152 °C.

Synthesis of the dication

To a solution of *N*,*N*′-bis(2-aminophenyl)-1,2-ethanediamine (0.24 g, 1 mmol) and 2-pyridinecarboxaldehyde (0.43 g, 4 mmol) in methanol (50 mL), manganese chloride (0.13 g, 1 mmol) was added and the reaction was stirred for 6 h at room temperature. Next, sodium perchlorate (0.245 g, 2 mmol) was added. When the solution volume was reduced to 10 mL by evaporation a precipitate formed. This was filtered off, washed with ether, and dried in vacuo. Vapour diffusion of diethyl ether into a solution of the dication in MeOH afforded pale yellow crystals. Yield: (31%), IR (KBr, cm^{-1}) 3050 ν(CH), 1591 ν(py), 1097 and 738 $\nu(ClO_4^-)$. Anal. Calcd for $C_{38}H_{32}Cl_2N_8O_8$: C, 57.08; H, 4.03; N, 14.01. Found: C, 57.16; H, 4.08; N, 13.96. Melting point: 111 °C.

Acknowledgments

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17. Compound **3**: $C_{38}H_{32}Cl_2N_8O_8$, $F_W = 799.62$, triclinic, space group $P\bar{1}$, $a = 9.437(2)$, $b = 11.967(3)$, $c = 15.871(4)$ Å, $\alpha = 86.137(4)$, $\beta = 81.274(4)$, $\gamma = 79.979(4)°$, $V = 1742.9(7)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.524$ mg/m^{-3}, $F(000) = 828$, $\lambda = 0.71073$, $T = 150$ K, crystal size = 0.23 × 0.23 × 0.19 mm, of the 19,953 reflections collected ($1.30 \leqslant \theta \leqslant 27.630$) 7830 [$R_{int} = 0.0516$] were independent, $R_1 = 0.0597$ ($I > 2\sigma(I)$) and $wR_2 = 0.1409$. Crystallographic data for the structure reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre, CCDC 691720. Copies of this information may be obtained free of charge front the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK(Telephone: (44) 01223 762910: (44) 01223 336033; or EMAIL: deposit@ccdc.cam.ac.uk.