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Electronic and steric effects of substituents on the conformational diversity and hydrogen bonding of *N*-(4-X-phenyl)-*N*′,*N*″-bis(piperidinyl) phosphoric triamides (X = F, Cl, Br, H, CH_3): A combined experimental and DFT study

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ABSTRACT

Phosphoric triamides of the general formula (4-X-C_6H_4NH)P(O)($NC_5H_{10})_2$, X = F (**1**), Cl (**2**), Br (**3**), H (**4**) and CH_3 (**5**), have been synthesized and characterized. X-ray crystallography at 120 K reveals that the compounds **1**, **3**, **4**·$\mathbf{H_2O}$ and **5** are composed of one, four, two and four conformers, respectively. DFT calculations were performed to investigate the electronic structures of the compounds. The X-ray data and DFT calculations revealed that the conformational diversity in these compounds is mainly governed by the steric effects of the substituent X rather than by electronic effects. Although substituent X does not participate directly in hydrogen bonding, the crystal packing of the compounds is influenced by the size of X. Atoms in molecules (AIM) and natural bond orbital (NBO) analyses confirm that the *para* substituent X has no significant effect on the electronic features of the amidic proton and the phosphoryl oxygen atom (O_P). Using X-ray crystallography, AIM and NBO analyses, the structural and electronic aspects of inter- and intramolecular hydrogen bonds of the compounds have been studied. The charge density (ρ) at the bond critical point (bcp) of the N–H bond decreases from the fully optimized monomers to their corresponding hydrogen bonded clusters. The N–H stretching frequency decreases from the calculated values to the experimental results.

1. Introduction

Phosphoric triamides have received considerable attention due to their applications as inhibitors of urease [1–3] and acetylcholinesterase [4,5] and as stereoselective catalysts [6–8]. Furthermore, we have already shown that phosphoric triamides can be considered as an efficient extracting agent for lanthanides [9]. The ring inversion and rotation of cyclic amines around the P–N bond provide different conformers in phosphoric triamides [10,11]. Such compounds with two [12–14], three [15,16] and four [17,18] conformers have been previously reported. The conformational diversity in these compounds creates a wide range of hydrogen bonds [17,18]. It is well known that hydrogen bonds play a key role in biochemical processes such as enzymatic activity [19,20] and protein–ligand interactions [21]. Moreover, physicochemical properties of compounds (boiling and melting points, density, dipole moment, etc.) depend on the presence of non-covalent interactions and intermolecular hydrogen bonds [22]. Hence, the analysis of hydrogen bonds is helpful to rationalize the structural and physicochemical properties of compounds. In previous works, we have performed conformational analysis of phosphoric triamides with three [16] and four conformers [17]. In this area, a comparison of the electronic and steric effects of substituents on the structure of conformers needs to be investigated. The major aim of the present work is to investigate which of the electronic or steric effects can influence the formation of various conformers. In the present study, five compounds with the formula (4-X-C_6H_4NH)P(O)($NC_5H_{10})_2$, X = F (**1**), Cl (**2**), Br (**3**), H (**4**) and CH_3 (**5**) have been synthesized and characterized. The solid state structures of compounds **1** and **3**–**5** were determined by X-ray crystallography. The compounds **1**, **3**, **4**·$\mathbf{H_2O}$ and **5** contain one, four, two and four conformers, respectively, in the solid phase. The X-ray structures were employed as references for quantum mechanical (QM) calculations at the B3LYP level. The electronic features of the hydrogen bonds were investigated by Natural Bonding Orbital (NBO) and Atoms in Molecules (AIM) analyses to rationalize the structural and physicochemical properties of the compounds. Moreover, infrared spectroscopy was used to get a more detailed insight into the structure of the hydrogen bonds.

2. Experimental

2.1. Instrumentation

^1H, ^{13}C and ^{31}P spectra were recorded on a Bruker Avance DRX 500 spectrometer. ^1H and ^{13}C chemical shifts were determined

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relative to internal TMS, and ^{31}P chemical shifts relative to 85% H_3PO_4 as an external standard. Infrared (IR) spectra were recorded on a Shimadzu model IR-60 spectrometer using KBr pellets. Melting points were obtained with an Electrothermal instrument. Single crystals of the compounds **1**, **3**, **4·H$_2$O** and **5** were obtained from a mixture of CH_3OH/H_2O at room temperature. X-ray data were collected on a Bruker SMART area detector [23] single crystal diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). All the structures were refined by full-matrix least-squares methods against F^2 with SHELXL-97 [24]. Routine Lorentz and polarization corrections were applied and an absorption correction was performed using the SADABS program [25] for compounds **3**, **4·H$_2$O** and **5**. The crystallographic data of compounds **1**, **3**, **4·H$_2$O** and **5** are summarized in Table 1.

2.2. General procedure for the synthesis of compounds *1–5*

The intermediates (4-X-C_6H_4NH)P(O)Cl_2 (X = F, Cl, Br, H and CH_3) were prepared according to the literature procedures [26]. Then, a solution of 4 mmol piperidine in dry acetonitrile (30 ml) was added dropwise to a stirred solution of 1 mmol (4-X-C_6H_4NH)P(O)Cl_2 at −5 °C. After 5 h stirring, the solvent was evaporated under vacuum. The resulting white product was washed with distilled water and recrystallized from a mixture of methanol and water.

2.3. N-4-fluorophenyl-N′,N″-bis(piperidinyl) phosphoric triamide (*1*)

Yield: 78%, m.p. 199 °C. ^1H NMR ($CDCl_3$, 500.13 MHz, 298 K): 1.43 (m, 8H, CH_2), 1.50 (m, 4H, CH_2), 3.10 (m, 8H, CH_2), 4.76 (d, ^2J(PNH) = 7.0 Hz, 1H, NH), 6.88 (m, 2H, Ar-H), 7.02 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.76 MHz, 298 K): 26.58 (s, CH_2), 26.28 (d, ^3J(P,C) = 5.2 Hz, CH_2), 45.73 (d, ^2J(P,C) = 2.2 Hz, CH_2), 115.49 (d, ^2J(F,C) = 22.4 Hz), 119.30 (m, ^3J[(F,C), (P,C)] = 6.9 Hz), 137.33 (s), 157.71 (d, ^1J(F,C) = 239.1 Hz) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 202.46 MHz, 298 K): 12.57 (s) ppm. $^{31}P\{^1H\}$ NMR (acetone-d_6, 162.01 MHz, 190 K): 10.58 (s) ppm. IR (KBr, cm^{-1}): 3180, 2930, 2820, 1602, 1501, 1437, 1379, 1332, 1280, 1208, 1185, 1066, 1024, 952, 929, 827, 716, 677, 550, 482.

2.4. N-4-chlorophenyl-N′,N″-bis(piperidinyl) phosphoric triamide (*2*)

Yield: 60%, m.p. 191 °C. ^1H NMR ($CDCl_3$, 500.13 MHz, 298 K): 1.44 (m, 8H, CH_2), 1.54 (m, 4H, CH_2), 3.05 (m, 8H, CH_2), 5.06 (d, ^2J(PNH) = 7.2 Hz, 1H, NH), 7.02 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar-H), 7.14 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.76 MHz, 298 K): 22.45 (s, CH_2), 26.27 (d, ^3J(P,C) = 5.0 Hz, CH_2), 45.71 (d, ^2J(P,C) = 2.1 Hz, CH_2), 119.13 (d, ^3J(P,C) = 6.3 Hz, C_{ortho}), 125.88 (s), 128.93 (s), 140.04 (s) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 202.46 MHz, 298 K): 12.33 (s) ppm. $^{31}P\{^1H\}$ NMR (acetone-d_6, 162.01 MHz, 190 K): 10.45 (s) ppm. IR (KBr, cm^{-1}): 3188, 2930, 1504, 1486, 1437, 1375, 1331, 1233, 1207, 1160, 1066, 951, 933, 718, 634, 556, 497.

2.5. N-4-bromophenyl-N′,N″-bis(piperidinyl) phosphoric triamide (*3*)

Yield: 73%, m.p. 197 °C. ^1H NMR ($CDCl_3$, 500.13 MHz, 298 K): 1.45 (m, 8H, CH_2), 1.55 (m, 4H, CH_2), 3.11 (m, 8H, CH_2), 4.76 (d, ^2J(PNH) = 5.4 Hz, 1H, NH), 6.96 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar-H), 7.30 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar-H) ppm. ^1H NMR (acetone-d_6, 400.22 MHz, 190 K): 1.44 (b, CH_2), 1.54 (b, CH_2), 3.09 (b, CH_2), 6.92 (b, Ar-H), 7.20 (b, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.76 MHz, 298 K): 24.58 (s, CH_2), 26.31 (d, ^3J(P,C) = 5.0 Hz, CH_2), 45.78 (d, ^2J(P,C) = 1.2 Hz, CH_2), 113.32 (s), 119.50 (d, ^3J(P,C) = 6.3 Hz, C_{ortho}), 131.95 (s), 140.50 (s) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 202.46 MHz, 298 K): 12.20 (s) ppm. $^{31}P\{^1H\}$ NMR (acetone-d_6, 162.01 MHz, 190 K): 10.48 (s) ppm. IR (KBr, cm^{-1}): 3140,

Table 1
Crystallographic data for compounds **1** and **3–5**.

	1	**3**	**4·H$_2$O**	**5**
Empirical formula	$C_{16}H_{25}FN_3OP$	$C_{16}H_{25}BrN_3OP$	$C_{32}H_{54}N_6O_3P_2$	$C_{17}H_{28}N_3OP$
Formula weight	325.36	386.26	632.75	321.39
Temperature (K)	120(2)	120(2)	120(2)	120(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$
Unit cell dimensions				
a (Å)	10.0001(11)	14.321(7)	12.106(3)	14.2998(10)
b (Å)	16.9181(18)	16.291(8)	12.548(3)	16.2595(11)
c (Å)	10.0303(11)	16.574(8)	12.650(3)	16.6649(12)
α (°)	90	73.986(10)	111.627(5)	73.878(10)
β (°)	99.805(2)	71.566(9)	96.733(5)	71.618(10)
γ (°)	90	80.593(10)	106.243(5)	81.295(10)
V (Å^3)	1696.8(3)	3514(3)	1700.6(7)	3523.7(5)
Z, D_{calc} (mg m^{-3})	4, 1.274	8, 1.460	2, 1.236	8, 1.212
Absorption coefficient (mm^{-1})	0.177	2.422	0.169	0.162
F(0 0 0)	696	1600	684	1392
Crystal size (mm)	0.35 × 0.15 × 0.10	0.10 × 0.10 × 0.05	0.22 × 0.18 × 0.17	0.35 × 0.24 × 0.20
θ Range for data collection (°)	2.04–28.07	1.63–26.02	1.77–26.00	1.31–25.00
Limiting indices				
	$-13 \le h \le 13$ $-22 \le k \le 12$ $-13 \le l \le 12$	$-17 \le h \le 17$ $-20 \le k \le 19$ $-20 \le l \le 20$	$-14 \le h \le 14$ $-12 \le k \le 15$ $-14 \le l \le 15$	$-17 \le h \le 12$ $-19 \le k \le 14$ $-19 \le l \le 19$
Reflections collected/unique	11704/4063 [R_{int} = 0.0438]	27603/12998 [R_{int} = 0.0584]	10874/6621 [R_{int} = 0.0326]	17884/12124 [R_{int} = 0.0370]
Completeness to θ	98.4%	93.8%	98.8%	97.8%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4063/0/199	12998/6/793	6621/0/428	12124/0/797
Goodness-of-fit on F^2	1.006	1.064	1.062	1.002
Final R indices	R_1 = 0.0520, wR_2 = 0.1165	R_1 = 0.0809, wR_2 = 0.1929	R_1 = 0.0668, wR_2 = 0.1301	R_1 = 0.0494, wR_2 = 0.0840
R indices (all data)	R_1 = 0.0789, wR_2 = 0.1308	R_1 = 0.1188, wR_2 = 0.2025	R_1 = 0.1044, wR_2 = 0.1445	R_1 = 0.1098, wR_2 = 0.0934
Largest difference in peak and hole (e Å^{-3})	0.390 and −0.297	4.651 and −1.186	0.348 and −0.364	0.301 and −0.357