C_3-SYMMETRIC AZAPHOSPHATRANES

Fredrik LAKE[1], Lars HAGBERG[+], Mats SVENSSON[2] and Christina MOBERG[3,*]

Department of Chemistry, Organic Chemistry, Royal Institute of Technology, SE-100 44 Stockholm, Sweden; e-mail: [1] lake@orgchem.kth.se, [2] matss@orgchem.kth.se, [3] kimo@orgchem.kth.se

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday in recognition of his outstanding contributions to the area of organic stereochemistry.

C_3-Symmetric azaphosphatranes, (3*S*,7*S*,10*S*)-2,3,7,8,9,10-hexamethyl-2,8,9-triaza-5-azonia-1-λ^5-phosphabicyclo[3.3.3]undecane chloride and (3*S*,7*S*,10*S*)-3,7,10-triisopropyl-2,8,9-trimethyl-2,8,9-triaza-5-azonia-1-λ^5-phosphabicyclo[3.3.3]undecane chloride, have been prepared starting from the corresponding chiral tripodal tetraamines and chlorobis(diethylamino)phosphane. The compounds are weak acids which are not fully deprotonated by potassium *tert*-butoxide. Density functional calculations of the compounds and their conjugate bases demonstrate that the weak acidity originates in a conformational change upon deprotonation leading to substantial steric repulsion.

Key words: Azaphosphatranes; C_3 Symmetry; Chirality; Basicity; Quantum chemistry; DFT calculations.

The consideration of molecular symmetry is sometimes important in asymmetric reactions and other chiral recognition processes. Symmetry can reduce the number of possible intermediates/transition states, thus increasing the probability of a successful result. Chiral molecules may contain proper rotational axes as their sole symmetry elements. In contrast to molecules which contain no element of symmetry and, therefore, are truly asymmetric (C_1-symmetric), molecules with rotational axes are dissymmetric and belong to one of the point groups C_n or D_n ($n > 1$) or to one of the less common groups *T*, *I* and *O*.

+ Present address: Karo Bio AB, Novum, SE-141 57 Stockholm, Sweden; e-mail: lars.hagberg@karobio.se.

By definition, C_2 symmetry is characterized by the fact that an identical situation is obtained upon rotation of the C_2-symmetric species 180° about the rotation axis. In an event involving chiral recognition, this implies that two complexes, which are identical in the C_2 case, would be diastereomeric in the C_1 case. With threefold symmetry each rotation of 120° yields an identical situation, thereby reducing the number of different complexes.

The realization of C_2 symmetry is well documented[1]. C_3-Symmetric ligands and reagents have been less commonly exploited and quite few examples of their use in asymmetric synthesis have been described[2]. Achiral ligands and reagents with threefold symmetry have been extensively investigated, however. Among these are tris(2-aminoethyl)amine (tren) and its derivatives[3]. We have reported on a method for the preparation of chiral, C_3-symmetric tren analogs[4]. Herein we describe how these derivatives have been employed for the preparation of chiral azaphosphatranes[5].

EXPERIMENTAL

Acetonitrile and dimethyl sulfoxide were distilled from calcium hydride and stored over activated 4Å molecular sieves. Chlorobis(diethylamino)phosphane (^{31}P NMR, C_6D_6: δ 154) was prepared according to a published procedure[6]. Potassium *tert*-butoxide was sublimed proir to use. $CDCl_3$ was stored over activated 4Å molecular sieves and C_6D_6 was used directly from an ampoule. All glassware was flame-dried prior to use and the reactions were performed under an atmosphere of nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Aspec 3000 instrument at 400 and 100.6 MHz, respectively, and ^{31}P NMR spectra were recorded on a Bruker DMX 500 instrument at 202.5 MHz. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

(3*S*,7*S*,10*S*)-2,3,7,8,9,10-Hexamethyl-2,8,9-triaza-5-azonia-1-λ^5-phosphabicyclo[3.3.3]undecane chloride (**2a**) and (3*S*,7*S*,10*S*)-3,7,10-triisopropyl-2,8,9-trimethyl-2,8,9-triaza-5-azonia-1-λ^5-phosphabicyclo[3.3.3]undecane chloride (**2b**)

Chlorobis(diethylamino)phosphane (**2a**; 27.7 μl, 0.132 mmol and **2b**; 26.2 μl, 0.125 mmol) was added dropwise over 5 min to a solution of the tetraamine (**1a**; 30.3 mg, 0.132 mmol and **1b**; 39.3 mg, 0.125 mmol) in dry acetonitrile (0.9 ml). The resulting mixtures were stirred overnight and the solutions were used directly in the deprotonation step. For spectral analysis, the solvent and diethylamine were evaporated and the crude products (>90% pure by NMR) isolated. Attempts to purify the products by chromatography, crystallization or preparative HPLC were unsuccessful.

Compound **2a**. ^{1}H NMR (400 MHz, $CDCl_3$): 5.20 d, 1 H, *J* = 506 (PH); 4.24 ddd, 3 H, *J* = 12.3, 11.5 and 5.2 (NCH_2); 3.11–3.02 m, 3 H (NCH); 2.54 d, 9 H, *J* = 18.3 (NCH_3); 2.50 dd, 3 H, *J* = 12.3 and 11.5 (NCH_2); 1.14 d, 9 H, *J* = 6.1 (CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): 54.0 d, *J* = 7.6 (NCH_2); 46.6 d, *J* = 3.0 (NCH); 31.8 d, *J* = 13.7 (NCH_3); 18.5 d, *J* = 6.1 (CH_3). ^{31}P NMR (202.5 MHz, $CDCl_3$): –7.9. HREI MS (EI, *m/z*): calculated for $C_{12}H_{28}N_4P^+$ 259.2052; found: 259.2051.

Compound **2b**. ^{1}H NMR (400 MHz, $CDCl_3$): 5.28 d, 1 H, J = 511 (PH); 4.06 ddd, 3 H, J = 12.4, 12.4 and 6.4 (NCH_2); 3.06–3.00 m, 3 H (NCH); 2.68 dd, 3 H, J = 12.4 and 12.4 (NCH_2); 2.52 d, 9 H, J = 17.4 (NCH_3); 2.16 m, 3 H (C**H**$(CH_3)_2$); 0.93 d, 9 H, J = 7.0 (CH_3); 0.76 d, 9 H, J = 6.7 (CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): 54.9 s (NCH); 47.7 d, J = 7.6 (NCH_2); 31.8 d, J = 15.2 (NCH_3); 26.8 d, J = 6.1 ($CH(CH_3)_2$); 17.2 s (CH_3); 13.9 s (CH_3). ^{31}P NMR (202.5 MHz, $CDCl_3$): –6.5. HREI MS (EI, *m/z*): calculated for $C_{18}H_{40}N_4P^+$ 343.2990; found: 343.2990.

(3*S*,7*S*,10*S*)-2,3,7,8,9,10-Hexamethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (**3a**)

The above solution of **2a** (0.132 mmol) in dry acetonitrile (1.15 ml) was added to potassium *tert*-butoxide (2.6 equivalents, 38.7 mg, 0.345 mmol) forming a yellow dispersion. The dispersion was stirred at room temperature for 3 h. The potassium *tert*-butoxide was then allowed to settle. ^{1}H NMR in dry C_6D_6 of the solution indicated that 70% of **2a** was deprotonated. All attempts to purify the product were unsuccessful.

(3*S*,7*S*,10*S*)-3,7,10-Triisopropyl-2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo-[3.3.3]undecane (**3b**)

The above solution of **2b** (0.125 mmol) in acetonitrile (0.9 ml) was added to a round bottomed flask and the solvent was removed. Potassium *tert*-butoxide (2.2 equivalents, 31.0 mg, 0.276 mmol) was added followed by dry dimethyl sulfoxide (0.7 ml). The yellow solution was stirred at room temperature for 2 h. The solvent was removed leaving a yellow oil which by ^{1}H NMR in dry C_6D_6 indicated that 70% of **2b** was deprotonated. All attempts to purify the product were unsuccessful. ^{31}P NMR (202.5 MHz, C_6D_6): 119.4.

DFT Calculations

Geometries and energies of all intermediates were calculated using the gradient-corrected hybrid density functional method B3LYP (ref.[7]) as implemented in the GAUSSIAN98 program[8]. The nature of the minima was confirmed from frequency calculations. We used a basis set of double-ζ valence quality of Huzinaga and Dunning[9] augmented with 1d function on P(0.37), N(0.80) and C(0.75). The energetics of **2a**, **2b**, **3a** and **3b** were then recalculated using the 6-311G(d,p) basis set[10]. This did not change the relative energies more than 1 kJ/mol.

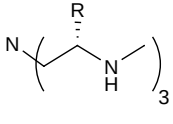
RESULTS AND DISCUSSION

C_3-Symmetric tripodal amines **1a** and **1b** reacted with chlorobis(diethylamino)phosphane in acetonitrile to yield azaphosphatranes **2a** and **2b**, respectively. The reactions were considerably slower than the analogous reaction with tris[2-(methylamino)ethyl]amine[11] (**1c**), requiring about 12 h reaction time at ambient temperature (compared to 1 h for **1c**).

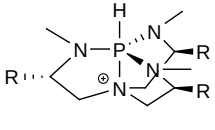
The reaction with **1b** was followed over time by ^{1}H NMR spectroscopy. The initial complex pattern of signals simplified as azaphosphatrane **2b** formed, reflecting the high symmetry of the product. ^{31}P NMR chemical shifts of –7.9 and –6.5 ppm in **2a** and **2b**, respectively, $^1J(^{31}P\text{-}^1H)$ of 506 and

511 Hz, respectively, as well as the presence of one *PNCH*$_2$ coupling (12.3 Hz for **2a** and 12.4 Hz for **2b**) are indicative of pentacoordinated phosphorus, in analogy with the situation in **2c** (ref.[12]). Coupling of all carbon atoms with phosphorus was observed in **2a**, whereas in **2b** no such coupling was observed for the carbon atoms bearing the isopropyl substituents and for the methyl carbons of those groups.

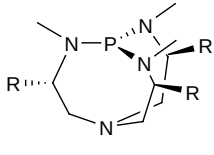
The proazaphosphatrane **3c** has been demonstrated to be an exceedingly strong base; an upper limit for the pK_a value of its conjugate acid in DMSO was estimated to 26.8 (ref.[13]). Strong bases such as *tert*-butoxide in DMSO (pK_a of *tert*-butanol in DMSO: 29.4 (ref.[14])) were thus required to deprotonate **2c** to the neutral compound. Increasing basicity for bases of similar structure has been shown to be linearely correlated with decreasing $^1J(^{31}P\text{-}^1H)$ values[13,15]. The values for **2a** and **2b** (506 and 511 Hz, respectively) are larger than that for **2c** (491 Hz) and lower basicity would thus be expected for the substituted derivatives. Compounds **2a** and **2b** proved to be more resistant to deprotonation than **2c**, however. Attemps to deprotonate **2b** using butyllithium, methyllithium, sodium hydride or sodium amide in THF were unsuccessful. Incomplete deprotonation of **2a** and **2b** (*ca* 70% by ^{1}H NMR) was achieved with *tert*-butoxide in acetonitrile and DMSO, respectively, thus indicating that **2a** and **2b** are weaker acids than **2c**.



1a - 1c



2a - 2c



3a - 3c

1 - 3	R
a	Me
b	i-Pr
c	H

Upon deprotonation, azaphosphatranes change their coordination at phosphorus from pentacoordinate to tricoordinate[16]. The ^{1}H NMR spectra of **3a** and **3b**, which could be partly deduced from the spectra of mixtures with the protonated compounds, are in accordance with that assumed coordination. Deprotonation led to a decrease of $^3J(^{31}P\text{-}^1H_{NMe})$ from 18.3 to 10.6 Hz for **2a** and from 17.1 to 11.9 Hz for **2b**. The NCH_3 protons underwent a downfield shift (from 2.06 to 2.54 Hz for **2a** and from 1.92 to 2.55 Hz for **2b** in benzene-d_6). The chemical shift difference for the protons in the methyl groups of the isopropyl substituent was smaller in **3b** (0.83 and 0.93 ppm) than in **2b** (0.69 and 1.10 ppm).

In order to get some insight into the reason for the reluctance to deprotonation of **2a** and **2b**, DFT calculations (B3LYP) of the two compounds and

their conjugate bases **3a** and **3b** as well as of compounds **2c** and **3c** were performed (see Fig. 1)

As expected, the change from pentacoordinated to tricoordinated phosphorus induced structural changes. In the protonated compounds the transannular phosphorus–nitrogen bonds were found to be close to perpendicular to the P–N_{eq} bonds. No significant structural differences between the compounds **2a**, **2b** and **2c** were found. The transannular P–N bond lengths decreased in the order **2c** (2.10 Å (ref.[17])) > **2a** (2.06 Å) > **2b** (2.04 Å). These P–N distances were found to be considerably longer in the deprotonated compounds (3.40, 3.30 and 3.49 Å in **3a**, **3b** and **3c** (ref.[18]), respectively). In contrast to the situation in compounds **2a**–**2c**, major structural differences were found in the deprotonated compounds **3a**–**3c**. The dihedral angle $C_{Me}N_{eq}CP$ was calculated to 180° in **3c**, 174° in **3a** and 170° in **3b**. In **3c**, the equatorial nitrogen atoms are thus perfectly sp^2-hybridized, leading to a stabilization of this structure compared to those of **3a** and **3b**. The dihedral angles $CMeN_{eq}CX$ (X = H, Me, iPr), reflecting the "twist" of the molecule, differ considerably: 20.6° in **3c**, 31.4° in **3a**, and 38.7° in **3b**. The absence of coupling between phosphorus and one of the protons at the methylene carbon in **2a** and **2b** is nicely explained by the calculated structures; the $PN_{ax}CH$ torsional angles were found to be –158 and 83° in both compounds, which is in agreement with the observed coupling constants[15], $^3J(PN_{ax}CH)$.

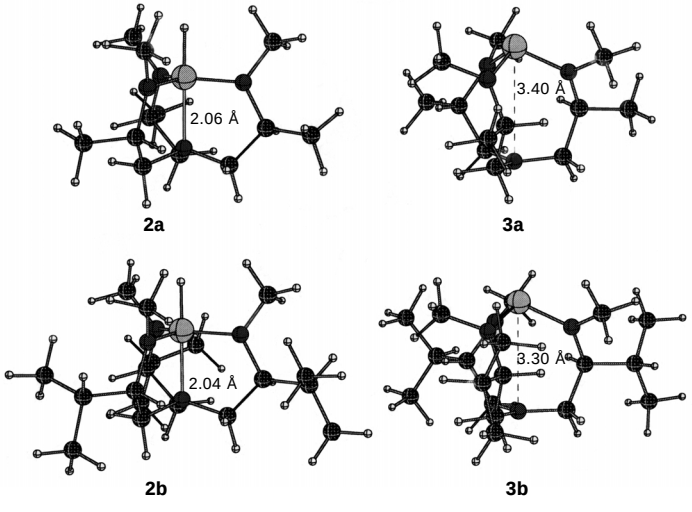


FIG. 1

B3LYP geometry-optimized structures of azaphosphatranes **2a**, **2b** and their deprotonated analogs **3a** and **3b**. The P–N_{ax} distances are indicated in each structure

The high basicity of the azaphosphatranes originates in the stabilization of the pentacoordinated structure. What is interesting to note from the present calculations, is that the energy required to deprotonate **3b** is 29.6 kJ/mol higher than that required for **3a**, which in turn is 38.6 kJ/mol higher than that required for **3c**. As indicated by our experimental results, **3a** and **3b** are thus stronger bases than **3c**. This is thought to be due to the severe sterical repulsion exhibited by the methyl group on nitrogen and the substituent on the neigbouring carbon atom induced by the conformational change occurring upon deprotonation.

In conclusion, C_3-symmetric azaphosphatranes, which are the conjugate acids of strong bases, have been prepared. In addition to experimental data, density functional calculations have been employed to elucidate the structure and behaviour of the compounds. The calculations lend credence to the assumed differences in acidity of the new azaphosphatranes. The deprotonated compounds have potential application as chiral bases[19] and ligands for transition metal ions.

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