Unexpected Keto-enol Tautomerism in the Cyclopyridinophane Class
Direct and indirect proofs

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The paper presents the synthesis of cyclo (bis-paraquat p-phenylene p-phenylene-carbonyl) tetrakis (hexafluorophosphate), named ‘CETOBOX’, and the closely related structural determinations. This compound exists in three tautomeric forms. These forms were evidenced by NMR-data (1H-NMR, TOCSY, COSY, NOESY), UV-Vis spectra coupled with pH measurements and by synthesis. As the ‘CETOBOX’ gives “in situ” only the corresponding monoylide, the synthesis of a new fluorescent indolizine cyclophane has been performed by a 3+2 cycloaddition. All structures of the new compounds presented herein have been established by NMR spectroscopy. Also, theoretical methods (MM3, AM1, AM1-COSMO and B88LYPDFT) have been used to determine the most stable conformer structures.

Keywords: CETOBOX, tautomeric forms, monoylide, indolizine cyclophane

The ‘Blue Box’, cyclobis (paraquat p-phenylene) tetrakis (hexafluorophosphate) 5 was synthesized by Stoddart et al [1] starting from 4,4'-bipyridine and 1,4-bis (bromomethyl) benzene, in two ground steps, described in scheme 1. However, by a template cyclization of the salt 3 in presence of 1,5-bis[2-(2-hydroxy)ethoxy] naphthalene, better yields are obtained for the final product 5 [2].

The molecular recognition properties of ‘Blue Box’ have recently drawn great attention due to its important applications in the design and synthesis of various electrochemically active molecular systems [3-15]. Many molecular machines based on ‘Blue Box’ take into consideration two key properties of this compound: i) the ability to interact with guests by π–π stacking and charge-transfer interactions [1, 16-17] and ii) the presence of a rigid cavity which helps to trap the guests, giving inclusion complexes [18-22]. The host-guest chemistry of the ‘Blue Box’ is the traditional starting point to explore its molecular recognition properties. It turns out to be a multipurpose host which can bind with a wide range of substrates [23]. The early work on the host-guest chemistry of ‘Blue Box’ was crucial to the ultimate development of artificial molecular machines.

The discovery of its inclusion complexation led to an exploration to find out which guests are recognized by the tetracationic host. It was found that it is an excellent receptor for a wide range of guests containing π-electron-rich aromatic rings, such as dioxynaphthalene-based compounds [24-25], biphenyl [26], benzidine [26], and indole [27] and their derivatives[28] in both organic and aqueous solutions. The tetracationic cyclophane was also found to recognize numerous small bioactive molecules (amino acids possessing electron-rich aromatic subunits [29], neurotransmitters [30] and phenyl D-glyco-pyranosides [31-32]) by forming stable inclusion charge-transfer complexes. Tetrathiafulvalene and its derivatives [33] are among the very few non-aromatic compounds that complex strongly with ‘Blue Box’.

The formation of strong inclusion complexes between ‘Blue Box’ and π-electron-rich substrates was recognized [34-35] as the signal to use appropriate donors as templates to direct the formation of the host molecule (template-directed synthesis [36-43]). The ability of the tetracationic cyclophane to form inclusion complexes provides the unique opportunity to construct large, ordered molecular assemblies such as catenanes and rotaxanes, using the templating actions inherent in the interlocked compounds themselves as they are formed [44-50].

As a part of our ongoing research program in the construction of new molecular nanomachines for the detection of Volatile Organic Compounds (VOCs), we synthesized for the first time a new asymmetric cyclopyridinophane moiety, similar to the Blue Box, but which contains a specific methylene group that it is very useful for further functionalisations of the cyclophane structure.

Experimental part

1,1’-{(1-methylene-carbonyl phenylene-4-methylene) bis[4,4’-bipyridinium] bis(hexafluorophosphate) (7)

A solution of 6 (3.42 mmol) in acetonitrile (40 mL) was added over 1 hour to a solution of 4,4’-bipyridil 1 (17.15

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Scheme 1. Synthesis of “Blue Box”
mmol) also in acetonitrile (70 mL) heated under reflux. The reaction mixture is kept under reflux and nitrogen atmosphere, with stirring, for another hour. After cooling to room temperature, the crude blue precipitate was filtered off and washed with a large amount of acetonitrile before being dissolved in a small volume of methanol (4-5 mL). The resulted solution was passed through a silica gel column with a mixture of MeOH-aqueous NH₄Cl 2 mol L⁻¹ solution (3:2) as the eluant. The fractions containing the salt (RF = 0.32) were combined and concentrated under vacuum. Finally, the resulted solid was then dissolved in water (400 mL) and a saturated aqueous solution of NH₄PF₆ was added until no further precipitation was observed. The obtained orange solid salt 7, as hexafluorophosphate, was filtered and successively washed with large quantities of water (50 mL) and ethyl ether (30 mL).

Yield = 60%.

Melting point: 222 °C;

IR (cm⁻¹): 555.6, 620.2, 996.5, 1219.6, 1407.6, 1642.8, 1701.6, 3130.8, 3647.9;

¹H-NMR spectra, DMSO-d₆, δ (ppm): 6.09 (s, 2H, H.), 6.55 (s, 2H, H.), 6.85 (d, 2H, H.), 7.55 (d, 2H, H.), 8.15 (d, 2H, H.), 8.5 (d, 2H, H.), 9.08 (d, 2H, H.), 9.44 (d, 2H, H.), 9.8 (s, 2H, H.), 10.2 (s, 2H, H.);

¹³C-NMR spectra, DMSO-d₆, δ (ppm): 61.3 (C1), 66.8 (C2), 121.3 (C3), 123.3 (C4), 126.2 (C5), 130.2 (C6), 134.9 (C7), 142.6 (C8), 146.5 (C9), 151.1 (C10), 153.7 (C11), 191.1 (C12).

Cyclo(bis-paraquat p-phenylene p-penylene-carbonyl) tetrakis (hexafluorophosphate) (8)

In a 100 mL round-bottomed flask, the template 4 (3.6 mmol), 1,4-bis(bromomethyl)benzene 2 (1.2 mmol) and the salt 7 (1.2 mmol) were dissolved in dry DMF (50 mL). The homogenous reaction mixture was stirred over 6 days, in absence of light, under nitrogen atmosphere and at room temperature. By vacuum distillation of DMF, a brown viscous solid was separated. This one was dissolved in 20 mL aqueous ammonium chloride solution (2 mol L⁻¹). In order to eliminate de template 4, a liquid-liquid extraction between this solution and chloroform was performed over 3 days. Next, the aqueous phase is concentrated and passed on a silica gel column using a mixture of MeOH - aqueous NH₄Cl 2 mol L⁻¹ solution - nitromethane (4:4:2) as the eluant. The fractions containing the salts (RF = 0.16) were concentrated. The crude salt was dissolved in water (350 mL) and the 'CETOBOX' 8 was precipitated by adding a saturated aqueous solution of NH₄PF₆ until no further precipitation was observed. The solid salt 8 after filtration was successively washed with large quantities of water (50 mL) and ethyl ether (50 mL). The yield in dry pale yellow salt 8 is 12%.

IR (cm⁻¹): 549.9, 855.4, 1211.0, 1443.1, 1631.1, 1701.6, 3130.8, 3648.0;

Elemental analysis: C 39.36% (39.39% found), H 2.84% (2.88% found), N 4.96% (4.93% found), O 1.42%, P 11%, F 40.42%.

Keto form, ¹H-NMR spectra, DMSO-d₆, δ (ppm): 5.80 (4H, H., H.), 5.91 (1H, H.), 5.97 (1H, H.), 6.42 (2H, H.), 7.95 (2H, H., H.), 7.68 (2H, H., H.), 7.91 (2H, H., H.), 8.00 (2H, H., H.), 8.02 (2H, H., H.), 8.62 (8H, H., H., H., H., H., H., H., H.), 8.78 (1H, H.), 8.96 (1H, H.), 9.08 (1H, H.), 9.24 (1H, H.), 9.36 (4H, H., H., H., H.), 11.21 (4H, H., H.), 12.78 (4H, H., H.),


Results and Discussion

Firstly, our aim was to introduce into the cyclophane structure one more reactive methylene group, able to furnish selectively, only one bipyridinium methyliide. Thus, a single site functionalization of a cyclophane structure could be achieved by one of all known chemical reactions involving the cycloimmonium ylides [51-53].

1Cyclo(bis-paraquat p-phenylene p-penylene-carbonyl) tetrakis (hexafluorophosphate)

We synthesized the cyclo(bis-paraquat p-phenylene p-phenylene-carbonyl) tetrakis(hexafluorophosphate) 8, named by us ‘CETOBOX’, by the template and clippings synthetic procedure used for ‘Blue Box’ (scheme 2).

Experimentally, two different chemical ways were tested in order to obtain the asymmetrical product 8, starting from (i) bipyridil 1 and 1'-bromo-4-bromomethyl acetophenone 6 (Scheme 2) and (ii) bipyridil 1 and α, α'-dibromo para-xylene 2 in the first step of synthesis, followed by the cyclisation of salt 7 with α, α'-dibromo para-xylene 2, or salt 3 with 1'-bromo-4-bromomethyl acetophenone 6.

In fact, only by the first synthetic way we achieved the ‘CETOBOX’ 8 with yields of 12-16%, calculated relative to the intermediate salt 7.

The initial salt 7, as bromide, obtained in the first step of synthesis is transformed in its hexafluorophosphate form to render it soluble in DMF. Thus, the second step of synthesis, see the cyclisation of 7 with α, α'-dibromo para-xylene 2 in presence of template 4, was performed in a homogenous organic media assured by DMF. Normally, the mixture of salts 8 as bromide and hexafluorophosphate resulted initially in the second step, must be transformed integrally in its hexafluorophosphate in order to obtain an unitary final ‘CETOBOX’ 8.

On the other hand, the hexafluorophosphate salt of 8 may be converted, by treatment with tetraethyl ammonium chloride in nitromethane, to the corresponding solid chloride [1] salt 8, which is soluble in aqueous media. However, it has to be mentioned that, in our hands, all synthesis of product 8 gave a mixture of the tautomeric forms 8a and 8b, as evidenced by the aliphatic part of the ¹H-NMR spectra, depicted in figure 1.
Figure 1a corresponds to the spectral measurement in DMSO-d$_6$ resulting directly from synthesis, while figure 1b is the spectrum obtained for the same synthetic mixture upon addition of D$_2$SO$_4$ (deuterated sulphuric acid). Indeed, the keto-enol equilibrium is sensitive to the presence of acid [54-56], and the addition of D$_2$SO$_4$ leads to a displacement in favor of the enolic form. As a

Fig. 1. $^1$H-NMR spectra of the synthetic tautomers: a) in DMSO-d$_6$ at room temperature; b) in DMSO-d$_6$ and D$_2$SO$_4$ at room temperature

Fig. 2. a) keto form $8a$ (DMSO-d$_6$, room temperature); b) enol form $8b$ (DMSO-d$_6$ and D$_2$SO$_4$, room temperature)
consequence, there is an extinction of the signals around 5.95 and 6.3 ppm, ascribed to the disappearance of the ketonic form (and especially of the methylene group bounded to the carbonyl group). Concomitantly, a new signal appears at 4.55 ppm as a result of the formation, in a little quantity, of the second enolic form 8b. Indeed, the cis and trans forms of the enol lead to rather different structures (see molecular modelling results in next section), in such a way that chemical displacements are not strictly identical from one enolic form to the other. In addition, the vinylic proton appears as a singlet at 6.31 ppm, but with a low integration, according to the deuteration resulting from the keto-enolic equilibrium in presence of the labile deuterium of D₂SO₄.

The sample in DMSO-d₆ and D₂SO₄ containing the enol form 8b in a dominant concentration (approximately 96%), helps the assignment without difficulty of the chemical shifts and couplings for the tautomeric forms 8a and 8b (fig. 2). For both structural determinations of tautomeric forms 8a and 8b, we also registered the ¹³C and DEPT spectra, in order to explain some evident differences in shieldings of methylene groups. The dipole-dipole couplings by NOESY and scalar couplings by COSY and TOCSY 1D were recorded as well, on a tautomeric mixture containing up to 80% keto form.

In order to obtain some structural information on the three tautomeric forms 8a, 8b, and 8c, we performed a molecular modelling study, based on molecular mechanics, AM1 semi-empirical and DFT calculations. These methods were systematically employed [57-63] for this type of charged molecular systems. In Table 1 are presented the values of ΔH (enthalphy of formation) calculated by AM1 (vacuum), AM1 (COSMO) and B88LYPDFT procedure methods from CACHE library [64].

To obtain these numerical data, we applied a general procedure presented in the specialized literature [65-67]. Briefly, the starting structures generated by the CAChe editor were firstly optimized by MM3 method. The most stable conformer obtained for every case was successively optimized by AM1 (vacuum) and AM1 (COSMO) methods. Finally, only for the most stable conformer found by this last method is developed the geometry optimization using the Density Functional Theory and the B88LYP hybrid functionals. DFT and AM1 (COSMO) calculations are still expected to be more desirable for the estimation of molecular stabilities of this type of molecules. As a result, in figure 3 are given the most stable conformers of the tautomeric forms 8a, 8b and 8c obtained by the DFT calculations.

Both methods indicate the same decreasing order of their stabilities: 8a > 8b > 8c. As experimentally observed by NMR, the ketonic form is more stable than the enolic ones, while the enol trans form is predominant when compared to the cis isomer. In addition, on a structural point of view, it is obvious that the introduction of the carbonyl unit on the cyclophane leads to deformations of the macrocycle, in such a way that methylene groups are not equivalent any more, as found by NMR. These findings also explain that certain methylene groups lead to a doubled signal (5.91 and 5.97 ppm for 8a, 4.19, and 4.23 ppm for 8b), the two protons being exposed to different environments.

Moreover, the significant differences in enthalphy of formation (7.66 kcal/mol between 8a-8b, by DFT) suggested us to study this dynamic chemical equilibrium by pH variation. In order to achieve this, we developed a spectrometric study on the passage of enol forms 8b and 8c to the keto forms 8a and then to its corresponding cyclophane monoylide 9. We recall that ¹H-NMR spectra of 'CETOBOX' in DMSO-d₆, and D₂SO₄ indicated the presence of enol forms in a great majority.

Thus, to a solution of 'CETOBOX' in water (10⁻⁵ mol. L⁻¹) containing 0.09 mol. L⁻¹ hydrochloric acid was added a solution of sodium hydroxide also in water. The concentrated solutions of sodium hydroxide used in titration were added in small volumes with a micropipette. The overall dilution error is less than 0.06% (0.5 mL). The titration spectra were recorded for every pH measurement on a common UV-VIS spectrophotometer. The evaluation of the apparent pkH values was performed using the Henderson-Hasselbach equation adapted for spectrometric titration [29].

\[
pk_{a} = \text{pH} - \log \frac{A_{\text{max}} - A}{A - A_{\text{min}}} \quad (1)
\]

where Aₘₐₓ is the maximal absorbance of the conjugated acid or conjugated base function in the titration, Aₘᵢₙ is the minimal absorbance of the same conjugated form and A represents the average of all recorded absorbances due to the conjugated form. During titration, isobestic points could be observed at 214 and 245 nm, thus demonstrating the simultaneous presence of only two species. Two pkH values were calculated and the mixture composition in tautomeric and ylide forms as a function of pH was evaluated (fig. 4).

These data show that up to pH=1.71 the enol forms 8b and 8c are dominantly. For a range of pH comprised between 1.71 and 8.16 the principal product in the mixture is the keto form 8a. Beyond pH=8.16 we observe the formation of the cyclophane monoylide form 9. Normally, we tried to exploit these quantitative data from synthetic point of view. This aspect, reinforcing the existence of a tautomeric equilibrium, will be treated at
the end of the next section on the synthesis of fluorescent cyclophane indolizine (compound 12).

2, 1-(4-nitrophenoxy carbonyl)-7-(4'-pyridinium-1'-methyl p-phenylene paraquat p-phenylene keto-) 3 indolizine tris(hexafluorophosphate)

The procedure employed for the preparation of 12 starting from 'CETOBOX' 8 and 4-nitrophenyl propynoate 10 in presence of triethyl amine (TEA) is concisely presented in scheme 3.

The mixture of 8 and 10 in 1:1 molar ratio solved in DMF is gradually treated with TEA. The monoylide 9 generated "in situ" by a 3 + 2 cycloaddition with 10 forms initially the unstable cycloadduct 11 which spontaneously discards the hydrogen to furnish the fluorescent indolizine cyclophane 12.

The structure of product 12 has been established by NMR spectroscopy in DMSO-d6. Experimentally, their presence was proved by NMR spectroscopy, UV-Vis spectroscopy coupled with pH titration and by synthesis. Theoretically, using MM3, AM1, AM1-COSMO and B88LYP-DFT procedures, the most stable conformers of every tautomeric form has been established. The 'CETOBOX' 8 furnishes only the corresponding monoylide 9 which by a 3+2 cycloaddition permits the synthesis of a fluorescent indolizine cyclophane 12. Principally, all structures of the new compounds presented in this paper have been determined by NMR spectroscopy (1H and 13C-NMR, TOCSY, COSY and NOESY).

Conclusions

This article presents how the template synthesis of 'CETOBOX' 8 has been achieved and the use of this syntho for obtaining other supramolecular assemblies containing this cyclophane moiety (see compound 12). The 'CETOBOX' exists in three tautomeric forms. Experimentally, their presence was proved by NMR spectroscopy, UV-Vis spectroscopy coupled with pH titration and by synthesis. Theoretically, using MM3, AM1, AM1-COSMO and B88LYP-DFT procedures, the most stable conformers of every tautomeric form has been established. The 'CETOBOX' 8 furnishes only the corresponding monoylide 9 which by a 3+2 cycloaddition permits the synthesis of a fluorescent indolizine cyclophane 12. Principally, all structures of the new compounds presented in this paper have been determined by NMR spectroscopy (1H and 13C-NMR, TOCSY, COSY and NOESY).

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