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Structure and dynamics of pyrimidine-based macrocycles in solution

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ABSTRACT

The conformational structure of macrocycles obtained from two thiopyrimidine and uracil nucleic acids linked by polymethylene spacers is determined by the length of the spacers, intramolecular NH bonding, pH and solvent. In $CDCl_3$, NH–O═C hydrogen bonding can impact the overall stabilization of the folded conformation, however spatial preorganization to such hydrogen bonding is a prerequisite. Protonation leads to disruption of intramolecular hydrogen bonds, destabilization of the folded conformation and to strong counterion assisted self-aggregation of macrocyles which can be destroyed in polar solvents.

One of the methods in rational design of new biologically active compounds is the combination of a priori active (pharmacophore) units and their spatial preorganization by different spacers.[1–3] Distinct architecture can be achieved using rigid linkers. The use of labile spacers results in macrocycles and acyclic structures with more conformational flexibility. In addition, the use of units prone to weak non-covalent interactions opens the way to fine tuning of the 3D and supramolecular structure of such systems. In this respect, macrocyclic derivatives of nucleic acids bonded by different spacers are very promising.[4,5]

However, for rational design of such compounds it is necessary to know their 3D structure, the main factors that determine their geometry and energy. Particularly significant is to predict correctly the influence of weak intra- and intermolecular interactions and solvent effects on the macrocyclic structure and on the structure of their complexes as well. It is important to have such data in solution as most metabolic processes and reactions occur in this state.

These non-covalent interactions are responsible for recognition and complexation of ligands (guests) with receptors/targets (DNA/RNA). The potential to recognize and bind is also determined by the conformational structure of the host and guest, which are also partly controlled by weak intramolecular dispersion interactions. Therefore, investigation of such interactions has been of significant interest for a long time and there have been a number of publications in recent years.[6–8] However, there are many computational studies and very limited experimental data, particularly in solution. Thus, in spite of a number of studies devoted to this problem, there is still a lot to be understood.

There are intrinsic obstacles to the investigation of such interactions because it is very difficult to 'measure' small indications of non-covalent interactions, and to separate the different terms of these interactions from each other. In addition, a problem arises due to the variety of tautomeric and charged forms which contribute to the net non-covalent interactions, which are solvent and pH dependent.[9–11] This complicates the overall picture and can lead to an enormous number of energy minima on the potential energy surface of such systems.

Nucleic acid-based macrocycles are of interest for their biorelevancy, selective complexation ability towards different functional groups, and there have been a number of biochemical investigations with such systems.[12–14] There are various examples of the design of macrocyclic and acyclic derivatives of thymine, uracil and pyrimidine fragments preorganized by aliphatic and other spacers.[15–17]

These macrocycles are also of interest from another point of view—as models to investigate intra- and intermolecular non-covalent interactions. A new type of pyrimidinophane containing uracil and thiopyrimidine moieties bridged by different aliphatic chains was elaborated (Scheme 1).[18,19] According to IR data in solution, these macrocycles have both free and intramolecular hydrogen bonded NH protons.[18] In general, this could lead to some folded conformation(s). The non equivalency of the H5 protons of the thiopyrimidine moieties in ^{1}H NMR spectra indirectly supports this hypothesis. That is, these protons are far from the asymmetric uracil moiety, therefore their non-equivalency might be ascribed to a folded conformation in solution that transfers the information

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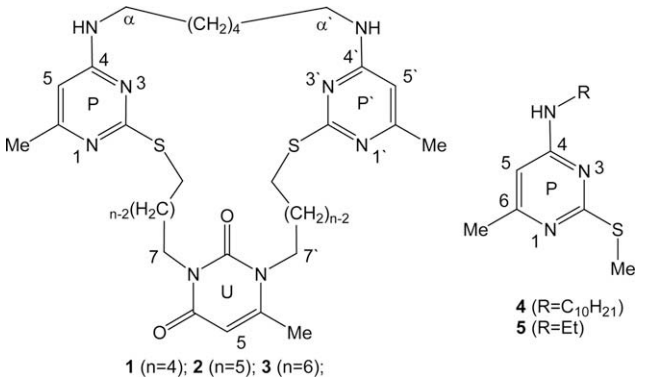

Scheme 1.

about the asymmetry to the thiopyrimidine rings. However, no support for the overall structure of the macrocycles has been provided yet.

Taking into account the above facts and considerations, we have undertaken to find out whether the folded structure of these macrocycles exists in solution. In this Letter, we present preliminary results on the conformational analysis of three macrocycles **1–3** by dynamic NMR and quantum chemical methods. In addition, model compounds that mimic different parts of the macrocycles were also prepared and investigated.

In the room temperature ^{1}H NMR spectra of the title macrocycles, there were only minimal differences. In all the compounds, there was only a small non-equivalence of the H5(P) protons and broadening of the CH_2 protons adjacent to NH (Fig. 1a for **1**). Attempts to obtain information on the folded structure at room temperature by NOE measurements were unsuccessful. In the 1D DPFGSE and 2D NOESY spectra (in $CDCl_3$) there were no 'non-trivial' NOEs that could be ascribed to such geometry.

Decreasing the temperature has a significant impact on the ^{1}H NMR spectra. At ca. 273–263 K there was coalescence of the spectra (Fig. 1b) and then at ca. 233 K slow exchange was observed (on the NMR time scale) (Fig. 1c). At a lower temperature, (ca. 223–213 K) there was an indication of the second dynamic process that mainly affected the NH and H5 signals (Fig. 1d). While the first process (broadening at ca. 273 K) is similar in all these compounds, the second process is less pronounced in **2** and more marked in **1** (Fig. 1e and d).

In order to clarify the nature of these processes, dynamic NMR experiments on the simpler thiopyrimidine-containing model **4** were carried out. ^{1}H (Fig. 2), ^{13}C, ^{1}H–^{13}C and ^{1}H–^{15}N 2D HSQC/HMBC and NOESY experiments at different temperatures allowed us to conclude that the first process is rotation around the C4–NH bond which produces two conformations: *Z* and *E* (Fig. 3), the latter being dominant (0.26 kcal/mol) in $CDCl_3$. This conclusion is supported additionally by the fact that the barrier of the process derived from line shape analysis for **4** ($\Delta H^{\#}$ = 15.8 kcal/mol) is in good agreement with the theoretical barrier (HF/6-31G) calculated for rotation around the C4–NH bond in the simpler model **5** ($\Delta E^{\#}$ = 14.4 kcal/mol).[20]

It is important that in **4**, indications of the second process were also seen at T = 223–213 K (Fig. 2d), which was very similar to those observed in compounds **1–3**. To explain this broadening of the signals, several likely processes might be invoked. With **4,**

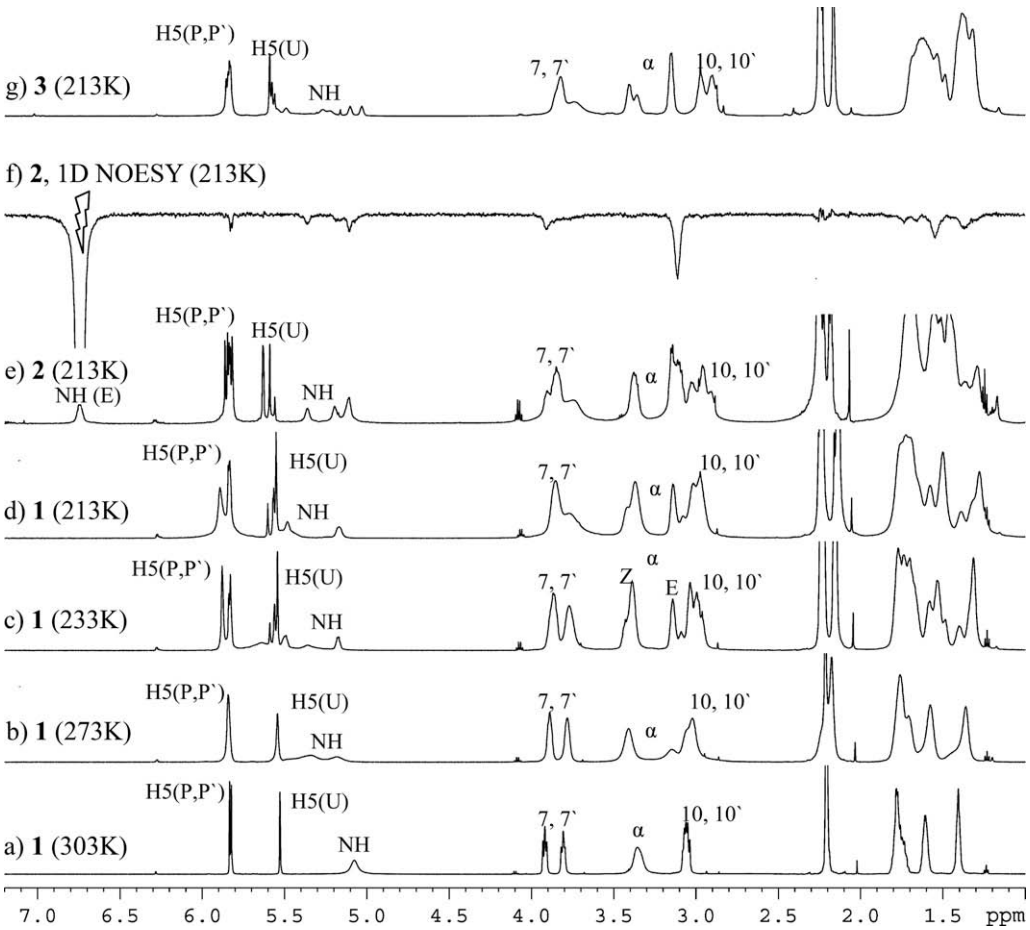

Figure 1. ^{1}H NMR spectra in $CDCl_3$ at different temperatures of **1** (a–d), **2** (e); 1D NOESY of **2** (f); **3** (g).