

Design, modeling and synthesis of molecular tweezers with self-assembly properties

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ABSTRACT

Development of molecular tweezers depends on the design and synthesis of reliable spacers. Two new classes of spacers based on functionalized dibenzo[a,j]xanthene are described. Molecular tweezers **4**, **5** and **6** with adjustable cavity are designed and synthesized. Single crystal X-ray diffraction shows self-assembly and recognition of **4** in the solid state; with the π -stacking, CH/O and CH/ π interactions being the driving forces. The intermolecular interactions in **5** and **6** are so strong that do not allow dissolution of **5** and **6** in any known solvent.

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1. Introduction

Synthetic molecular receptors have been designed and synthesized for studying the molecular recognition processes and the weak intermolecular forces operative in drug-receptor binding. Molecular tweezers are a class of synthetic receptors with open cavities which are capable of binding guest molecules using non-covalent interactions [1]. Most studies of molecular tweezers are focused on tweezers having rigid spacer and usually two aromatic pincers [2]. It has been shown that neutral aromatic substrates bind to the cavity of tweezer pincers by π - π and CH/ π interactions [1f,1g]. In molecular tweezers, the spacer should maintain the pincers in parallel alignment at effective distance normally about 7 Å [1g–3]. The requirement of keeping parallel pincers at a suitable distance from each other is limiting so there are not many known structural motifs to be used as spacer. Functionalized dibenzox[a,j]xanthene with proper structural units are good candidates for constructing reliable rigid spacers to be used for building up the molecular tweezers; dibenzo[a,j]xanthene has shown therapeutic, biological and anti-inflammatory activities as well [4–6].

2. Results and discussion

In xanthenes and dibenzo[a,j]xanthenes, 4H-pyran moiety determines the conformation of whole molecule. Conformation of

unsubstituted 4H-pyran is planar, but substitution of 4H-pyran at C-4 position with bulky substituents drives the molecule towards flattened boat form with pseudo axial orientation of substituent [7]. It has been shown that ring inversion in some substituted 4H-pyrans do not take place even at high temperature [8]. These conformational behaviors are completely imitated by 14H-2,12-dihydroxydibenzo[a,j]xanthene **1** and 14-(4-methylphenyl) 14H-2,12-dihydroxydibenzo[a,j]xanthene **2**. Furthermore, the bay region tolyl of **2** at C₁₄ has proper conformation [9] for construction of self-assembled structure. The hydroxyl groups at C₂ and C₁₂ positions in **1** and **2** are very suitable for building up pincers due to appropriate distance from each other (Figs. 1 and 2).

Geometry optimization of **1** by AM1 shows two conformations, planar and flattened boat, with planar form being more stable than the flattened boat by 5.3 kJ/mol, while DFT calculations by B3LYP method using 6-31G** basis set indicates the planar form as the only minimum energy conformation of **1** (Fig. 1). Geometry optimization of **2** by AM1 and DFT/B3LYP/6-31G** methods show the flattened boat as the only minimum energy form. The tolyl moiety in **2** could be oriented in two directions, eclipsed and gauche, defined by the dihedral angle of H₁₄–C₁₄–C₁₅–C₁₆ (Fig. 2). The AM1 calculations shows that eclipsed form is 13.5 kJ/mol more stable than the gauche one while DFT calculations shows that eclipsed form is the only minimum energy conformation (Fig. 2).

The spacers **1** and **2** were synthesized according to the Scheme 1. In contrast to the 14aryl-14H-dibenzo[a,j]xanthenes which are synthesized in high yields [10], synthesis of **1** and **2** suffers some drawbacks [11]. The yield of products could be increased by starting from the adduct **3** (Scheme 1). The molecular tweezers **4** and **5**

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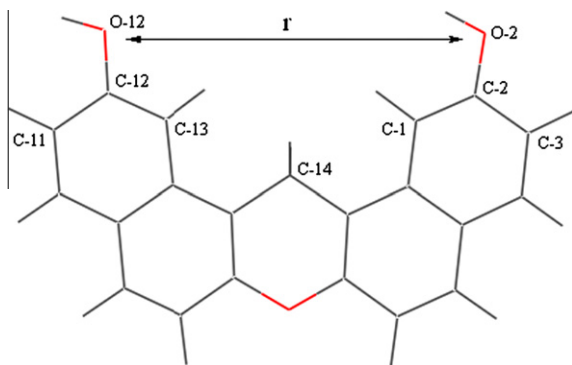


Fig. 1. The B3LYP/6-31G** optimized structure of spacer **1**. $r = 0.823$ nm, the distance of oxygen atoms of hydroxyl groups.

were synthesized by reacting **2** with benzyl and 1-(chloromethyl) naphthalene; **6** was synthesized by reacting **2** with 1-(2-bromoethoxy) naphthalene (Scheme 1).

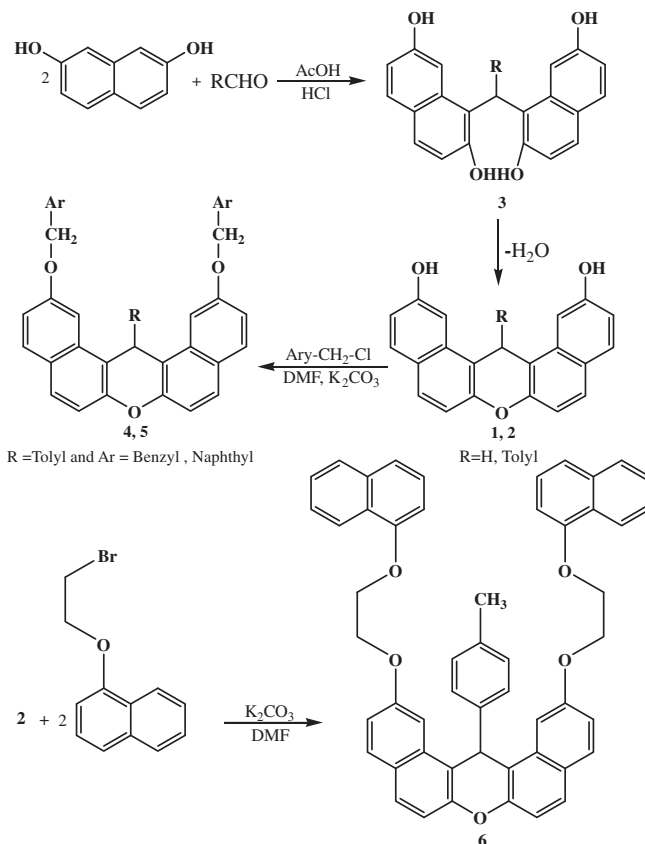
For conformational analysis of **4**, **5** and **6**; conformations of sub-structures were considered. The conformation of $-\text{CH}_2\text{R}$ group attached to 2-hydroxy naphthalene moiety in **4**, **5** and **6** could be derived from the 2-methoxy naphthalene. It has been shown that 2-methoxy naphthalene adopts syn (*s-cis*, $\phi = 0^\circ$) and anti (*s-trans*, $\phi = 180^\circ$) forms [12] with a population ratio 19:1 between syn and anti rotameric isomers at 305 K [13].

Conformational analysis of syn and anti forms of benzyl 2-naphthyl ether moiety in **4** were performed by AM1 and energy minima thus obtained were re-optimized by B3LYP/6-31G** calculations. Two conformations were found for syn and anti forms, i.e. syn-a; syn-g and anti-a; anti-g (Fig. 3, Table 1). It should be mentioned that in syn-g and anti-g forms, the dihedral angle of $\text{C}_{\text{sp}2}-\text{C}_{\text{sp}2}-\text{O}-\text{C}_{\text{sp}3}$ is close to zero as found in aryl methyl ethers [14]. It has been shown in a recent study that the conformational preference of benzyl methyl ether is type and basis set dependent [15], however this was not taken into consideration for the conformational analysis of benzyl 2-naphthyl ether moiety in **4**.

In **4**, considering syn-a and anti-a conformations of benzyl 2-naphthyl ether moiety, the two O-benzyl arms could be oriented in three distinct directions; syn-a, syn-a; anti-a, anti-a and syn-a, anti-a (or anti-a, syn-a) (Fig. 4). The AM1 calculations shows that

syn-a, syn-a should be the most populated form in the gas phase (Table 2); in the solid state syn-a, syn-a form is the only observed one.

If syn-a and syn-g conformations of benzyl 2-naphthyl ether moiety are considered for conformational analysis of **4**, six possible combinations of syn-a and syn-g conformations (without counting enantiomers) are possible for the two benzyl 2-naphthyl ether moiety in **4**, i.e. syn-a, syn-a; syn-a, syn-g-up; syn-a, syn-g-down;



Scheme 1. The paths for synthesis of spacers **1** and **2** and molecular tweezers **4–6**.

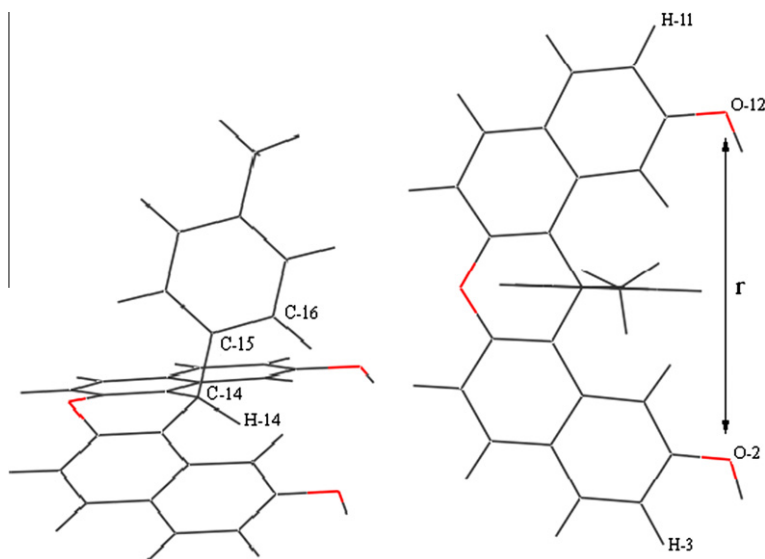


Fig. 2. The B3LYP/6-31G** optimized structure of spacer **2** (left, side view; right, top view). $r = 0.819$ nm, the distance of oxygen atoms of hydroxyl groups.

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