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X-ray guided ^{1}H NMR analysis of pinched cone calix[4]arenes

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ABSTRACT

The analysis of structural parameters of azobenzene- and stilbene-bridged calix[4]arene obtained from AM1 calculation are in good agreement with those obtained from X-ray crystallography. The bridge longer than 9.0 Å such as *p,p-trans*-azobenzene and *p,p-trans*-stilbene cannot be constructed over the narrow rim of calix[4]arene through two ethylene oxide linkers. The *m,m*-stilbene bridge is the most promising photo switch because its shorter *cis* stereoisomer (5.85 Å) allows calix[4]arene to assume the perfect cone conformation, whilst its longer *trans* stereoisomer (8.00 Å) forces calix[4]arene to adapt a pinched cone conformation. The pinched cone conformation has longer distances between the neighbouring phenoxyl groups causing the weaker intramolecular hydrogen bonding and the upfield shifts of the phenolic proton signals to below 7.00 ppm. This upfield shift is useful for quick identification of pinched cone conformation of new calix[4]arene compounds.

1. Introduction

Supramolecular interaction is the vital initial process triggering biological and chemical events. Studies on binding between converging sites of synthetic hosts with diverging sites of guest molecules or ions have progressively provided valuable information towards understanding of the supramolecular interaction of complicated natural molecules [1]. Much attention has recently been paid to achieve the binding selectivity between the host and the guest molecules by controlling the size and shape of the binding cleft of the host molecule [2]. A host molecule that can controllably switch its binding selectivity as desired is rare [3] but extremely desirable for various applications including imitating biological events.

Owing to its pre-organized structure, calix[4]arene is one of the most established molecular platforms for constructing three-dimensional hosts for molecules or ions [4]. The structure of calix[4]arene consists of four phenol rings linked together with four methylene units in a circular fashion producing a basket like architecture [5]. Flipping of one or more phenyl rings around the flexible methylene linkages allows calix[4]arene to exist in one or more of the four main conformers *viz.* cone, partial cone, 1,2-alternate and 1,3-alternate [6]. The cone conformer, which is the most stable conformation for unmodified calix[4]arene, has all four hydroxyl groups oriented along the same rim of the basket to maximize the intramolecular hydrogen bonding among them. If two of the four phenol rings are tilted over from the perfect circular alignment to adopt an oval-shaped basket, the resulting conformer is called a pinched cone [7]. The difference in the cavity shapes between cone and pinched cone provides an opportunity to regulate the selectivity of calix[4]arene hosts towards ionic or molecular guests. The guidelines for synthesis and analysis by ^{1}H NMR of calix[4]arene derivatives for cone and 1,3-alternate conformers using alkali metal templates have been well established [4b,8]. The use of aromatic proton signals in ^{1}H NMR have been proposed for discrimination between cone and pinched cone conformation of calix[4]arene [9]. Unfortunately, the unambiguous assignment of aromatic proton signals of calix[4]arenes are not viable for many derivatives, especially when the calix[4]arenes possess aromatic substituents.

We have previously reported the synthesis of calix[4]arene derivatives (**1**–**3**) containing a geometrically photoisomerizable bridge, azobenzene or stilbene (seeFig. 1), over its narrow rim [10]. The *meta* stilbene bridge is particularly of interest as the photo-switching between a binding and non-binding states of ***cis-m-2*** and ***trans-m-2*** [11]. The switching of the binding properties have been hypothesized as a result of the switching between a cone and pinched cone conformation of the calix[4]arene upon *cis*/*trans* photoisomerization of the stilbene bridge. The inability of

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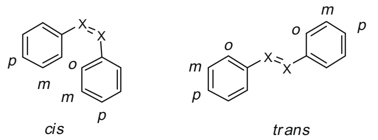
***m-trans*-3** to form 1,3-altermate conformation in the Cs^+-template synthesis also implied its pinched conformation [12]. To realize if a calix[4]arene derivative is in a pinched cone conformer, a single crystal of the compound was required for X-ray crystallography. We have re-examined the X-ray and AM1 geometry optimized structures of these compounds that leads to guidelines for quick identification of pinched cone conformation by using NMR signals of phenolic protons of calix[4]arene as reported herein. Unlike the aromatic proton signals, the hydroxyl proton signals of calix[4]arenes can be readily assigned and confirmed by deuterium exchange with D_2O that is attractive to be used for quick discrimination of cone and pinched cone conformation of new calix[4]arene derivatives.

2. Results and discussion

The length of relatively rigid azobenzene and stilbene units can be calculated using simple computational routines for geometry optimization, such as AM1 [13]. The calculated bridge length is dependent not only on the *cis/trans* geometrical isomers but also on the regio-positions to which the bridge is connected (Table 1). The calculated unit length strongly supports the previous synthesis results. For azobenzene-bridged calix[4]arenes, only *trans* configurations of the ortho and meta isomers (***o*-1** [10a] and ***m*-1** [10c]) were obtained. The stereospecificity was attributed to the instability of *cis*-azobenzenes, whilst the unsuccessful isolation of the coupling product from the *p*-isomer is well supported by the meticulously long length of the *trans* isomer (9.21 Å). For the stilbene-bridged calix[4]arene, five isomers of **2** (***o-cis*-2**, ***o-trans*-2**, ***m-cis*-2**, ***m-trans*-2** and ***p-cis*-2**) and five isomers of **3** (***o-cis*-3**, ***o-trans*-3**, ***m-cis*-3**, ***m-trans*-3** and ***p-cis*-3**) were all successfully isolated [10b,10c]. The isolated products showed the preference of *cis* stereoisomers for all regioisomers that are well substantiated by the short distance between the opposite hydroxyl groups of calix[4]arene (at only 4.0 Å) [14] in comparison to the bridge length. The results clearly demonstrate that the calculated lengths of the bridging units can be used as a quantitative specification of the bridge length (<9.0 Å) which may be constructed over the narrow rim of calix[4]arene.

Two new X-ray structures (***m-cis*-2** and ***m-cis*-3**) in combination with three previously reported structures (***o-trans*-1**, ***m-trans*-1**, ***o-cis*-2**) are shown in Fig. 2. The X-ray structures reveal that these bridged calix[4]arenes assume a cone conformation. To obtain adequate structural parameters for conformation analysis, the structures of all synthesized compounds were computationally calculated with AM1 geometry optimization. The distances between neighbouring phenolic oxygen atoms on the calix[4]arene rim obtained from the AM1 geometrically optimized structures agree very well (<5% difference) with those obtained from the X-ray structures (Table 2) justifying that the structural parameters obtained from AM1 structures are suitable for further conformation analysis.

Table 1
The AM1 calculated distance between various symmetrical positions on phenyl rings of azobenzene and stilbene.



azobenzene: X = N
stilbene: X = CH

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Isomer	Molecular lengths of			
	Azobenzene (Å)		Stilbene (Å)	
	cis	*trans*	*cis*	*trans*
o–o	3.48	5.05	3.51	5.24
m–m	5.90	7.81	5.85	8.00
p–p	8.32	9.21	8.35	9.39

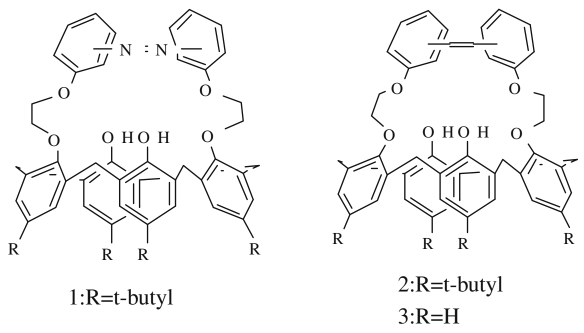

Fig. 1. Structural formulae of azobenzene-bridged calix[4]arene and stilbene-bridged calix[4]arenes.

Re-examining the ^{1}H NMR spectra of all synthesized compounds, we found that the phenolic protons display conspicuous chemical shifts. The signals of phenolic protons in *m-trans* and *p-cis* isomers appeared significantly upfield comparing to those of the rests (representatively shown in Fig. 3). The upfield shifts in the chemical shifts suggest that the intramolecular hydrogen bonding between the phenoxyl groups in the *m-trans* and *p-cis* isomers is relatively weaker than those of the other isomers.

To relate the chemical shifts of the phenolic protons to the molecular structures, the distances of the four pairs of neighbouring phenoxyl oxygen atoms around the calix[4]arene were averaged and presented along with the chemical shifts of the corresponding calix[4]arene derivatives (Table 3). The compounds with an average O—O distance longer than 3.0 Å show the signals of phenolic protons below 7.0 ppm whilst the compounds with an average O—O distance shorter than 3.0 Å show the signals above 7.0 ppm (Table 3). This correlation of the average O—O distances with the chemical shifts is a strong evidence to support that the upfield chemical shifts are the result of weaker hydrogen bonding between the neighbouring phenoxyl groups due to the distortion of the calix[4]arene rim caused by the longer azobenzene and stilbene bridges i.e. *m-trans* and *p-cis* isomers (bridge length > 7.0 Å, Table 1).

The plot between the average O—O distances and the chemical shifts shows a striking division of the compounds into two groups (Fig. 4) suggesting the possibility to use the phenolic ^{1}H NMR signals for identifying the highly distorted or pinched cone conformer of calix[4]arene derivatives. It is important to point out here that the distances between the neighbouring phenoxyl protons observed by X-ray crystallography and AM1 calculation are so varied that the classification between cone and pinched cone conformation cannot be well justified by using just individual or a pair of distances. This variation in the distances is attributed to the fact that the structures derived from both X-ray crystallography and AM1 calculation are static. On the other hand, the chemical shifts observed by ^{1}H NMR in solution are the average values resulting from the dynamic exchange process of the intramolecular hydrogen bonding. It is thus reasonable that the chemical shifts are more correlated with the average distances and they can be very useful for conformation analysis of new calix[4]arene derivatives in solution. The conformational information in solution is important for explaining and predicting the conformational related binding properties of calix[4]arene in host–guest chemistry.

To apply our method for classification of cone and pinched cone conformation by ^{1}H NMR spectrum on previously reported