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## Calix[4]phyrins. Effect of Peripheral Substituents on Conformational Mobility and Structure within a Series of Related Systems

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**Abstract:** A new, stepwise synthesis of calix[4]phyrins is described. It relies on the condensation of a ketone with pyrrole to form a dipyrromethane containing a quaternary carbon center that is subsequently condensed with an aromatic aldehyde. This methodology, in contrast to the previous rational approach described by this group (involving formation of a trisubstituted dipyrromethane via the condensation of an aldehyde with pyrrole, followed by condensation of this dipyrromethane with acetone), allows for a variety of bulky, ketone-derived substituents to be incorporated into the meso-like positions. The resulting systems, while all containing the same central macrocyclic core, display conformational properties that reflect the nature of these meso-like substituents; these conformational features were independently assessed by X-ray diffraction analysis, NMR spectroscopy, and quantum chemical calculations.

### Introduction

Calixphyrins are a class of hybrid molecules that lie at the structural crossroads between porphyrins and calixpyrroles.<sup>1</sup> Porphyrins, long known for their versatile metal cation coordination chemistry, are macrocycles that contain only sp<sup>2</sup>-hybridized bridging meso-carbon atoms within their main, central framework. Calixpyrroles, on the other hand, are porphyrin analogues that contain pyrroles bridged exclusively by sp<sup>3</sup> meso-carbon centers and are systems that have enjoyed a renaissance in recent years thanks in part to their remarkable anion-binding properties.<sup>2</sup> Calixphyrins bear analogy to both the porphyrins and calixpyrroles and are macrocyclic analogues

that contain a mixture of sp<sup>2</sup>- and sp<sup>3</sup>-hybridized meso-carbon bridges.<sup>1,3</sup> This leads to partial interruptions in the conjugation pathway of the molecule, introduces novel structural features, and leads to interesting anion and cation recognition properties. It also allows for modular syntheses. In this paper, we present a detailed study of the conformational properties of a range of novel calix[4]phyrin derivatives of general structure **1** that bear meso-aryl substituents in opposing positions [5,15-porphodimethenes according to standard porphyrin nomenclature; calix[4]phyrins-(1.1.1.1) using the more readily generalized nomenclature we have recently introduced<sup>1a</sup>], as well as a new, stepwise synthesis that allows for their preparation (cf. Scheme 1 and discussion below). The calix[4]phyrins reported here represent a well-defined series in which the effect of peripheral substituents on the overall structure and conformational behavior of ostensibly similar oligopyrrolic macrocycles may be effectively probed. This has been done by both experimental and calculation-based methods.

### Results and Discussion

**Preparation of Calixphyrins.** In previous work<sup>3a</sup> we described a straightforward, rational synthesis of calix[4]phyrins

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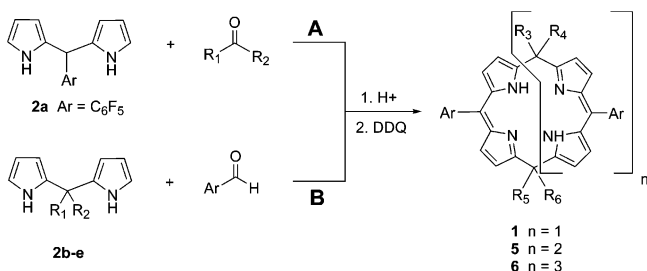
<sup>‡</sup> The University of Texas at Austin.

<sup>§</sup> Laboratory of NMR Spectroscopy, Institute of Chemical Technology.

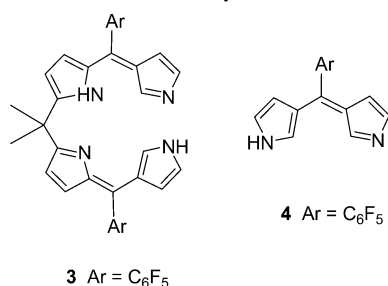
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**Scheme 1.** Alternative Condensation-Based Approaches to the Synthesis of Calix[4]phyrins<sup>1,3 a</sup>

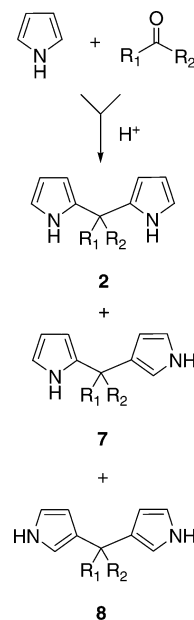
<sup>a</sup> For series **a**,  $R_1-R_6 = \text{CH}_3$ ,  $\text{Ar} = \text{C}_6\text{F}_5$ . For series **b**,  $R_1-R_2 = R_3-R_4 = R_5-R_6 = \text{cyclohexan-1,1-diyl}$ ,  $\text{Ar} = \text{C}_6\text{F}_5$ . For series **c**,  $R_1-R_2 = R_3-R_4 = R_5-R_6 = \text{fluoren-9,9-diyl}$ ,  $\text{Ar} = \text{C}_6\text{F}_5$ . For series **d**,  $R_1-R_6 = \text{Ar} = \text{C}_6\text{H}_5$ . For series **e**,  $R_1 = \text{CH}_3$ ,  $R_2 = \text{C}_6\text{H}_5$ ,  $R_3(R_4) = R_5(R_6) = \text{C}_6\text{H}_5$ ,  $R_4(R_3) = R_6(R_5) = \text{CH}_3$ ,  $\text{Ar} = \text{C}_6\text{F}_5$  (mixture of isomers for **1e**, **5e**, and **6e**).

**Scheme 2.** Open-Chain Byproducts Isolated in the Course of Preparing **1a** in Accord with Pathway A of Scheme 1

of generalized structure **1** ( $R_3 - R_6 \neq \text{H}$ ). It involves the use of an aromatic aldehyde to prepare a substituted dipyrromethane, such as **2a**, followed by condensation with acetone and follow-up DDQ-induced oxidation, as shown in Scheme 1, pathway A. Applying this synthetic methodology to pentafluorobenzaldehyde to form the dipyrromethane, acetone to close the ring, dichloromethane as the solvent, and TFA as the acid catalyst led to formation of the desired target **1a** in excellent yield (90%). Under these conditions, the open-chain byproducts **3** and **4** (Scheme 2) are produced and could be isolated in yields of 7% and 0.5%, respectively. However, no higher order species (e.g., **5a** or **6a**) were detected, in contrast to what was observed when similar reactions were carried out in acetonitrile.<sup>3a</sup> A byproduct was also detected,<sup>3d</sup> but not identified, when a procedure analogous to that of pathway A was used to prepare calix[4]-phyrins from aromatic  $\alpha,\beta$ -diketones.<sup>3c-e</sup>

The isolation of compound **3** can be ascribed to the presence of an impurity, namely, the  $\alpha,\beta$ -linked dipyrromethane **7a** (Scheme 3), which could either have been present in samples of **2a** or formed under the reaction conditions. Likewise, the formation of compound **4** is thought to reflect the presence of the  $\beta,\beta$ -linked dipyrromethane **8a** (Scheme 3) in the reaction mixture used to produce **1a**, either because it is an impurity in the initial  $\alpha,\alpha$ -dipyrrolylmethane **2a** sample<sup>4</sup> or because it is formed as the result of rearrangements taking place under the conditions of the final ring-forming reaction.

The fact that both **3** and **4** could be isolated is considered noteworthy. It highlights the fact that oligopyrrolic precursors linked via the  $\beta$ -pyrrolic positions are inherently less reactive than those linked via  $\alpha$ -positions. Reflecting such a differential

**Scheme 3.** Preparation of Dipyrromethanes **2** and Possible Minor Isomers **7** and **8**<sup>a,b</sup>

<sup>a</sup> Higher order open-chain oligopyrroles products that can be formed under these or related conditions are not shown. <sup>b</sup>Series **a**:  $R_1 = \text{C}_6\text{F}_5$ ,  $R_2 = \text{H}$ . Series **b**:  $R_1-R_2 = \text{cyclohexan-1,1-diyl}$ . Series **c**:  $R_1-R_2 = \text{fluoren-9,9-diyl}$ . Series **d**:  $R_1 = R_2 = \text{C}_6\text{H}_5$ . Series **e**:  $R_1 = \text{CH}_3$ ,  $R_2 = \text{C}_6\text{H}_5$ .

reactivity is the fact that under the reaction conditions, **3** and **4** do not react to produce the corresponding “inverted” calixphyrins, as must necessarily be true, in whole or in part, in the case of the precursors, such as **2a**, that are linked through an  $\alpha$ -pyrrolic position. As importantly, the presence of **7** and **8** as impurities in the condensations carried out in dichloromethane, coupled with the known tendency to produce higher order species under alternative reaction conditions (e.g., when acetonitrile is used as a solvent<sup>3a</sup>), leads us to suggest that an alternative, and possibly improved, calix[4]phyrin synthesis would be beneficial. Further underscoring the need for such an alternative synthesis is the fact that even though the yield of **1a** is excellent when **2a** is condensed with acetone, efforts to generalize the chemistry of Scheme 1, pathway A via the use of other ketones have so far met with little success in our hands. Presumably, this lack of success reflects the fact that the larger ketones we tested in this context, namely cyclohexanone, acetophenone, and benzophenone, are simply less reactive than acetone. On the other hand, the Scott group has recently found that aromatic  $\alpha,\beta$ -diketones, which are expected to be more reactive, give calixphyrin-type products in preparative yields of up to 20%.<sup>3c-e</sup>

The alternative calix[4]phyrin synthesis we wish to report here (Scheme 1, pathway B), relies on the production first of a highly substituted dipyrromethane (e.g., **2b-e**), followed by condensation with various aromatic aldehydes [ $\text{C}_6\text{H}_5\text{CHO}$  and  $\text{C}_6\text{F}_5\text{CHO}$  in the present study, either in the presence or absence of acid catalyst as required by the reactivity of the aldehyde (cf. Scheme 3)].<sup>5</sup> After condensation, the system is subject to oxidation with DDQ, as in the previous procedure. The advantage of this approach is that the  $\text{sp}^3$ -hybridized centers get “built in” to the macrocyclic framework prior to the critical ring-forming step. This allows for the “placement” of bulkier

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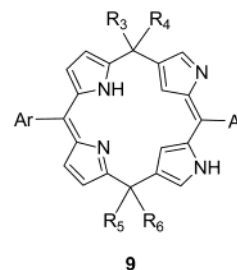
groups on the  $sp^3$ -hybridized bridging carbons than is possible using the original synthetic methodology. The presumed success of this procedure reflects the fact that (i) oligopyrroles formed from aldehydes are inherently unstable under the acid-catalyzed conditions used to produce calixphyrins (vide supra) and (ii) acetone and higher order ketones are less reactive than aldehydes, an attribute that makes them much less suitable for use as reaction partners in the final, ring-forming condensations.

It is important to note that we are not the first to explore a stepwise approach analogous to that shown in Scheme 1, pathway B. In particular, Scott and co-workers recently applied a similar strategy to dipyrromethanes prepared from aromatic  $\alpha,\beta$ -diketones, albeit without appreciable success.<sup>3e</sup> However, using this stepwise strategy we were able to prepare calix[4]phyrins **1b–e**. In the case of the cyclohexandiyl (**2b**) and methylphenyl (**2e**) derivatives, we also isolated or detected the corresponding calix[6]phyrins (**5**) and/or calix[8]phyrins (**6**). While the yields are low, often less than 10% in the final ring-forming reaction, it is important to appreciate that (i) the requisite dipyrromethanes, **2b–e**, are easy to obtain in one step from inexpensive, commercially available starting materials, (ii) the calix[4]phyrins products themselves are well-behaved, stable, and easily purified by column chromatography, and (iii) the preparation allows the synthesis of compounds that are not readily available via alternative strategies. In addition to its synthetic utility, however, this new procedure is likely to be useful because it highlights the differing reactivity of various macrocycle-forming precursors.

For instance, the observation that minor products, such as **3** and **4**, could be isolated in several instances, such as when dipyrromethane **2a** was reacted with acetone in dichloromethane (vide supra), leads us to speculate that ketones lack the reactivity needed to condense effectively with precursors such as **3** and **4** so as to produce aza-confused calixphyrins, such as **9**, in appreciable quantities. This lack of reactivity, in turn, allows these open-chain intermediates to be isolated. On the other hand, aldehydes, being generally more reactive than ketones, are presumed capable of reacting with various  $\beta$ -pyrrole-linked intermediates to effect ring closure. Indeed, when dipyrromethane **2** from acetone (cf. generalized structure **2** in Scheme 3;  $R_1 = R_2 = CH_3$ ) is condensed with perfluorobenzaldehyde, calix[4]phyrin **1a** is obtained unaccompanied<sup>6</sup> by appreciable quantities of open-chain products, such as **3**, or aza-confused calixphyrins, such as **9**. In point of fact, to date, the ring-inverted system **9** was only observed in those cases where the starting  $\alpha,\alpha$ -dipyrromethane **2**, specifically **2c** and **2d**, is contaminated with the isomeric  $\alpha,\beta$ -dipyrromethane **7**. For instance if  $\alpha,\alpha$ -dipyrromethane **2c** containing  $\alpha,\beta$ -dipyrromethane **7c** as an impurity is condensed with pentafluorobenzaldehyde, the N-confused calix[4]phyrin **9c** is obtained as a minor byproduct with the same molecular mass as the dominant product, the “regular” calix[4]phyrin **1c**. Purifying **2c** so it is free of **7c** precludes formation of **9c**. The <sup>1</sup>H NMR spectrum of calixphyrin **9c** shows two signals for the NH protons and two AB systems corresponding to the pyrrole CH protons (i.e., four doubled signals, integrating for 2H each). Similar features are seen in the spectrum of **9d**. Such findings are consistent with products **9c** and **9d** having  $C_2$  symmetry. This then leads to the conclusion

that the two pyrrole protons are attached to  $\beta$ -pyrrolic carbon atoms, i.e., calixphyrins **9c** and **9d** are actually doubly aza-confused.

**Scheme 4.** Double Aza-Confused Calix[4]phyrin<sup>a</sup>



<sup>a</sup> Ar and  $R_3$ – $R_6$  as per series **d** of Scheme 1.

In no cases were products analogous to **3** isolated in any of the reactions carried out using the new procedure (Scheme 1, pathway B). Such findings are consistent with the notion that under the reaction conditions associated with condensation of an aldehyde with a dipyrromethane containing an  $sp^3$  center (e.g., **2b–e**), the various reaction intermediates are configurationally stable.

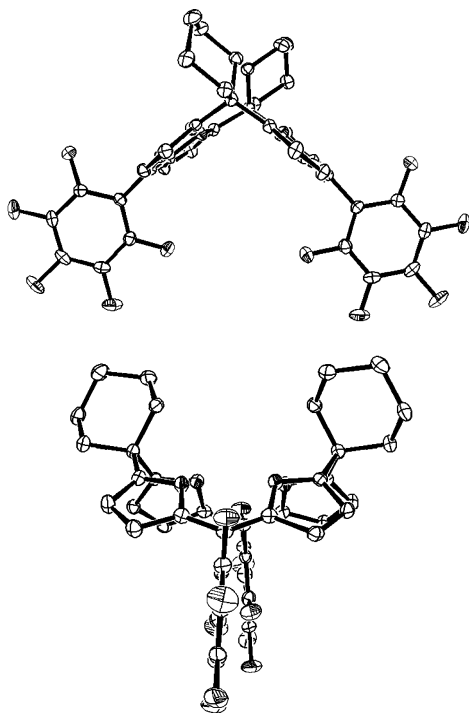
It is also of interest to note that no evidence for the formation of any mono aza-inverted calixphyrin was obtained. Such a result, while perhaps surprising, is completely consistent with the known reactivity of  $\alpha,\beta$ -linked dipyrromethanes. Pure  $\alpha,\beta$ -dipyrromethane **7a** reacts, for instance, with pentafluorobenzaldehyde to give only the CCNN isomer (no CNCN) of doubly aza-confused porphyrin and an analogous corrole derivative.<sup>7</sup> From this result, we infer that  $\alpha,\beta$ -dipyrromethanes of type **7** are more likely to condense head-to-head than head-to-tail. An alternative explanation is that open-chain tetrapyrrolic intermediates produced as the result of head-to-tail condensations exist in conformations that are not amenable to cyclization and thus undergo oligomerization to produce intractable polymeric materials. In any event, the high relative yields of **9**, as compared to those of **1**, seen in certain cases support the notion that head-to-head condensations of **7** can take place readily and that the resulting intermediates cyclize rapidly in the presence of an aromatic aldehyde (e.g., benzaldehyde or pentafluorobenzaldehyde) and an acid catalyst.

**Product Characterization. X-ray Diffraction Analyses.** The new calix[4]phyrins **1b–e**, as well as the “inverted” species **9c,d**, were fully characterized by spectroscopic means. With the exception of NMR spectral features that could be ascribed to conformational effects and NH tautomeric exchange (vide infra), the data obtained in all cases were fully consistent with the proposed structures. With the exception of **1a** and the cis isomer of **1e**, the calix[4]phyrins were further characterized by X-ray diffraction. The resulting structures are presented in Figures 1–4. Analysis of these structures reveals that, as a general rule,<sup>1,3</sup> calix[4]phyrins of this type adopt a “gable” or “rooflike” (i.e., V shaped) conformation with the bend occurring along the axis defined by the two  $sp^3$ -hybridized meso-carbon atoms (i.e.,  $C^{10}$  and  $C^{20}$ ).

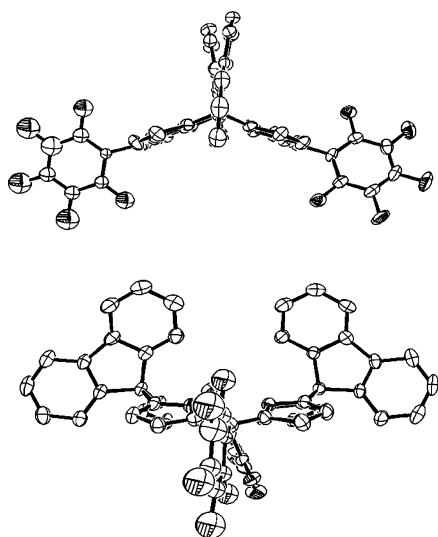
While the extent of bending is different for each of the individual structures, similar conformations are seen in the case of **1b**, **1c**, and **1d**, with these calix[4]phyrins displaying roughly

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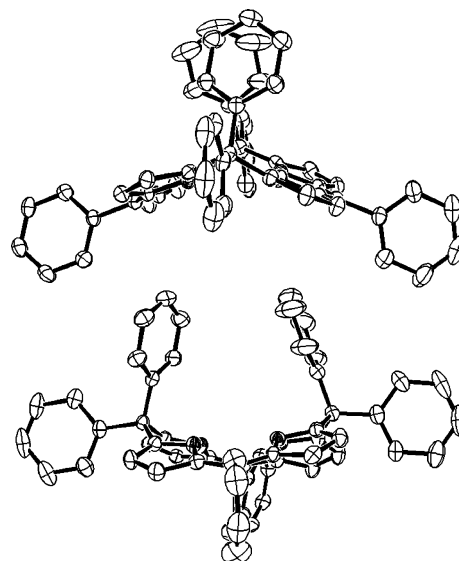


**Figure 1.** Single-crystal X-ray structure of **1b**. Displacement ellipsoids are scaled to the 50% probability level. All hydrogen atoms have been removed for clarity.

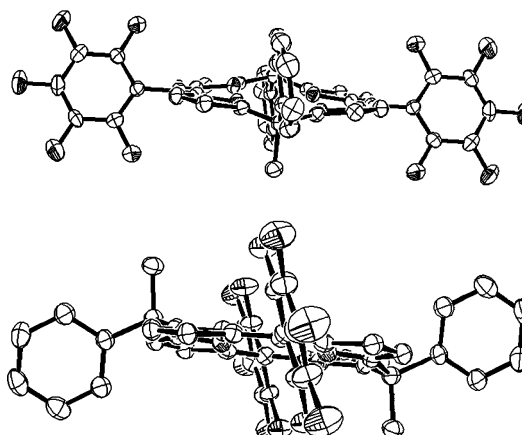


**Figure 2.** Single-crystal X-ray structure of **1c**. Displacement ellipsoids are scaled to the 50% probability level. All hydrogen atoms have been removed for clarity.

$C_2$  symmetry (cf. Figure 5 for a schematic representation of the relevant limiting conformational forms). For calix[4]phyrin **1a**, we also predict a V-shaped conformation, on the basis of prior structural analyses of similar calix[4]phyrins derived from acetone.<sup>3a,8</sup> By contrast, the X-ray structure of *trans*-**1e** reveals a molecular core that, although close to planarity, is somewhat twisted and hence of overall  $C_i$  symmetry. A similar structure was observed earlier in the case of a less substituted calix[4]phyrin analogue (cf. Scheme 1, general structure **1**,  $R_3 = R_5 = H$ ,  $R_4 = R_6 = i\text{-Pr}$ ,  $\text{Ar} = H$ ).<sup>9</sup> Unfortunately, all efforts to obtain diffraction grade crystals of the other configurational isomer,



**Figure 3.** Single-crystal X-ray structure of **1d**. Displacement ellipsoids are scaled to the 50% probability level. All hydrogen atoms have been removed for clarity.



**Figure 4.** Single-crystal X-ray structure of *trans*-**1e**. Displacement ellipsoids are scaled to the 50% probability level. All hydrogen atoms have been removed for clarity.

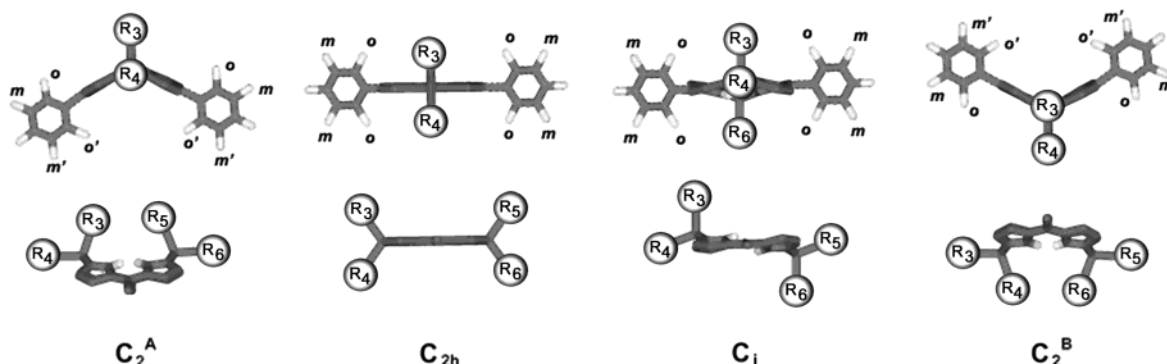
namely *cis*-**1e**, met with failure. Nonetheless, this latter system is of interest because, as a consequence of possessing two different substituents (methyl and phenyl) on each of the  $sp^3$ -hybridized meso-carbon atoms (as is true for *trans*-**1e**) and being in a *cis* configuration (in contrast to *trans*-**1e**), it can exist in two different  $C_2$  forms that are chemically and energetically nonequivalent. This nonequivalence is unique among the calix[4]phyrin-(1.1.1.1) systems considered in this study.

**Conformation Effects.** Left indeterminate by the above solid-state analyses, however, is the question of whether compounds of general structure **1** would also adopt nonplanar conformations in solution and, if so, under what conditions. A nonplanar conformation has been proposed in the recent literature,<sup>3c-e</sup> on the basis of the observation of fewer signals in the NMR spectra than would be expected for calix[4]phyrins of  $C_2$  symmetry, as seen in the solid state. This reduction in signal count was ascribed to fast “flexing” between the  $C_2^A$  to  $C_2^B$  conformations (see Figure 5). However, such a reduction in signal count would also be observed were the calix[4]phyrin in question to adopt a

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**Figure 5.** Limiting conformations for calix[4]pyrins of general structure **1** (Ar = C<sub>6</sub>F<sub>5</sub>) as determined by molecular modeling. The top row shows the equivalent and nonequivalent fluorine atoms, while the one below it shows the same conformers rotated by 90° in the *x*-*z* plane with the perfluorophenyl groups excluded. The relevant symmetry groups are also given.

conformation with higher symmetry in solution. To distinguish between these two limiting explanation, various calix[4]pyrins were studied using molecular modeling techniques. The goal of the computations was to find the lowest energy conformations of calix[4]pyrins **1a–e** and to assess their stability relative to both the corresponding next highest energy conformation and the transition state associated with conformational interconversion. Although such studies were not expected to model in detail the solution-phase environment, they were expected to allow an assessment of whether fast conformational exchange could occur.

By molecular modeling, four possible limiting conformers for the basic calix[4]pyrin skeleton of generalized type **1** (Figure 5) were deduced. (Note that conformers  $C_2^A$  and  $C_2^B$  are not identical in the case of calixpyrin *cis*-**1e**, where  $R_3 \neq R_4$  and  $R_5 \neq R_6$ .) The most prominent result to emerge from these calculations is the finding that for all compounds **1a–e**, the V-shaped conformers,  $C_2^A$  and  $C_2^B$ , are preferred energetically relative to either the planar  $C_{2h}$  or twisted  $C_i$  forms (Figure 5). Except in the case of *cis*-**1e**, the  $C_2^A$  and  $C_2^B$  conformations are energetically equivalent, as noted above. For this latter species, the calculations reveal a greater stability for the  $C_2^A$  form, with the methyl groups in “equatorial” positions and the phenyl groups in “axial” positions ( $R_3 = R_5 = \text{Ph}$ ,  $R_4 = R_6 = \text{CH}_3$ ), relative to the corresponding  $C_2^B$  form. This finding that the  $C_2^A$  form of *cis*-**1e**, wherein the more bulky phenyl groups are in the “axial” positions instead of the less bulky methyl groups, is in agreement with a single-crystal X-ray diffraction analysis of another *cis*-configured calix[4]pyrin;<sup>1c</sup> in this latter instance, the bulky *tert*-butyl groups, rather than the smaller hydrogen atoms, are in found in the “axial” positions (cf. Scheme 1, general structure **1**,  $R_3 = R_5 = t\text{-Bu}$ ,  $R_4 = R_6 = \text{H}$ , Ar = Ph; see also Figure 5).

In general, the above findings are in agreement with the X-ray results from the present study. The one exception is calix[4]pyrin *trans*-**1e**, where the  $C_i$  conformer was observed experimentally. In this case, the calculations predict the  $C_2$  as being the most stable conformer. Because the energy difference between the two conformers in question is relatively high (17 kJ/mol), we do not believe that the disagreement reflects a computational error. Rather, we suggest that the apparent dichotomy is best explained in terms of difficult-to-model crystal packing forces.

The results of the calculations, as well as relevant experimental data obtained from solution-phase NMR spectroscopic

**Table 1.** Characteristics of Calixpyrins Considered in This Study

	<b>1a</b>	<b>1b</b>	<b>1c</b>	<b>1d</b>	<i>trans</i> - <b>1e</b>	<i>cis</i> - <b>1e</b>
X-ray conformer	—	$C_2$	$C_2$	$C_2$	$C_i$	—
$\Delta E$ (kJ/mol)	35	53	8	19	17	4
conformer $C_x$	$C_{2h}$	$C_i$	$C_i$	$C_i$	$C_i$	$C_2^B$
$T_C$ (°C)	−55	95	< −100	~ −100	< −100	> 110 <sup>a</sup>
$\Delta G^*_{TC}$ (kJ/mol)	42	71	d	b	d	> 77
TS barrier (kJ/mol)	33	71	8	29	29	29
$T_H$ (°C)	< −100 <sup>a</sup>	−50	−5	−80	< −100 <sup>a</sup>	−90
$\Delta G^*_{TH}$ (kJ/mol)	d	45	54	< 34	—	b

<sup>a</sup> A coalescence temperature of this type is expected to exist; however, it could not be observed experimentally within the temperature limits imposed by the solvent. <sup>b</sup> We were unable to record a  $\Delta\nu$  value of sufficient reliability to permit an accurate  $\Delta G^*_{TC}$  calculation. <sup>c</sup> Such a coalescence temperature is presumed to exist; however, it was not observed within the available temperature limits. <sup>d</sup> To the extent such a coalescence temperature exists, it could not be observed, presumably as the result of a low barrier for conformational interconversion, a high level of molecular symmetry, or both.  $T_H$  and  $T_C$  denote the experimentally observed NMR coalescence temperatures, assigned to tautomeric NH proton exchange and calixpyrin ring toggling, respectively.  $E_C$  is the transition state barrier derived from the temperature-dependent NMR experiments, the term TS barrier corresponds to the calculated (BPW91/6-31G\*\*) height of the transition state corresponding to the energetic barrier with respect to the lowest energy state associated with toggling, while  $\Delta E$  refers to the calculated (BPW91/6-31G\*\*) relative energies of the two lowest-energy conformers  $E(C_x) - E(C_2)$ . The symmetry of the lowest energy state is assumed to be  $C_2$  as indicated, whereas that of the next highest energetic state,  $C_x$  is indicated in the appropriate line. This latter symmetry was not arbitrarily assumed or constrained during the process of optimization.

experiments (see below), are summarized in Table 1. This table also includes the calculated difference in absolute energy ( $\Delta E$ ) between the lowest energy  $C_2^A$  conformer and the next highest energy form, the  $C_i$  or  $C_{2h}$  or  $C_2^B$  conformer, as appropriate. This latter next highest energy state is designated as  $C_x$  for the purposes of the calculations and is given in the line below the one containing the  $\Delta E$  values.

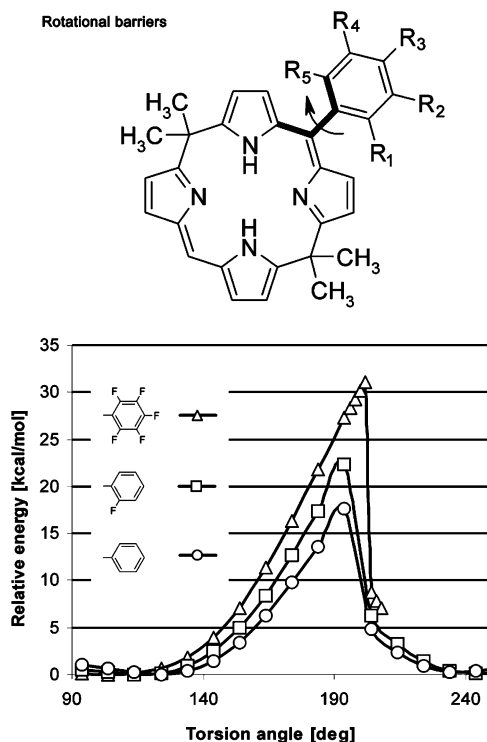
In contrast to what is likely to be true in the case of the  $C_{2h}$  conformers, the  $C_2$  and  $C_i$  conformers are expected to be characterized by chemically nonequivalent substituents on the  $sp^3$ -hybridized carbon atoms (cf. Figure 5). In addition, the  $C_2$  conformer also bears phenyl substituent on the  $sp^2$  bridging atoms that contain a pair of nonequivalent atoms (e.g., *o* and *o'*). Since we never observe a nonequivalence for the substituents on the  $sp^3$  centers without observing a corresponding nonequivalence for the substituents on the  $sp^2$  carbon atoms, we infer that the  $C_i$  conformer is not present to an appreciable extent and generally exclude it from the following discussion for the sake of clarity. Thus, to the extent that the theoretical prediction that the  $C_2$  conformer is the thermodynamically most stable gets translated into the observation of only a single, nonfluxional

species in solution, the perfluorophenyl groups being attached to the two  $sp^2$ -hybridized meso-carbon atoms of a calix[4]phyrin would be expected to give rise to five (or up to five) signals in the  $^{19}\text{F}$  NMR spectrum (*o*-, *o'*-, *m*-, *m'*-, and *p*-fluorine atoms) of **1a**, **1b**, **1c**, and **1e**. Similar considerations would hold for the proton and carbon signals of a phenyl group, were it bound in these same positions (cf. structure **1d**).

In the case of *cis*-**1e** and **1b**, the expected five signals are seen at room temperature in solution (e.g.,  $\text{CDCl}_3$ ,  $\text{CD}_2\text{Cl}_2$ ,  $\text{DMSO}-d_6$ ), meaning that these calixphyrins exist as the  $C_2$  conformers at that temperature. However, in the case of **1a**, **1c**, and *trans*-**1e**, only three signals are observed under these same conditions. In addition, it was found that the number of signals varied as a function of temperature, with a coalescence temperature ( $T_c$ ) being observed, from which a value of  $\Delta G^\ddagger_c$ , which characterizes this phenomenon, could be computed. Both sets of values are included in Table 1. No such  $\Delta G^\ddagger_c$  values could be calculated for systems **1c** and *trans*-**1e** since, even at  $-100^\circ\text{C}$ , no evidence of coalescence was observed.

One explanation for the coalescence observed in the case of, for example, **1a** could be a fast rotation of the perfluorophenyl group attached to the  $sp^2$ -hybridized meso-carbon atoms. Such rotations would lead to one average signal for both *o*-fluorine atoms, and one peak for both *m*-fluorine atoms. Including the signal expected for the *p*-fluorine atom, the next result would be three signals, as observed by experiment. Additionally, it is known that atropoisomers (rotamers) of 5,10,15,20-tetrakis(2-fluoro-5-methoxyphenyl)porphyrin can be separated<sup>10</sup> at  $10^\circ\text{C}$ . It is considered likely that the rotational barrier of this aryl substituent when present on an  $sp^2$ -hybridized calix[4]phyrin carbon atom will be very similar to that seen in the case of the corresponding porphyrins. It is also probable that the rotation barrier for a perfluorophenyl subunit will be greater than for the 2-fluoro-5-methoxyphenyl substituent. We thus do not think that perfluorophenyl ring rotation can account for the experimental findings.

To put the above conclusion on a more firm footing, and in consideration of whether it could be extrapolated to the corresponding phenyl ( $\text{C}_6\text{H}_5$ ) systems, a potential energy scan of the torsion angle was carried out.<sup>15</sup> Here, to minimize computational difficulties and reduce the need for computer time, a model compound with fewer atoms was employed. This model and the rotation being considered are defined in Figure 6. As expected, the torsion barrier is lowest for an unsubstituted phenyl group (Figure 6,  $R_1\text{--}R_5 = \text{H}$ , 75 kJ/mol). This conclusion is consistent with what one would infer from a consideration of the experiment, since the relevant experimental values<sup>11,12</sup> for porphyrin derivatives are about 71 kJ/mol. One fluorine in an ortho position (Figure 6,  $R_1 = \text{F}$ ,  $R_2\text{--}R_5 = \text{H}$ ) significantly hinders the rotation (computed barrier 96 kJ/mol), a finding that is again in good agreement with the experimental value<sup>10</sup> (92 kJ/mol) obtained by studying compounds analogous to our model system. Finally, the use of a perfluorinated phenyl (Figure 6,  $R_1\text{--}R_5 = \text{F}$ ) provides the highest barrier of 134 kJ/mol. If we take this latter value and compute the coalescence temperature corresponding to perfluorophenyl rotation for derivatives **1b** and *cis*-**1e**, one would expect the coalescence



**Figure 6.** Computational study of phenyl rotation in a series of model compounds.

temperature to be in excess of  $380^\circ\text{C}$ . This is obviously not in agreement with experiment, since the coalescence temperature observed for **1b** is  $95^\circ\text{C}$ . We thus do not believe that the dynamic NMR behavior of, especially, **1a** can be linked to perfluorophenyl rotation. Such a conclusion is in accord with the observation<sup>12</sup> that the perfluorophenyl ring, when attached as a meso substituent to porphyrin derivatives, is conformationally stable up to  $130^\circ\text{C}$ .

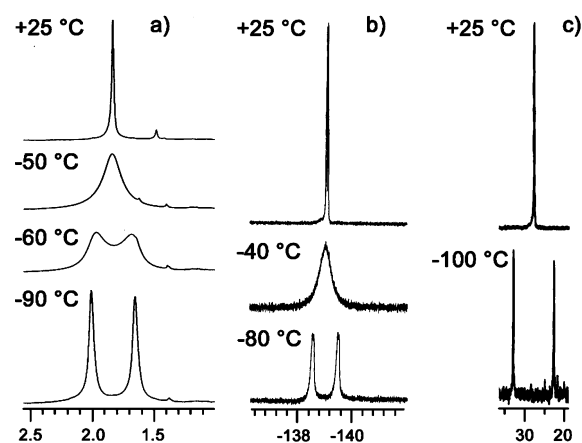
In considering alternative explanations for the coalescence of the signals ascribed to the aryl substituents bound to the  $sp^3$ -hybridized meso-carbon atoms, it is important to note that these signals do not provide the only evidence of the dynamic behavior seen in the NMR spectra of compounds of general structure **1**. For instance, at  $25^\circ\text{C}$  the  $^1\text{H}$  NMR spectrum of **1a** is characterized by one singlet at ca. 1.9 ppm, corresponding to four methyl groups bound to the  $sp^3$ -hybridized carbon atoms, which separates into two peaks upon cooling to ca.  $-55^\circ\text{C}$ . Splitting is also observed for the carbons of the methyl groups (Figure 7). While not studied in full temperature-dependent detail, as were the *meso*-aryl signals discussed above, such an observation is qualitatively consistent with the freezing out of a dynamic conformational motion at low temperature. Obviously, this motion cannot reflect *meso*-aryl group rotations and must have a basis in some other kind of molecular motion.

Given the fact that *meso*-phenyl or perfluorophenyl group rotations cannot explain the full body of experimental findings and are inconsistent with the results of calculation, we propose that the temperature-dependent coalescent behavior seen for the *meso*-aryl and, in the case of **1a**, *gem*-dimethyl signals, is the result of more global conformational changes. Specifically, we suggest that in those compounds where a coalescence temperature for the *meso*-aryl signals is observed (i.e., **1a** and **1d**), the systems in question exist in solution in their respective  $C_2$  forms but are interconverting ("toggling") rapidly between their

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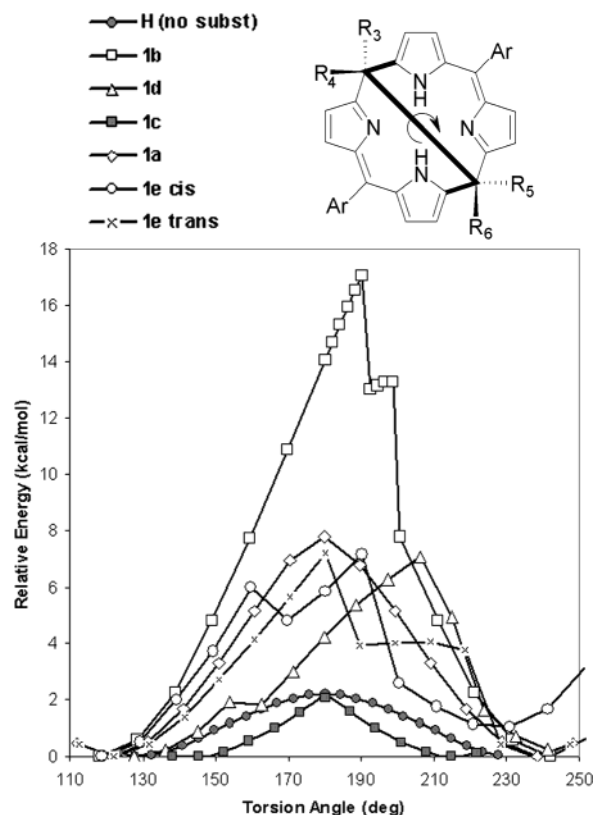


**Figure 7.** Temperature-dependent NMR spectroscopic changes ascribed to freezing of molecular motions of **1a** in its  $C_2$  conformeric form: (a)  $^1\text{H}$  NMR spectra of methyl groups; (b)  $^{19}\text{F}$  NMR spectra of *o*-fluorine atoms of the perfluorophenyl groups; (c)  $^{13}\text{C}$  NMR spectra of methyl groups.

respective energetically equivalent  $C_2^A$  and  $C_2^B$  forms (which are illustrated in Figure 5) at room temperature. Such fast motion makes these species spectroscopically indistinguishable from the corresponding flat form, namely the conformer with  $C_{2h}$  or  $C_i$  symmetry. Similar considerations hold in the case of **1b**, with the obvious important exception that temperatures above room temperature (ca. 95 °C) are required to induce toggling. In the case of calixphyrins **1c** and *trans*-**1e**, where no coalescence is observed even at the lowest temperatures probed (ca. –100 °C), the observation of fewer than five distinct *meso*-aryl resonances can also be explained in terms of these two calixphyrins existing as the  $C_i$  or  $C_{2h}$  conformers in solution, especially since it is the  $C_i$  conformer that is seen in the solid-state structure of *trans*-**1e**. In other words, because no coalescence temperature is observed, it is impossible to distinguish between a system that undergoes fast toggling between disparate  $C_2$  conformers or simply exists in a higher symmetry conformation. Here, it should be noted that in the case of these two compounds (**1c** and *trans*-**1e**), the  $C_i$  and  $C_{2h}$  conformers are of high symmetry, either as a result of their inherent structure or because equivalent moieties are found on both the  $\text{sp}^2$ - and  $\text{sp}^3$ -hybridized *meso*-carbon atoms.

The case of *cis*-**1e** is somewhat different, since the two  $C_2$  conformers are of different energy. Thus, fast toggling motions would not be expected; indeed, five peaks are seen for the *meso*-aryl substituents, even at the highest temperatures probed by experiment (ca. 110 °C).

It is worth noting that the Zn complex **1c**–Zn, prepared in the course of this study (vide infra), and **1c** give rise to essentially identical  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectral patterns. This is consistent with these two species adopting identical conformations, although it does not necessarily prove it. Nonetheless, it is intuitively reasonable to expect that a fast toggling between the  $C_2^A$  and  $C_2^B$  conformers is likely to be precluded in the case of **1c**–Zn. Thus, we propose that this metalated species, and by inference its metal-free precursor, **1c**, probably exist in solution as the symmetric  $C_{2h}$  conformer. Consistent with this suggestion is the finding by others that several metalated calix[4]phyrins were found to exist in the form of their respective  $C_2$  conformers<sup>1b,d,3e</sup> or slightly distorted  $C_{2h}$  conformers<sup>1c</sup> in the solid state.



**Figure 8.** Computed energetic barriers for conformation changes. The conformations at local minimum are near to  $C_i$  conformers.

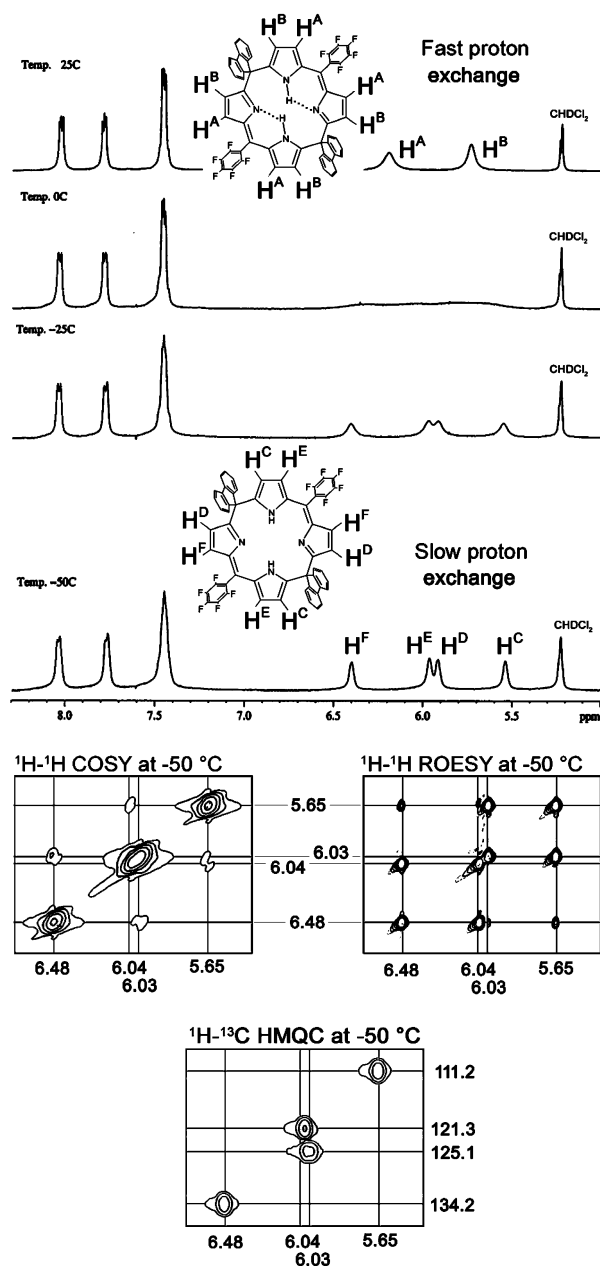
To obtain insight into the energetics and flexibility of the calixphyrin system, we scanned an arbitrary torsion angle for all the derivatives and for each value computed an optimized energy. The angle is defined in Figure 8.

Since the proposed toggling process reflects a relatively simple motion, and the molecules are relatively rigid, we propose that the dependence of the energy on the angle is closely related to the ease of flipping between the two conformers,  $C_2^A$  to  $C_2^B$ . To the extent such an assumption is valid, it allows the energy of the transition state to be estimated (see TS Barrier values in Table 1). These computed values should then be in direct proportion to the experimentally observed  $\Delta G^\ddagger_c$  values, a correspondence that, if observed, would provide support for our proposed conformational interconversion hypothesis.

The lowest energy barrier (8 kJ/mol) was found for calixphyrin **1c**. Somewhat surprisingly, this barrier is essentially equal to the one that we found for an unsubstituted calixphyrin, a species referred to as a porphyrin dimethene in the classic porphyrin literature<sup>1</sup> (Scheme 1, general structure **1**,  $\text{R}_3\text{--R}_6 = \text{Ar} = \text{H}$ ). Whether this agreement is fortuitous or not, the key point is that the very low calculated energy barrier means that this calixphyrin (**1c**) is expected to undergo fast conformational exchange in solution. Such a prediction is completely consistent with a failure to observe coalescence at temperatures at or above –100 °C. By contrast, the highest computed energy barrier was found for calixphyrin **1b**. This is in agreement with the observed high value for  $\Delta G^\ddagger_c$  and is not surprising given the restricted motion of the cyclohexanediyl ring residue.

Interestingly, the four compounds **1d**, **1a**, *cis*-**1e**, and *trans*-**1e** all exhibit almost identical computed energy barriers of about 30 kJ/mol. This means that there is a rather large mismatch





**Figure 9.** (Top) Temperature dependent  $^1\text{H}$  NMR spectra of **1c** recorded in  $\text{CD}_2\text{Cl}_2$  showing the changes occurring as the result of “freezing out” the proposed process of NH tautomeric exchange. Such a reduction in motion is manifest in terms of the change in the number of  $\beta$ -pyrrolic proton signals. (Bottom) Low-temperature COSY, ROESY, and HMQC spectra recorded at  $-50\text{ }^\circ\text{C}$  in  $\text{CD}_2\text{Cl}_2$  and connectivities observed at  $-50\text{ }^\circ\text{C}$ .

between this theoretical energy barrier (29 kJ/mol for the specific case of *cis*-**1e**) and the corresponding experimental value,  $\Delta G^*_\text{C}$  ( $>77\text{ kJ/mol}$ ). This discrepancy is rationalized in terms of the inequality of the  $\text{C}_2^{\text{A}}$  and  $\text{C}_2^{\text{B}}$  conformers in the case of this specific, less symmetric system. The energy difference between the two forms is predicted to be about 4 kJ/mol. Presumably, this preference for one particular conformer makes toggling less facile than would be predicted from calculations based on a simple thermodynamic model.

**NH Tautomerism in Calix[4]phyrins.** In addition to coalescence behavior ascribable to conformational toggling, a second coalescent temperature,  $T_{\text{H}}$ , is observed in the case of several of the systems and is linked to NH hydrogen tautomerism. Due to fast proton exchange within the calix[4]phyrin

core, only two doublets (AB system) are observed for the pyrrole protons in the  $^1\text{H}$  NMR spectrum, and only two singlets for the  $\beta$ -carbon atoms and two singlets for the  $\alpha$ -carbon atoms of the pyrroles are seen in the  $^{13}\text{C}$  NMR spectrum at higher temperature. At lower temperatures, the NH exchange process is slowed. This can result in a “freezing out” of the individual low-energy tautomers, resulting in a doubling in the number of the  $\beta$ -pyrrole atom signals. Such a doubling in the signals is in fact observed in the case of, for example, **1c**, both in the  $^1\text{H}$  ( $\text{H}^{\text{C}}$ ,  $\text{H}^{\text{D}}$ ,  $\text{H}^{\text{E}}$ ,  $\text{H}^{\text{F}}$ ) and  $^{13}\text{C}$  NMR spectra (Figure 9). The high-temperature tautomeric exchange process and its ‘freezing out’ was also demonstrated via ROESY experiments, where exchange cross-peaks ( $\text{H}^{\text{C}} \leftrightarrow \text{H}^{\text{D}}$ ,  $\text{H}^{\text{E}} \leftrightarrow \text{H}^{\text{F}}$ ) as well as COSY connectivities ( $\text{H}^{\text{C}} \leftrightarrow \text{H}^{\text{E}}$ ,  $\text{H}^{\text{D}} \leftrightarrow \text{H}^{\text{F}}$ ) were observed (Figure 9). On the other hand, little change in the chemical shift of the other calixphyrin signals, including those for the NH protons, was not seen, presumably as the result of these changes being inherently very small. The values of the activation free energies,  $\Delta G^*_\text{H}$ , deduced from the experimentally observed coalescence temperatures, are given in Table 1.

The process of NH tautomeric exchange has been intensively studied<sup>13</sup> in the case of porphyrins, and the corresponding  $\Delta G^*_\text{H}$  values usually range from 37 to 59 kJ/mol. In the case of calix[4]phyrins **1b–d**, where coalescence is observed, the  $\Delta G^*_\text{H}$  values were found to lie in a similar energetic range, i.e., from 34 to 54 kJ/mol. Since no coalescence is observed in the case of **1a** and *trans*-**1e**, the corresponding  $\Delta G^*_\text{H}$  values, although not specifically defined, are probably lower. Thus, there appears to be a significant difference, at least 20 kJ/mol, and likely more, in the energy required to effect tautomerization in this well-defined set of calix[4]phyrins. Interestingly, but not surprisingly, given the independent motions they define, these energies and the rates of tautomerization that they reflect are not seen to correlate with the rate of conformational toggling.

However, these motions could correlate with the ease of metalation. In the presence of many metal salts, such as zinc(II) acetate, most porphyrins<sup>14</sup> and the prototypical calix[4]phyrin, species **1a**,<sup>3a</sup> undergo metal insertion readily at temperatures of about  $60\text{ }^\circ\text{C}$ . However, calix[4]phyrin **1c**, the congener with the highest tautomerization coalescence energy, like several other special exceptions known in the porphyrin literature,<sup>14</sup> requires a reaction temperature above  $170\text{ }^\circ\text{C}$  for successful metalation by zinc acetate. Left undetermined at present is whether the ease of metalation is correlated with overall conformational flexibility. Current work, therefore, is focused on exploring in detail the metalation behavior of calix[4]phyrins in an effort to address just this issue. We are also working on studying the NH tautomerization process using advanced computational methods, in analogy to what has been done in the case of porphyrins.<sup>13,15</sup>

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## Conclusions

In this report, we have shown the utility of a new approach to aryl-functionalized calix[4]pyrins that allows the incorporation of bulky substituents into the macrocycles. The result is a series of well-defined congeners whose conformational behavior, specifically a “toggling” between two limiting  $C_2$  forms, is found to be directly related to the choice of substituents. We also show that it is possible to model and predict this conformational toggling behavior, including the energies required to effect exchange. Although not treated by calculation, we also show that there is a relationship between calix[4]pyrin structure and the rate of NH tautomerism. Finally, in the context of this study, we have prepared and characterized the first doubly aza-inverted calix[4]pyrins (**9**), a system that contains  $sp^3$  carbons in positions 5 and 15. Current work is devoted to exploring the metalation properties of calix[4]pyrins of general structure **1** and determining how the ease of metalation and the structures of the resulting complexes depend on both the conformational flexibility of the systems in question and the rate of NH tautomerization. Preliminary work, involving a comparison of systems **1a** and **1c**, leads us to suggest that such correlations

exist and could be quite important in terms of, for example, influencing the rate of metalation, and, possibly, complex stability.

The conformational and tautomeric exchange behavior of the new calix[4]pyrins prepared in the context of this work were studied by NMR spectroscopy. Generally, at high temperatures time-averaged signals of various species can be observed. At lower temperatures, where the rate of chemical exchange becomes slower, resonances of less symmetrical structures can be identified. Temperature dependent  $^1H$ ,  $^{13}C$ , and  $^{19}F$  NMR spectroscopy has thus served as an excellent tool for studying the dynamic behavior of calix[4]pyrins. It is thus likely to be useful as well in the analysis of more complex calix[ $n$ ]pyrins, including higher order species where  $n > 4$ .<sup>3a,b</sup> Studies along these lines are currently in progress.

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**Supporting Information Available:** Synthetic and computational experimental details; X-ray data for the new structures reported here (compounds **1b**, **1c**, **1d**, and *trans*-**1e**) as CIF files; UV–vis spectra for compounds **1b**, **5b**, **1c**, and **9c**; ROESY, COSY and HMQC spectra for **1c**;  $^1H$  NMR spectra for compounds **1b**, **1c**, **1c**–Zn, **1d**, *cis*-**1e**, *trans*-**1e**, **3**, **4**,  $\alpha,\alpha,\alpha$ -**5e**,  $\alpha,\alpha,\beta$ -**5e**, **9c**, and **9d**; and  $^{13}C$  NMR spectra for compounds **1c** (at 50 and  $-50$  °C in solution and at 23 °C in the solid state) and **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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