ORIGINAL PAPER

Socrates Alikhanidi · Victor Kuz'min

Stereodesign of chiral *para*-substituted calix[4]arenes

Abstract According to the hypothesis that the chirality of molecule hosts is a cause of their enantioselectivity, the chirality of *para*-substituted calix[4]arenes was analyzed quantitatively. The relationship between types of *para*-substituents and the dissymmetry of the 2D (two-dimensional) entrance into the cavity and the whole 3D (three-dimensional) cavity of calix[4]arenes was studied by means of the enantiomer dissimilarity factor (EDF) method for quantitative evaluation of molecular chirality. The design of the most chiral, and probably enantioselective, *para*-substituted calix[4]arenes was planned such that all four substituents should be different and the two largest should be near each other (adjacent). It was, on the other hand, shown that the 2D chiral entrance determines chirality of the whole 3D structures of these molecules. This phenomenon is interpreted as an example of the chirality transition from 2D into 3D space.

Keywords Stereodesign · Quantitative chirality · QSPR · Enantioselective hosts · Calixarenes

Introduction

Enantioselectivity is one of the most interesting properties of a macrocyclic complexant caused by chirality. A significant part of enantiomer separation science is the technology for extraction of optically active compounds by means of chiral hosts [1, 2, 3]. In this connection, calixarenes are interesting for use as the macrocyclic hosts and complexants. Here, calix[4]arenes (structure 1 in Fig. 1a) form complexes with metal ions, and with neu-

S. Alikhanidi · V. Kuz'min (✉)
Department of Organic Chemistry,
I. I. Mechnikov Odessa National University,
2 Dvoryanskaya Street, Odessa 65100, Ukraine
e-mail: victor@farlep.net
Tel.: 380 482 225127, Fax: 380 482 652012

tral molecules such as acetone, toluene, etc. [4]. Several functionalized calix[4]arenes can involve other classes of compounds [5]. Chiral calixarenes are attractive as stereoselective hosts but have not been studied adequately [6].

A possible way of designing the chiral cavity is the use of different *para* substituents within calix[4]arene [4]. By using the enantiomer dissimilarity factor method (EDF) [7] suggested previously by the authors, we tried to solve the following problem – what types of *para* substituents lead to the most chiral structure?

Objects

Structure 1 is chiral when either all substituents R_1–R_4 differ (e.g. four kinds: A, B, C, D) or only two R_x are the same but not located opposite each other (e.g. three kinds: A, B, C). So, the following non-equivalent combinations can lead to chiral *para*-substituted calix[4]arenes (Fig. 2).

As an example, we use the halogens F, Cl, Br, I as R_x. Thus, one has 15 chiral *para*-halogen-substituted calix[4]arenes (3 with four different substituents and 12 with three different substituents, see Scheme 1)

Conformations adopted by calix[4]arenes can be categorized in four classes: the cone, the partial cone, the 1,2-alternate, and the 1,3-alternate [4]. The preferred conformation for the carbon skeleton of the inclusion complexes is, however, the cone with the averaged C_{4v} symmetry (Fig. 1b) [4]. The nature of *para* substituents does not play a significant role in the conformation of carbon skeleton [8], because of the long distances between substituents. For example, in a C_{4v} cone the distance between nearest substituents is more than 6 Å assuming the van der Waals'radius of iodine to be 2.15 Å [9]. The conformation and stereochemical configuration of structure 1 can be fixed by replacement of hydroxy group by larger group, e.g. *tert*-butoxy [10].

Fig. 1 *para*-Substituted ca-
lix[4]arene – formula (**a**) and
spatial structure in the cone
conformation (**b**). The entrance
into the cavity (see text) was
constructed from *para* substitu-
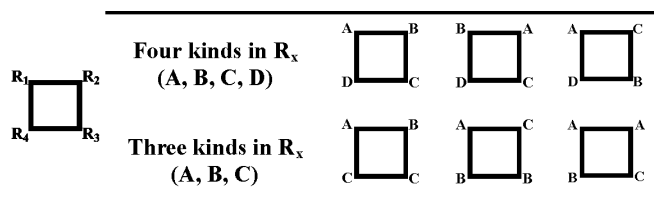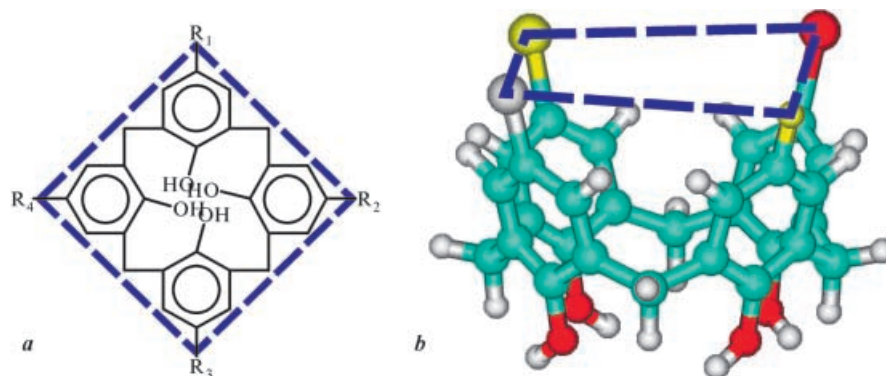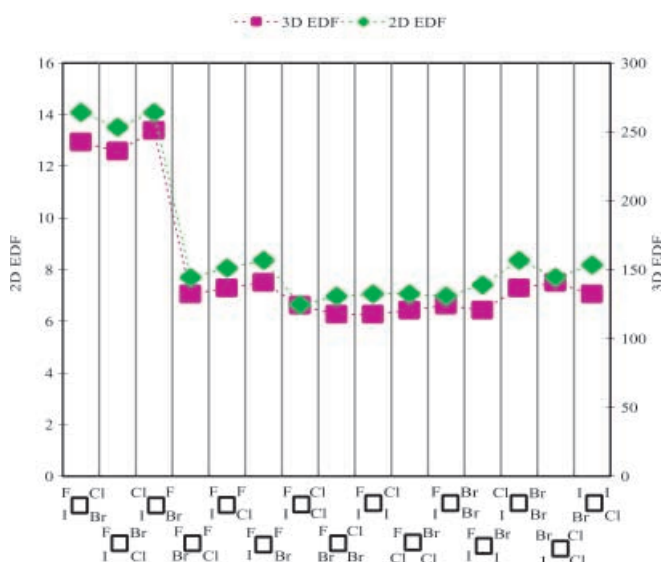ents and is marked by the dot-
ted quadrilateral

Fig. 2 Combination of the four substituents leads to chiral ca-
lix[4]arenes

Fig. 3 The enantiomer dissimi-
larity factor (EDF) method: the
difference between the enantio-
mers (here four-substituted
methane) of a structure is as-
sumed as the chirality value.
Difference is defined as the
minimum sum of squares of
distances between atoms of
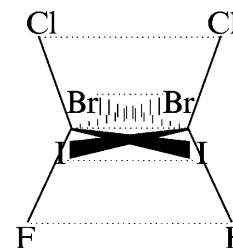enantiomers

Scheme 1 2D chirality values of the entrance into the cavity and
3D chirality values of the spatial structure of *para*-halogen-substi-
tuted calix[4]arenes

$$\text{EDF} = \sum_{i=1}^{N} w_i \| \mathbf{r}_i - \mathbf{pair}(r_i) \|^2 \qquad (1)$$

where N is the number of points (atoms) of the object; w_i is the
weight factor of point i of the object – here the van der Waals' radii
are used – which describe the size of atoms; $\mathbf{r}_i$ is the radius-vector
of point i of object; $\mathbf{pair}(r_i)$ is the radius-vector of point i of the
reflected object, and is the assignment of point $\mathbf{r}_i$ (the search for
the optimum assignments between points of the initial and reflect-
ed objects is a special combinatorial task). The EDF value should
be minimized by variation of the orientation of the reflected object
relative to the initial one. As a test, an achiral object has a zero
EDF value.

The general structure of the algorithm is shown below.

1. Allocate non-equivalent points (atoms) of the object to groups.
   Each group contains atoms of the same type. Within this task,
   atoms are distinguished by their nature (by location in periodic
   table).
2. Select consecutively one of 10 initial preset positions of the re-
   flected object. Positions are chosen using the principal axes of
   the object and operations of improper axes S_1, S_2, S_4.
3. Minimize Eq. (1) by determination of the optimum assignment
   of all its atoms to all atoms of the original one in the current
   orientation of the reflected object. This combinatorial problem
   corresponds to the search for minimum cost matching in a bi-
   partite graph, and can be solved efficiently (its algorithm
   scales polynomially) [13].
4. Minimize Eq. (1) by determination of the optimum orientation
   of the reflected object under the current assignment of atoms
   of the original object. This task can be solved analytically [7].
5. If the EDF value is decreased by step 4, go back to step 3. Oth-
   erwise, take the next initial orientation of the reflected object
   (step 2). If all have been examined, the algorithm finishes and
   it is necessary to choose a minimum EDF value.

The EDF method for evaluation of 3D and 2D chirality of struc-
tures, together with the folding–unfolding [14, 15] method and the
asymmetry function [16, 17] method for quantitative measurement
of different molecular asymmetries are included in the program
DisFact [18].

Method

For quantifying the chirality of an object we use the EDF meth-
od [7], which is based on the search for maximum overlap of the
original and reflected objects (Fig. 3). This task involves different
optimization problems. In contrast with known approaches [11,
12], within the EDF method effective optimization procedures are
employed and the whole algorithm was defined in detail. Its cor-
rectness was demonstrated on model structures of various
types [7].

According to the EDF method, the chirality measure of a point
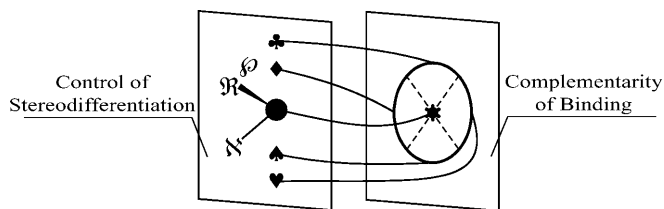object is determined from:

Fig. 4 The two levels of chiral recognition

Discussion and results

Firstly, the main premises of our investigation should be considered.

1. For analyzing *para*-substituted calix[4]arenes for stereoselectivity of complex formation, the structure of the host molecule was varied (15 chiral *para*-halogen-substituted calix[4]arenes) under the assumption that the chiral guest molecule (both enantiomers) always has the same structure and its reaction center (the group enabling complex formation with the calixarene, e.g. $-NH_3^+$) is completely complementary to the cavity formed by the donor "preorganized" for co-operatively binding centers of the macrocyclic complexant. *para* Substituents of host molecules do not affect the process of complex formation dramatically. They do the "fine tuning" by creating the intermolecular forces chiral field, which differentiate between the interaction of enantiomers of guests molecules with the host, as shown in Fig. 4.

If all four *para* substituents are same, there is no stereoselectivity, because the interaction energies of the host molecule with both enantiomers of the guest molecule are identical. If the substituents are different, then they (as mentioned above) form an intermolecular chiral force field providing enantioselectivity. So, our basic hypothesis is that the more chiral the structure (under the formalism of the EDF model), the higher the level of chirality of the intermolecular force field created by that structure. This hypothesis has been proved by study of the helical twisting power of chiral dopants in nematic mesophases [19].

2. Another premise concerns the concept of chirality "transitions" for objects of different dimensions. In the calixarenes studied, the substituents (spherical halogen atoms) are achiral, but form chiral 2D figures (dissymmetric "entrance" into the calix[4]arene cavity), which is, naturally, 3D-achiral. The spatial structure of unsubstituted calix[4]arene is also achiral in 3D. The combination of these two fragments (calix[4]arene plus substituents) leads, however, to a chiral structure (Fig. 5).

So, it can be supposed that the level of 3D chirality of *para*-halogen-substituted calix[4]arenes is connected closely with the 2D chirality of the figure constructed by the halogen atoms ("entrance" into the cavity). To evaluate 2D chirality, this "entrance" was approximated by the
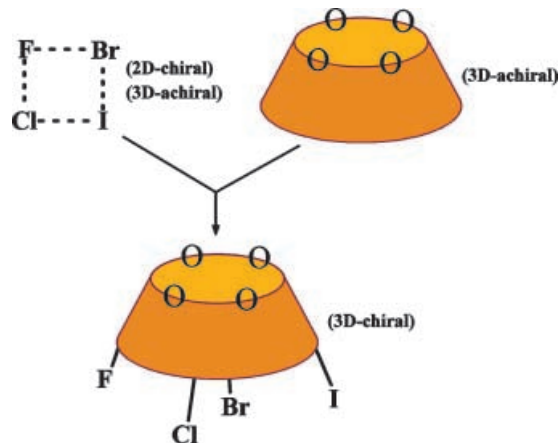

Fig. 5 "Transition" of chirality from a 2D object ("entrance" into the calix[4]arene cavity constructed from four halogen atoms) to a 3D object (*para*-halogen-substituted calix[4]arenes)

corresponding plane square, where the vertices are *para* substituents.

Results from estimation of the chirality of *para*-halogen-substituted calix[4]arenes and 2D chiral entrances into their cavities are shown in Scheme 1. From analysis of this scheme it can be concluded that the chirality of the whole 3D cavity of calix[4]arenes is just determined by the 2D chirality of squares constructed by the *para* substituents (correlation coefficient between corresponding chirality values is R = 0.993). Thus, the calculated results prove our premises.

On the other hand, one can see that most chiral structures have four different substituents, where the two largest are adjacent. We propose that such a location of the substituents provides maximum chirality of the intermolecular force field in the region of space where the stereoselectivity is controlled (see our first premise above). This information for design of the most chiral *para*-substituted calix[4]arenes might be of interest for directed synthesis.

Supporting information available

Structures of all objects examined as PDB files and their pre-calculated chirality parameters. For visualization of objects, their best-overlapped enantiomers and viewing of chirality values, the programme DisFact can be downloaded [18].

References and notes

1. *Comprehensive Supramolecular Chemistry*; Szejtli, J., Osa, T., Eds.; Pergamon: Oxford, 1996.
2. *Recent Advances in Chiral Separations*; Stevenson, D., Wilson, I. D., Eds.; Plenum: New York, 1990.

146

3. *Chiral Separations. Applications and Technology*; Ahuja, S., Ed.; American Chemical Society: Washington, DC, 1997.

4. *Calixarenes: a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer V., Eds.; Kluwer: Dordrecht, London, Boston, 1990.

5. Danil de Namor, A. F.; Cleverly, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *7*, 2495.

6. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *8*, 3313.

7. Alikhanidi, S. E.; Kuz'min, V. E. *Reports of NAS of Ukraine*. **1999**, *3*, 138.

8. Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

9. Gordon, A. J.; Ford, R. F. *The Chemist's Companion.* Wiley Interscience: New York, London, Sydney, Toronto, 1970.

10. *Host Guest Complex Chemistry Macrocycles. Synthesis, Structure, Applications.* Vögtle, F., Weber, E., Eds.; Springer: Berlin, Heidelberg, 1985.

11. Gilat, G. *J. Phys. A: Math. Gen.* **1989**, *22*, L545.

12. Buda, A. B.; Auf der Heyde, T.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 989.

13. Christofides, N. *Graph Theory. An Algorithmic Approach*; Academic: New York, London and San Francisco, 1975.

14. Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1992**, *114*, 7843.

15. Alikhanidi, S.; Kuz'min, V. *J. Mol. Model.* **1999**, *5*, 116.

16. Kuz'min, V. E.; Stel'makh, I. B.; Bekker, M. B.; Pozigun, D. V. *J. Phys. Org. Chem.* **1992**, *5*, 295.

17. Alikhanidi, S. E.; Kuz'min, V. E. *J. Structural Chem.* **2000**, *4*, 795.

18. DisFact software for quantitative analysis of chirality and specific asymmetry of molecular structures: version 3.22, 2000 (for x86 computers under Microsoft Win32 or Win32s OS), authors are S. Alikhanidi and V. Kuz'min from Odessa National University of Ukraine. For free demo version (calculates asymmetry for structures with 12 atoms maximum) and more information, see URL: http://theochem.chat.ru/disfact.htm

19. Alikhanidi, S. E.; Kuz'min, V. E.; Kutulya, L. A. *Functional Materials*. **1999**, *4*, 710.