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# Design, synthesis, and enantiomeric recognition of dicyclodipeptide-bearing calix[4]arenes: a promising family for chiral gas sensor coatings

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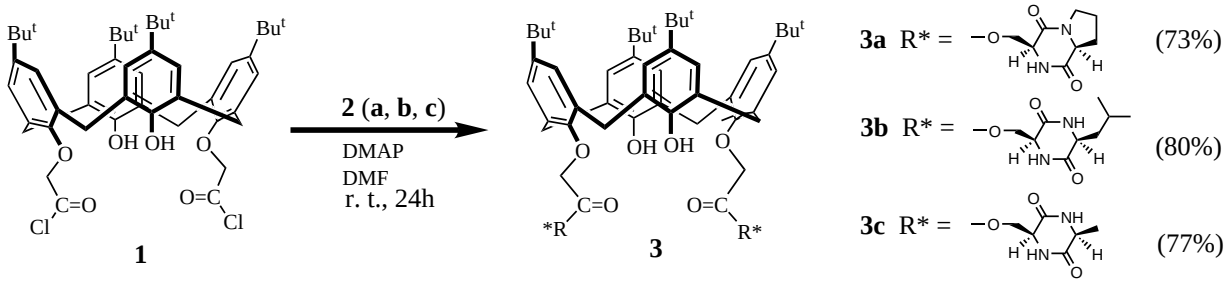
**Abstract**—Three novel dicyclodipeptide-bearing calix[4]arenes were synthesized by reacting 1,3-di(chlorocarbonylmethoxy)-*p*-*tert*-butylcalix[4]arene with serine-containing cyclodipeptides. This family of host molecules was found to bind much more favorably with (*R*)-methyl lactate than with its (*S*)-enantiomer, especially at low analyte concentration, by using the quartz crystal microbalance (QCM) method, and thus render it as a good new candidate for chiral gas sensor coatings. 

Enantioselective recognition of chiral antipodes is considered one of the most interesting and challenging tasks in modern chemistry. This is primarily because this type of discrimination has many applications in bio-sciences and implications for understanding life processes. However, it is not very easy to achieve under normal chemical conditions because the chemical and physical properties of enantiomers are identical in a non-chiral environment. A useful application of chiral recognition for chemical processing can be found in gas chromatography (GC) by using chiral stationary phase materials. However, GC is not an on-line procedure and thus is not suitable for immediate monitoring of industrial processes. In this connection, gas sensors, such as the quartz crystal microbalance (QCM),[1] with good selectivity for enantiomers, need to be developed. The central question is, of course, to find suitable chiral host molecules for the coating various gas sensors.

Although the principles of interaction in GC and in gas sensors are similar, chiral discrimination of the latter is much more difficult to achieve because a gas sensor has only one theoretical plate to use, whereas GC uses thousands of absorption–desorption processes.[1] Therefore, to find suitable materials for useful chiral gas sensors becomes a key issue for the success of this technique. However, only a few cyclodextrin derivatives[2a,c] and one chiral amide receptor[2b,d] have been reported so far as chiral coatings for gas sensors.




**2a:** cyclo(pro-ser), **2b:** cyclo(leu-ser), **2c:** cyclo(ala-ser)

**Scheme 1.** Synthesis of dicyclodipeptide-bearing calix[4]arenes.

*Keywords*: cyclodipeptides; calixarenes; chiral discrimination; quartz crystal microbalance.

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We have recently carried out research on the synthesis and recognition properties of some chiral residue modified calixarenes[3] and cyclopeptides.[4] We noted that there is one case in the literature that demonstrates the high catalytic efficiency of cyclodipeptides on the asymmetric synthesis of cyanohydrins (ee, 97%).[5] This inspired us to design new calixarenes linked to cyclodipeptides at their lower rim in the hope of finding new coatings for chiral gas sensors. In this paper, we report the synthesis of three novel bicyclodipeptide-bearing calix[4]arenes and their applications as chiral coatings for gas sensors to discriminate the enantiomers of methyl lactate. Preliminary QCM results show that this family of compounds is very promising for use as chiral coatings for the chiral recognition by gas sensors.

The synthesis of the bicyclodipeptide-bearing calix[4]arenes is very straightforward and is shown in Scheme 1. The starting cyclodipeptides **2a**–**c**, all contain hydroxy-bearing serine residues, and so react with the calix[4]arene dichlorides **1**. The choice of the other residues (in the present work, Pro, Leu, Ala) in the cyclodipeptides was made considering the steric factors of the side chains in order to cause variation of induced chirality. The synthesis of the three cyclodipeptides was based on a literature procedure.[6] The calix[4]arene dichloride derivative **1** was prepared by the reaction of the corresponding diacid with oxalyl chloride.[7] Subsequent treatment of the dichloride with the cyclodipeptides in the presence of 4,4′-dimethylaminopyridine (DMAP) in DMF afforded the required products, isolated in 73, 80, and 77% yields, respectively, for **3a**–**c** after column chromatography on silica gel. The products were identified by IR, $^1$H NMR and FAB-MS.[8]

Evaluation of the ability of **3a**–**c** to act as chiral sensor coatings discriminating between the enantiomers of methyl lactate was achieved using a quartz crystal microbalance which is extremely sensitive to mass change. As shown by Sauerbrey,[9] the resonance frequency of a QCM changes in proportion to the mass deposited onto or removed from the surface of the crystal. The dropping coating technique was used to prepare sensor coatings of **3a**–**c**. The detailed experimental set-up was as described in a previous report.[10]

In these experiments, all three bicyclodipeptide-bearing calix[4]arenes showed higher sensitivity to (*R*)-methyl lactate than to its (*S*)-enantiomer. In Fig. 1, the QCM signals of the chiral sensor coating **3a** (represented by frequency shifts) are given with respect to the analyte gas composition ((*R*)-, and (*S*)-methyl lactate). As can be seen in this Figure, at the same concentration the (*R*)-enantiomer shows significantly larger sensor responses (represented by frequency shifts) than the (*S*)-enantiomer.

Sensor responses of **3a** upon exposure to different concentrations of (*R*)- or (*S*)-methyl lactate are displayed in Fig. 2. For the (*S*)-enantiomer, the nearly linear absorption isotherm, which is generally regarded as a physisorption process,[11] is shown. However, for the (*R*)-enantiomer, the absorption isotherm deviates significantly from linearity and the initial slope of the (*R*)-enantiomer curve is steeper than that of the (*S*)-enantiomer curve, indicating that the specific, preferential analyte/coating interaction occurs especially in the low concentration range.[12] Similar results were also achieved for coatings **3b** and **3c**.

The resolution of the discrimination of the optical antipodes depends on the relative differences in the sensor signals of both enantiomers: the larger the relative difference, the better the chiral discrimination. Working on the results of the lactates, the ratios of the (*R*)- to (*S*)-signals (chiral discrimination factors: $\alpha = \Delta f_{(R)}/\Delta f_{(S)}$) were evaluated according to Bodenhöfer's definition.[2c] As shown in Fig. 3, all three coatings show considerable chiral discrimination for the enantiomers of methyl lactate. Similar to Bodenhöfer's findings,[2d] the $\alpha$ values rise with decreasing analyte concentration, which results from the domination of the specific absorption of the (*R*)-enantiomer, especially in the low concentration range.

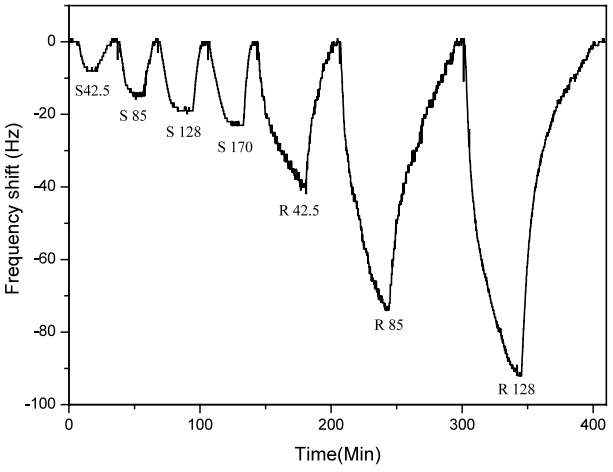


**Figure 1.** Signals from the chiral sensor coating **3a** upon exposure to analytes at 298 K. The numbers after the letters give the concentrations of the analytes used in μg/L (*R*=(*R*)-methyl lactate, *S*=(*S*)-methyl lactate).

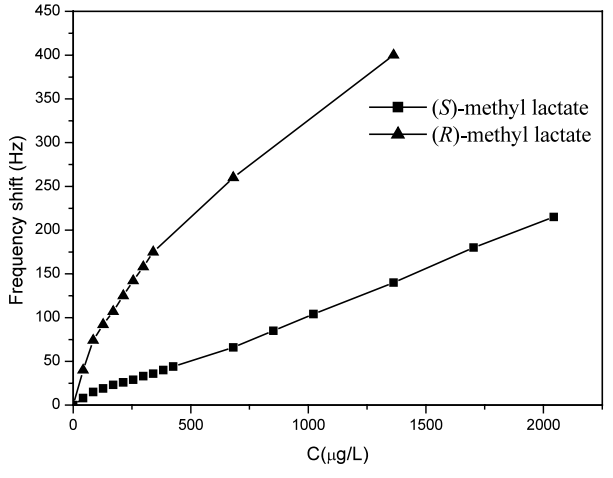


**Figure 2.** Sensor responses of a sensor coated with **3a** upon exposure to different concentrations of (*R*)- and (*S*)-methyl lactate at 303 K.

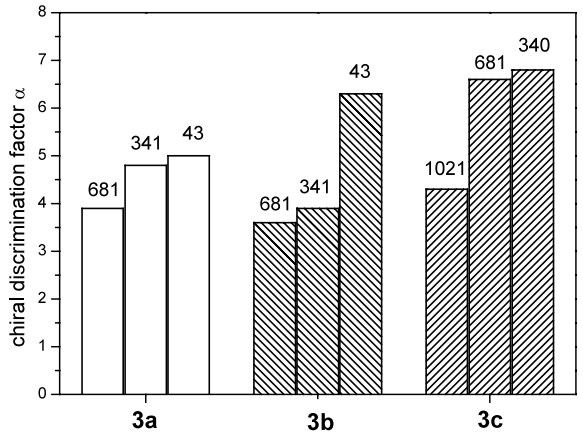


**Figure 3.** Discrimination factors for enantiomers of methyl lactate; the numbers on the top of the bars give the concentrations of the analytes used in μg/L.

In addition, partition coefficients $K$[13] were used to evaluate the sensitivity of these coatings to analytes. Fig. 4 shows the comparison of $K$ values for the (*R*)- and (*S*)-enantiomers in the same concentration for the three coatings. The larger $K$ values for the (*R*)-enantiomers than for the (*S*)-enantiomers reveal that these coatings are more sensitive for the (*R*)-enantiomer.

In summary, we have designed and synthesized three chiral bicyclodipeptide-bearing calix[4]arenes for application in gas sensors, and we have shown that all of these compounds show significant chiral discrimination for the enantiomers of methyl lactate. Detailed studies on the structural characteristics of these coatings and comprehensive trials on various chiral analytes are in progress in our laboratory.

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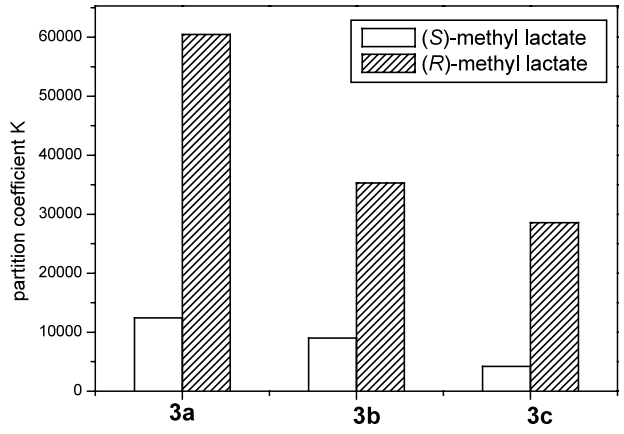


**Figure 4.** Partition coefficients with an analyte concentration of 341 μg/L.

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8. Analytical data for **3a**: yield 73%; mp 165–169°C; $[\alpha]_D^{30}=-33.5$ (*c* 1.0, MeOH); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.29 (br, 2H, NH), 7.89 (br, 2H, OH), 7.09 (br, 8H, ArH), 4.85 (br, 4H, $OCH_2$), 4.48, 4.39, 4.37, 4.19, 3.41, 2.16, 1.77 (all signals very broad), 1.18 (s, 18H, Bu$^t$), 1.09 (s, 18H, Bu$^t$) ppm; IR (paraffin oil): 3450 (OH), 3242 (NH), 1753 (C=O, ester), 1673 (C=O, amide); FAB-MS: 1097.0 $(M+1)^+$. For **3b**: yield 80%; mp 169–173°C; $[\alpha]_D^{30}=-42.3$ (*c* 1.0, MeOH); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.42 (br, 2H, NH), 8.24 (br, 2H, NH), 7.85 (s, 2H, OH), 7.09 and 7.10 (2s, 8H, ArH), 4.84 (m, 4H, $OCH_2$), 4.32–4.53 (m, 8H), 4.25 (br, 2H, Ser H$^\alpha$), 3.81 (br, 2H, Leu H$^\alpha$), 3.38 (d, 4H, $J=12.9$ Hz, Ar-$CH_2$-Ar), 1.76–1.85 (m, 4H, Leu H$^\beta$), 1.44–1.65 (m, 2H, Leu H$^\gamma$), 1.17 (s, 18H, Bu$^t$), 1.09 (s, 18H, Bu$^t$), 0.85 (dd, 12H, $J=3.3$ Hz, $J=6.3$ Hz, Leu $CH_3$) ppm; IR (paraffin oil): 3461 (OH), 3196 (NH), 1759 (C=O, ester), 1681 (C=O, amide); FAB-MS: 1129.3 $(M+1)^+$. For **3c**: yield 77%; mp 174–178°C; $[\alpha]_D^{30}=-30.6$ (*c* 1.0, MeOH); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.35 (br, 2H, NH), 8.19 (br, 2H, NH), 7.85 (s, 2H, OH), 7.06 and 7.08 (2s, 8H, ArH), 4.82 (s, 4H, $OCH_2$), 4.26–4.48 (m, 10H), 3.91 (m, 2H, Ala H$^\alpha$), 3.39 (d, 4H, $J=12.9$ Hz, Ar-$CH_2$-Ar), 1.27 (d, 6H, $J=7.2$ Hz, Ala H$^\beta$), 1.15 (s, 18H, Bu$^t$), 1.06 (s, 18H, Bu$^t$) ppm; IR (paraffin oil): 3450 (OH), 3195 (NH), 1759 (C=O, ester), 1681 (C=O, amide); FAB-MS: 1045.0 $(M+1)^+$.
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13. $K=C_f/C_g$, where $C_g$ is gas concentration in the air and $C_f$ is that in the film. See: Nakamura, K.; Nakamoto, T.; Moriizumi, T. *Sens. Actuators B* **2000**, *69*, 295–301.