

Hydrogen Bonded Calix[4]arene Aggregates

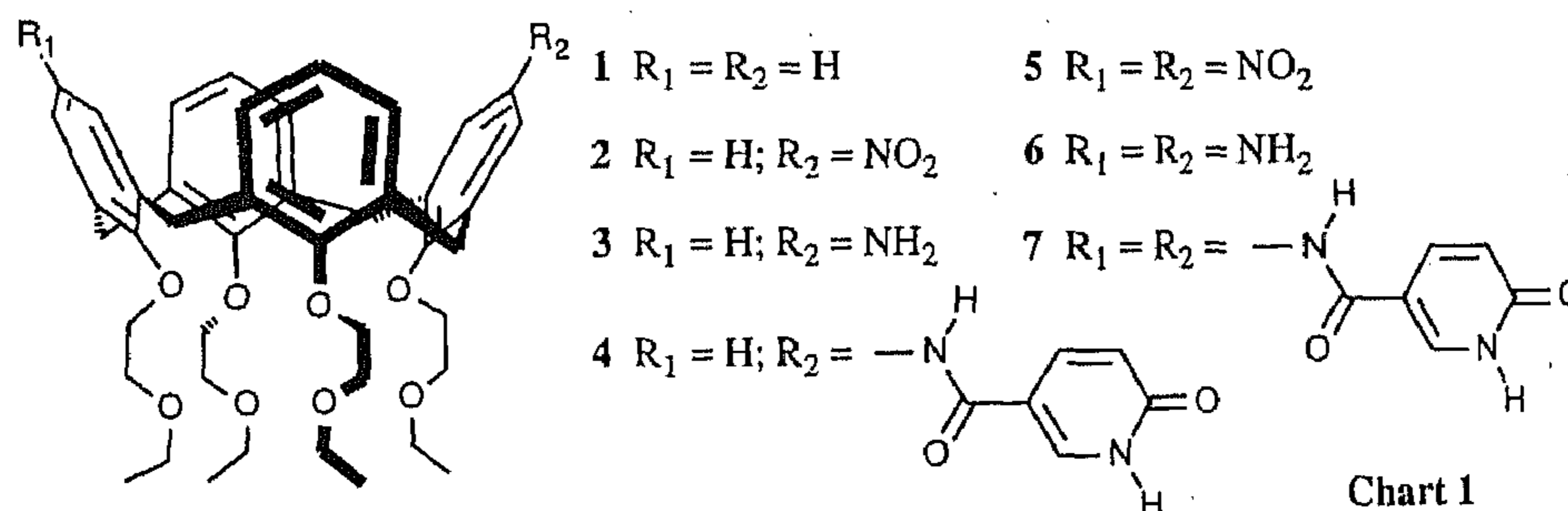
Jan-Dirk van Loon, Rob G. Janssen, Willem Verboom and David N. Reinhoudt*

Laboratory of Organic Chemistry, P. O. Box 217, 7500 AE Enschede, The Netherlands

Abstract. Calix[4]arenes in a rigid cone conformation that contain selfcomplementary α -pyridone moieties at the upper rim, form aggregates in CDCl_3 solution, which can be denatured by the formation of a complex with urea derivatives.

Calix[4]arenes¹ are a well established class of compounds in supramolecular chemistry. Recently we reported the synthesis of double^{2,3} and triple³ calix[4]arenes, in which two, or three calix[4]arene moieties are connected *covalently* by bridges at the lower rim. In this paper we describe preliminary results on multi-calix[4]arene systems based on *hydrogen-bonded* interactions.

CPK-models suggested that calix[4]arene in a rigid cone conformation, that contain self-complementary α -pyridone moieties⁴ (e.g. **4** and **7**) at the upper rim, could form double calix[4]arenes by multi-hydrogen-bonded interactions. Nitration of tetrakis(2-ethoxyethoxy)calix[4]arene **1**⁵ (Chart 1)



under carefully controlled conditions with acetyl nitrate in CH_2Cl_2 at room temperature afforded the diametrically substituted dinitrocalix[4]arene **5**⁶ in 30-40% yield together with 20% of mononitrated product **2**.⁷ Remarkably no proximally 1,2-dinitrated products could be isolated. The reason for the regioselectivity is not known, but the result is in agreement with the observation of Pochini et al.⁵ that the Gross-formylation of **1** also occurs with 1,3-selectivity. The ^1H NMR spectrum of **2** shows two AB systems at δ 4.57, and 3.16, and at δ 4.47, and 3.20, that are typical for a monosubstituted calix[4]arene in the cone conformation.

Reduction of **2** with hydrazine and Raney nickel afforded the monoaminocalix[4]arene **3** in 98% yield, which shows in the ^1H NMR spectrum a singlet for the aromatic protons of the aniline moiety at δ 5.96. Condensation of **3** with 6-hydroxynicotinic acid using carbonyl diimidazole as a coupling reagent, afforded 80% of calix[4]arene monopyridone **4**. The singlet of the pyridone NH in the ^1H NMR spectrum of **4** in CDCl_3 shifts downfield at higher concentration,⁸ and this indicates association of the pyridone moieties. The dimerization constant K_D ($100 \pm 20 \text{ M}^{-1}$), determined by the method of Horman and Dreux,⁹ is comparable to the dimerization constant of 2-pyridone.¹⁰

The disubstituted calix[4]arene **7** was synthesized in the same way from 1,3-diaminocalix[4]arene **6**.⁷ In contrast to the spectrum of the monopyridone **4**, the ^1H NMR spectrum of **7** in CDCl_3 shows broad peaks for all protons. This indicates a reduced flexibility of the calix[4]arene due to the formation of associates. Evidence for the formation of associates was provided by the FAB-mass spectrum that showed molecular ion peaks not only for the monomeric species ($M^+ = 985$), but also for the dimer ($M^+ = 1970$) as well as the trimer ($M^+ = 2955$). A *number* average molecular mass $M_N = (\sum n_i M_i) / (\sum n_i)$ in ethanol-free CHCl_3 was determined by vapour pressure osmometry (VPO). In the concentration range 8-50 mM a value of 5100 ± 300 was obtained.¹¹ The *weight* average molecular mass M_W was determined by light scattering and Figure 1 shows the Zimm plot of calix[4]arene **7**, which gives an apparent mass $M_W(\text{app})$ of 29000 ± 3000 at extrapolated values of zero concentration and zero angle.¹² The Zimm plot shows a concentration dependent $M_W(\text{app})$ with higher values for $M_W(\text{app})$ at higher concentration, which indicates aggregation phenomena.¹³ At 10.3 mM $M_W = 70000$ and a polydispersity index M_W/M_N of 13.7 was calculated,¹⁴ which shows that the structure of **7** apparently does not result in the specific formation of a double calix[4]arene, but rather forms a broad oligomer distribution.¹⁵ This means that the aggregation of **7** can be regarded as an example of the multiple equilibrium model that is used to describe the formation of micelles.¹⁶ Slow evaporation of the solvent of a solution of **7** in CHCl_3 resulted in the formation of a gel.

The fact that calix[4]arene **7** does not form one particular assembly (e.g. a dimer) can be explained by its inherent flexibility. Generally, in solution tetraalkylated calix[4]arenes in the cone conformation do not attain a symmetrical and rigid geometry, but interconvert rapidly between two distorted cone topomers.^{7,17} This means that the angle between the pyridone moieties may vary between approximately 0 and 90° .

Although compound **7** is flexible in solution, the calix[4]arene skeleton forces the pyridone moieties to converge and CPK models suggest that urea derivatives should be able to 'denature' the multi-calix[4]arene systems by the formation of a complex via a complementary hydrogen bond pattern (Chart 2). The addition of one equivalent of imidazolidone **8** has a significant effect on the signals of both **7** and **8** in the ^1H NMR spectrum. The imidazolidone NH becomes sharp and shifts downfield (0.25 ppm at 1 equivalent), indicating the formation of a well-defined hydrogen bond, and the broad signals of the methylene bridge protons in **7** become sharper. Addition of more equivalents of **8** results in further sharpening of the signals. Initially a 1:1 complex is formed, which is converted into a 1:2 complex upon addition of more equivalents of imidazolidone (**8**). This was indicated by the fact that the ^1H NMR signal of the pyridone NH shows two singlets at δ 12.2 and 13.0 for 8:7 ratios > 1 .¹⁸ In addition, the number average molecular mass M_N , determined by VPO, at 8:7 ratios > 1 deviate from a 1:1 complexation and correspond well to a 1:2 complex at 8:7 ratios > 4 .

N-Methylimidazolidone (**9**) can only interact with one pyridone moiety, and the ^1H NMR signal of the

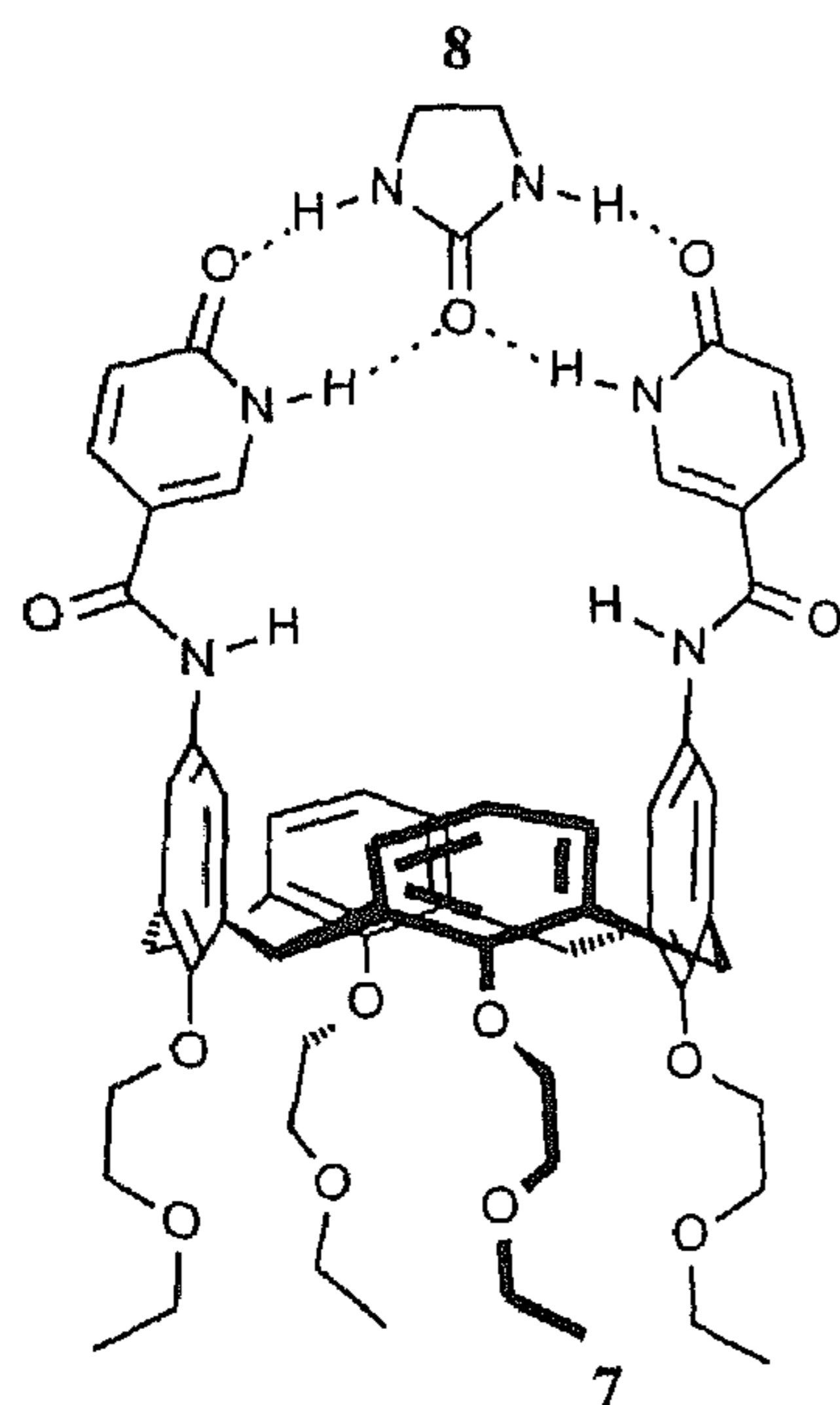


Chart 2

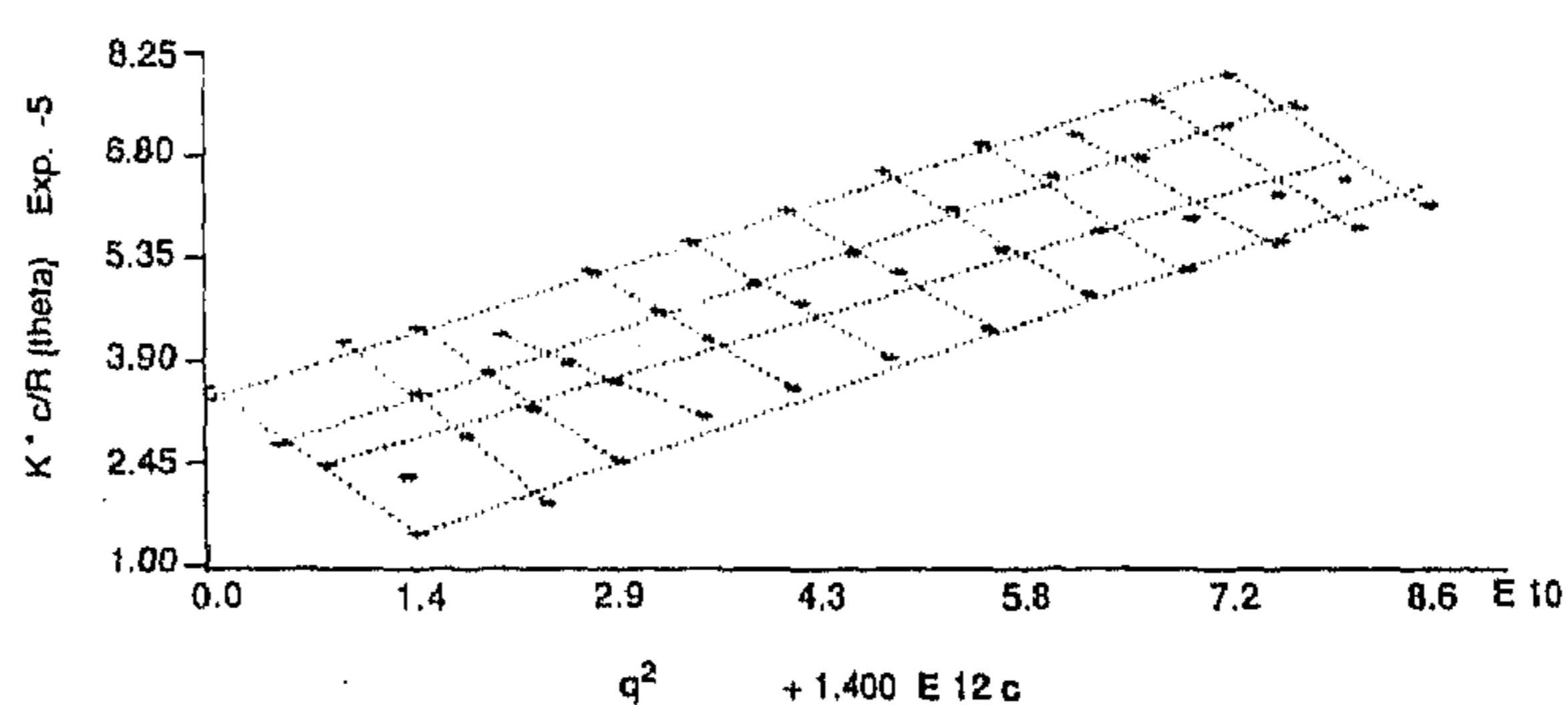
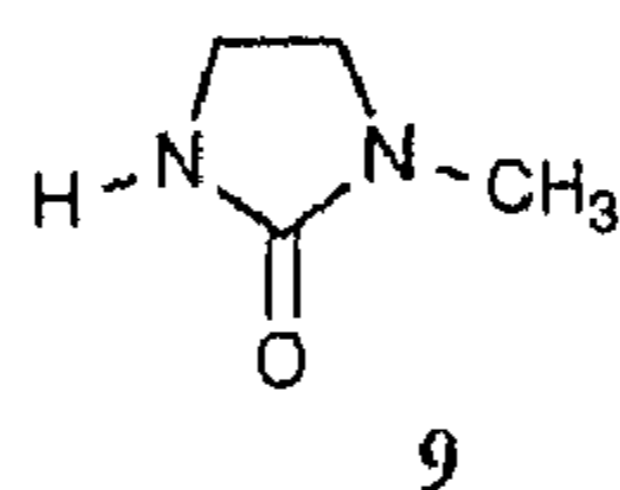


Figure 1. Zimm plot of compound 7.

pyridone NH shows no discontinuity and the spectrum remains broad, even at a large excess of 9. This suggests that imidazolidone 8 enhances the denaturation of the oligomers by its ability to form a 1:1 complex, in which both pyridone functions are blocked to interact with other calix[4]arenes (Chart 2). The strong interaction between 7 and urea derivatives was further illustrated by the fact that a 5 mM solution of 7 in CDCl_3 is able to solubilize urea with an extractability Z of 0.35 ± 0.01 equivalents of urea per equivalent of receptor. The amount of extracted urea was determined titrimetrically.¹⁹ On the assumption that a 1:1 complex is formed and that the degree of oligomerization of the uncomplexed host is not effected²⁰ one can estimate a lower limit for the association constant of $5.6 \pm 1.1 \times 10^3 \text{ M}^{-1}$.

The present work shows that calix[4]arenes in a rigid cone conformation, that contain selfcomplementary α -pyridone moieties at the upper rim, form non-specific aggregates in CDCl_3 solution, which can be denaturated by the formation of a complex with urea derivatives. Future investigations are directed towards multi-calix[4]arene systems with a well-defined geometry.

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 - One would expect that the M_N decreases at lower concentrations of **7**, but due to the detection limit of VPO no values for M_N could be obtained at concentrations < 8 mM.
 - Gel permeation chromatography (GPC) gave an $M_W(\text{app})$ of 24000 ± 3000 and an M_N of 11000.
 - This includes both the aggregation between the monomers and the aggregation with solvent molecules.
 - It should be noted that linear extrapolation to zero concentration (and zero angle) only gives an *apparent* M_W , since one would expect the molecular mass of the monomer at zero concentration as a result of the complete dissociation of the aggregates. As a consequence the polydispersity index is only meaningful if M_N and M_W values are determined at the same concentration. The highest concentration (10.3 mM) for which an $M_W(\text{app})$ of 70000 was determined just overlaps with the range (8-50 mM) for which an M_N was measured, which provides a polydispersity index M_W/M_N of 13.7.
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 - Although in principle the M_N decreases at lower concentrations of **7**,¹¹ a linear extrapolation to concentrations in the order of 5 mM is reasonable.

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