Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1469–1476

TETRAHEDRON

The synthesis of tetracarbonyl derivatives of thiacalix[4]arene in different conformations and their complexation properties towards alkali metal ions

Ivan I. Stoikov,[a] Omran A. Omran,[a] Svetlana E. Solovieva,[b] Shamil K. Latypov,[b] Konstantin M. Enikeev,[b] Aidar T. Gubaidullin,[b] Igor S. Antipin[a,*] and Alexander I. Konovalov[b]

[a]*Kazan State University, Kremlevskaya str. 18, Kazan 420008, Russian Federation*
[b]*A.E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences Arbuzov str. 8, Kazan 420088, Russian Federation*

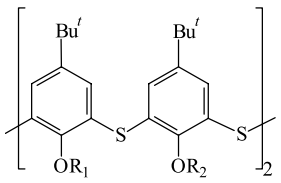
Received 19 September 2002; revised 9 December 2002; accepted 9 January 2003

Abstract—The three conformations of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(benzoyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene **1**: *cone*, *partial cone* and 1,3-*alternate*, were prepared by the treatment of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol (TCA) with α-bromo acetophenone in the presence of appropriate alkali carbonate M_2CO_3 (M=Na, K, Cs) as base catalyst in acetonitrile. Structure of the conformers were established by ^{1}H NMR, ^{1}H–^{1}H COSY, 1D NOE, 2D ROESY and X-ray experiments. The alkali cation binding selectivity of the obtained macrocycles was investigated by the ion-pair extraction method.

1. Introduction

Calixarenes are one of the most important macrocyclic molecules as hosts for binding neutral and charged molecules.[1–3] These compounds can be easily synthesized from cheap and commercially available starting materials, e.g. 4-*tert*-butylphenol and formaldehyde. Because of the many possibilities for modification of the upper and/or the lower rims a wide variety for calixarenes has been prepared.[4,5] Replacement of the original methylene bridges between the aromatic units in calixarenes by sulfur atoms has been reported recently, leading to thiacalix[4]arenes (TCA).[6–8] Thiacalix[4]arenes were found to bind transition metal ions very well without the introduction of supplementary ligating groups at the lower or upper rims owing to the coordination of the bridging sulfur atom with metal ions.[9–11]

As a part of our efforts to understand 'structure—ion recognition' relationships, we report herein the stereoselective synthesis of three conformations of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(benzoyl) methoxy]-2,8,14,20-tetrathiacalix[4]arene **1** and comparison of alkali cation binding ability of three conformational isomers of **1** and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene **2**.[12–14]



Compd.	R_1	R_2
TCA	H	H
1	CH_2COPh	CH_2COPh
2	CH_2COOEt	CH_2COOEt
3	H	CH_2COPh

2. Results and discussion

Although TCA exists in the *cone* conformation the complete *O*-alkylation of the OH groups of TCA can theoretically lead to the formation of four possible conformational isomers: *cone*, *partial cone*, 1,2- and 1,3-*alternates*. Nevertheless, direct alkylation by alkyl halogenides in acetone or acetonitrile gives the 1,3-*alternate* conformer as isolated product irrespective of the nature of the base catalyst.[15]

Reagents containing electrononegative groups such as

Keywords: thiacalix[4]arenes; synthesis; conformations; extraction.

* Corresponding author. Tel.: +7-8432-315463; fax: +7-8432-752253; e-mail: igor.antipin@ksu.ru

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00077-2

ethoxycarbonyl are capable of coordination with metal cations and allow stereoselective alkylation due to cation template effect. Miyano et al.[12] have developed the template approach to lower rim alkylation of TCA by ethyl bromoacetate. This was based on the application of different alkali carbonate M_2CO_3 (M=Na, K, Cs) as base catalyst in acetone at the reflux or DMF at 60°C. Reaction of TCA with ethyl bromoacetate in the presence of Na_2CO_3, K_2CO_3, Cs_2CO_3 gave the *cone*, *partial cone* and 1,3-*alternate* of tetra-O-alkylation product **2** in good yields ranging from 58 to 78% (after column chromatography). Later, Hosseini et al.[13] and Stibor et al.[14] investigated this reaction and the structure of the products in detail.

α-Bromoacetophenone is a less active electrophilic reagent than ethyl bromoacetate, therefore, harsher conditions for the alkylation reaction are needed. It was found that tetra-*O*-alkylation of TCA in acetonitrile at reflux allows high yields and stereoselectivity to be achieved. The treatment of TCA with α-bromoacetophenone in the presence of an alkali carbonate gives three conformational isomers out of the possible four, i.e. *cone*, *partial cone* and 1,3-*alternate*, as assigned by one- and two-dimensional NMR experiments (vide infra). No evidence of 1,2-*alternate* product formation in the reaction mixture was found. This might be attributed to the lowest thermodynamic stability of this conformer in the case of tetra-substituted derivatives of thiacalix[4]arenes. The selective formation of 1,2-*alternate* product was established for thiacalix[4]arenes, containing two bridge fragments at the lower rim.[16,17]

As in the case of the TCA reaction with ethyl bromoacetate, the alkali metal carbonates demonstrate a distinct influence on the conformational structure (Fig. 1) of the products obtained. Base catalyst Na_2CO_3 gave selectively *cone* conformer in the isolated yield of 68%. The fractional crystallization from chloroform–acetonitrile mixture was used for product separation instead of column chromatography.[12] Also *paco*-**1** was successfully isolated from the reaction mixture in 7% yield. The reaction in the presence of K_2CO_3 affords the only product, *paco*-**1**, in an isolated yield of 75%. Using Cs_2CO_3 as base catalyst led to the formation of 1,3-*alt*-**1** with 40% yield. It was easily separated from other products because it was practically insoluble in cold acetonitrile. Fractional crystallization from chloroform–acetonitrile mixture allowed the isolation of distal disubstituted derivatives **3** and *paco*-**1** in 15 and 7%, respectively.

Recently, the synthesis of 1,3-*alt*-**1** with very low yield (15%) was reported[18] by the reaction of TCA with α-chloroacetophenone in the presence of NaI in acetone at reflux during 2 days. However, the presented ^{1}H NMR spectrum does not completely correspond to the 1,3-*alternate* structure. The multiplets at 0.95–1.35 and 7.85–7.90 ppm were assigned to Bu^t and calixarene aromatic protons, respectively. Theoretically, in the ^{1}H NMR spectrum of symmetrical structures like 1,3-*alt*-**1** these protons should appear as singlets, but never as multiplets. Moreover, according to our results (vide infra) the multiplet at 7.85–7.90 ppm corresponds to the *ortho*-hydrogen atom of phenyl substituents at lower rim. The multiplicity of Bu^t signals can indicate the formation of a mixture of isomers with the predominance of 1,3-*alt*-**1**.

2.1. Structure analysis by NMR spectroscopy

The absence of methylene bridges, the proton signals of which are used for conformational structure assignment of normal calix[4]arenes, makes the determination of the conformation of thiacalix[4]arene derivatives difficult. So, the chemical shifts and resonance patterns of other protons as well as 2D NMR experiments (COSY, ROESY) were used to establish the structure of the obtained macrocycles.

In the unsymmetrical structure of *paco*-**1**, there are three non-equivalent *tert*-butyl groups which should give a 2:1:1 ratio of resonance patterns in the proton spectrum (Fig. 2). On this basis the isomer having Bu^t peaks at 1.13 (18H, s), 1.32 (9H, s) and 1.37 (9H, s) was defined as *partial cone*. Analysis of the splitting pattern of the calixarene aromatic protons and methylene groups of lower rim substituents confirm the *partial cone* structure as well. Each group of these protons appeared as two doublets and two singlets. This is in agreement with both theoretical calculations and experimental observations for similar compounds.[12,14] Aromatic shielding effect analysis is also in line with this conclusion.

All the protons of phenyl rings of the calixarene **1** platform are equivalent in the *cone* and 1,3-*alternate* conformations that is why their ^{1}H NMR spectra are very simple and similar: Bu^t (36H, s), –OCH_2CO– (8H, s), Ar-H (8H, s), *m*-Ph-H (8H, m), *p*-Ph-H (4H, m), *o*-Ph-H (8H, d) (see Section 4). Nevertheless, conformational assignment may be carried out by the comparison of methylene protons chemical shifts of –OCH_2CO– moieties. In 1,3-*alt*-**1**, these protons are in the shielding field of two adjacent phenyl groups so they should resonate at a higher field than those of the *cone* conformer. Thus, the isomers which exhibited CH_2 protons at 6.09 and 5.33 ppm were assigned to *cone*-**1** and 1,3-*alt*-**1**, respectively. Unlike *cone*-**2** and 1,3-*alt*-**2**, the peaks corresponding to Bu^t and calixarene aromatic protons

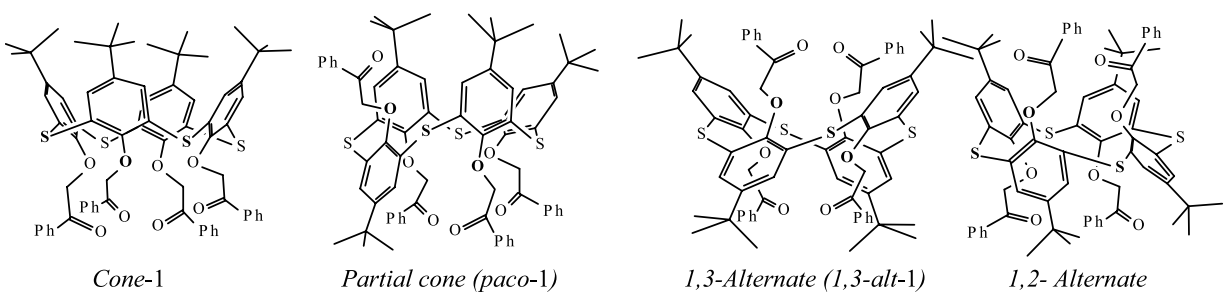


Figure 1. Four possible conformers of **1**.

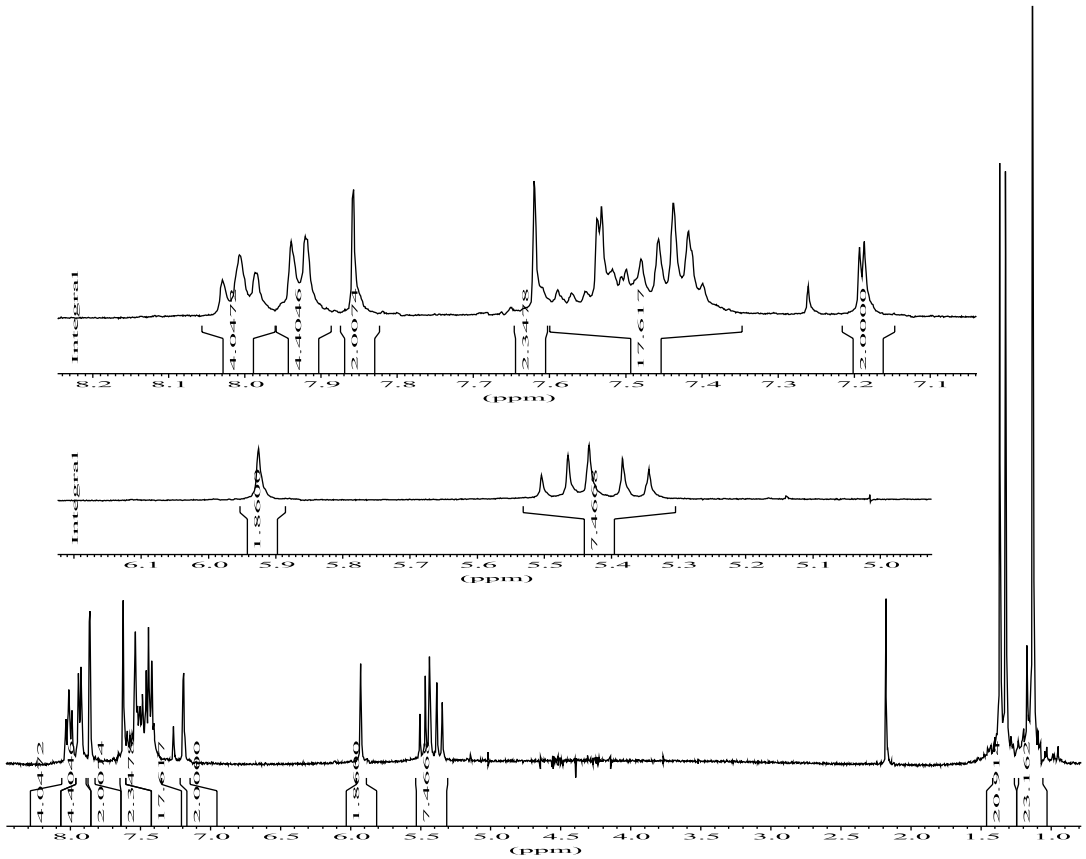


Figure 2. ^{1}H NMR spectrum of *paco*-**1**.

are not significantly distinguished for both isomers of **1** and cannot be used for the structure identification of the macrocycles.

The additional confirmation of this assignment was obtained from 2D ROESY experiments. These experiments were used to evaluate inter proton proximity because only closely situated protons give rise to the cross peaks in the 2D ROESY spectrum due to dipole-dipole interactions between them. In the spectrum of *cone*-**1** two strong interactions were observed: i) between *tert*-butyl (1.12 ppm) and aromatic protons of calixarene (ArH, 7.36 ppm), ii) between $-OCH_2CO-$ groups (6.08 ppm) and *ortho*-phenyl protons of narrow rim substituents (*o*-PhH, 7.96 ppm) (Fig. 3a). The spectrum of 1,3-*alt*-**1** contains additional cross peaks. Namely, the *tert*-butyl group (1.13 ppm) interacts not only with ArH (7.37 ppm) but also with the *ortho*-phenyl protons (*o*-PhH, 7.91 ppm) and $-OCH_2CO-$ groups (5.31 ppm). Moreover, there are cross peaks between the $-OCH_2CO-$ (5.31 ppm) groups and *o*-PhH (7.91 ppm) and ArH (7.37 ppm) (Fig. 3b). The interactions mentioned above are only possible for the 1,3-*alternate* conformation.

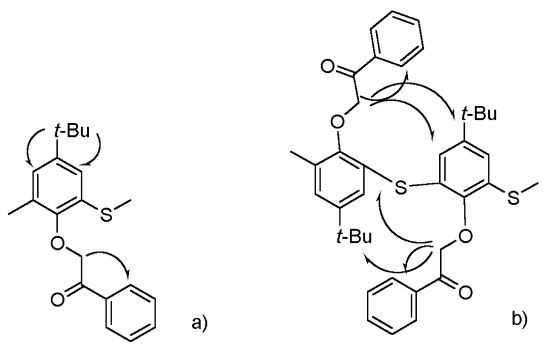


Figure 3. The important dipole–dipole interactions in *cone*-**1** (a) and 1,3-*alt*-**1** (b).

2.2. Alkali metal ions extraction

To evaluate the ability of the thiacalixarene derivatives **1** to recognize alkali metal ions, a liquid–liquid extraction (in mutually saturated water-dichloromethane system) of their picrate salts has been carried out and the extraction constants have also been determined. The extraction equilibrium is described by Eq. (1), where M^+, L, Pic^-, ML^+, and $ML_n^+Pic^-$ denote the metal ion, ligand (here, **1**), picrate anion, metal complex and ion-pair, respectively, while n is the number of ligands that react with one alkali metal ion.

$$M^+_{aq} + nL_{org} + Pic^-_{aq} \leftrightarrows ML_n^+Pic^-_{org} \quad (1)$$

The percentage extraction $E\%$ and extraction degree, α, were calculated according to Eq. (2).

$$E\% = \alpha \times 100\% = [ML_n^+Pic^-]_{org}/[Pic^-]_{aq,init} \times 100\% \quad (2)$$

The thermodynamic extraction constant, K_{ex}, is given by Eq. (3).

$$K_{ex} = [ML_n^+Pic^-]_{org}/[M^+]_{aq}[Pic^-]_{aq}[L]^n_{org} \quad (3)$$

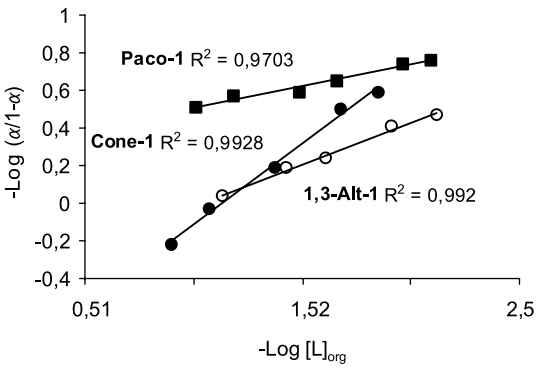


Figure 4. Plot of $\log(\alpha/1-\alpha)$ versus $\log[L]_{org}$ for lithium picrate extraction in mutually saturated water–dichloromethane solvent system by the three conformers of **1**.

To determine the stoichiometry coefficient n of the complexes forming in the organic phase Eq. (3) was converted into Eq. (4).

$$\log K_{ex} = \log(\alpha/1-\alpha) - \log[M^+]_{aq} - n\log[L]_{org} \qquad (4)$$

The plot of $\log(\alpha/1-\alpha)$ versus $\log[L]_{org}$ presents a straight line, slope of which equals to n. Hereafter, we will also use the host–guest ratio or complex stoichiometry L:M^+. Extraction constants K_{ex} are calculated using the intercept values (b).

$$b = \log K_{ex} + \log[M^+]_{aq} \qquad (5)$$

It was found that plots of $\log(\alpha/1-\alpha)$ against $\log[L]_{org}$ for lithium, sodium, potassium and cesium in mutually saturated water–dichloromethane solvent system were in all cases linear, and, therefore, Eq. 4 is valid. A representative example is presented in Figure 4 for lithium picrate and Table 1 gives the values of log K_{ex} and n.

Lithium picrate forms complexes in the organic phase with different stoichiometries: 1:1, 1:2 and 1:4 for *cone*, 1,3-*alternate* and *partial cone* of **1**, correspondingly. Thus four, two or one O–CH_2–C(O)Ph fragments can participate in the binding of Li^+. The possible structures of these complexes are schematically presented in Figure 5a–c.

To the best of our knowledge these are the first examples of the stoichiometry differing from 1:1 for complex of calix[4]arene derivatives with alkali metal ions. Only a 1:1 host–guest ratio was established for *cone*, 1,3-*alternate* and *partial cone* of **2** by ^{1}H NMR titration and for *cone* of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis-[(etoxy-carbonyl)methoxy]-calix[4]arene by the extraction method.[19,20]

The rather unpredictable stoichiometry of 1:4 for *paco*-**1** was only observed for the smallest alkali cation. It indicates that three O–CH_2–C(O)Ph groups cannot interact cooperatively with small Li^+ cation and each ligating unit binds it separately. In the case of 1,3-*alt*-**1** two pairs of O–CH_2–C(O)Ph fragments located on opposite sides of the macrocycle can participate in the interaction with two lithium cations according to simple structural considerations and the extraction data obtained. For the same reasons, the Li^+ cation is incorporated into the cavity formed by eight oxygen atoms at narrow rim of *cone*-**1**. As a result of different interaction cooperativity the extraction constants sharply decrease in the order of *cone*>1,3-*alternate*>*paco*. Naturally, *paco*-**1** conformer demonstrates the weakest extraction ability because each Li^+ interacts with only one O–CH_2–C(O)Ph fragment. Using an additive approach, log K_{ex} of 1,3-*alternate* should be double the *paco* value. It is in good agreement with experimental data: 1.51 and 0.77, correspondingly, and indicates the absence of steric hindrance for the binding of both lithium cations in 1,3-*alternate*-**1** conformation. The estimated log K_{ex} for *cone*-**1** is 3.1 (0.77×4) and significantly larger than the experimental value (2.05). So, the cavity formed by eight oxygen atoms at the narrow rim of the calixarene is too large to interact effectively with such a cation.

The increase of cation size leads to significant changes in complex stoichiometry and extraction selectivity. Complex stoichiometry of sodium, potassium and caesium cations with *paco*-**1** are practically equal to 1:1 (Fig. 5d). Unlike the small Li^+, these cations are able to interact cooperatively with three ligating groups located on the same side of macrocycle plane. A slight increase of host: guest ratio (1:1.3) in the case of Na^+ can be explained by weak binding of the cation by separately situated O–CH_2–C(O)Ph groups. This is not observed for softer K^+ and Cs^+ cations, in good agreement with the concept of hard–soft acids and bases.

The stoichiometry of 1,3-*alternate*-**1** complexes is either 1:2 or 1:1. Small Li^+ and Na^+ ions form 1:2 complexes. It means that in this case both pairs of O–CH_2–C(O)Ph fragments interact irrespective of each other and structural changes caused by ion complexation on one side of 1,3-*alt*-**1** do not cause significant hindrance for binding on the other. The situation sharply changed for larger alkali cations for which 1:1 stoichiometry was observed. So, 1,3-*alt*-**1** is unable to bind a second cation like K^+ or Cs^+. Such behavior could be rationalized in term of a negative allosteric effect[21–24] induced by a change of the conformer's spatial structure. In order to bind the first cation the molecular cleft formed by two ligating groups may expand

Table 1. Extraction constants log K_{ex} and stoichiometry complexes of **1** forming in the organic phase

	Li^+			Na^+			K^+			Cs^+		
	n^a	Log K_{ex}	E%[b]	n^a	Log K_{ex}	E%[b]	n^a	Log K_{ex}	E%[b]	n^a	Log K_{ex}	E%[b]
Cone-**1**	0.86	2.05	12	0.67	3.50	85	0.71	2.77	46	0.70	1.87	10
Partial cone-**1**	0.23	0.77	10	0.78	2.95	46	1.06	4.61	88	0.93	3.32	44
1,3-Alternate-**1**	0.44	1.51	19	0.59	2.22	33	1.00	5.45	99	0.92	4.33	76

[a] Average error of n is ±0.08.
[b] Extraction condition:[12] $[L(=1 \text{ or } 2)]_{org,init}=2.5\times10^{-3}$ M, $[MOH]_{aq,init}=0.1$ M, $[HPic]_{aq,init}=2.5\times10^{-4}$ M.

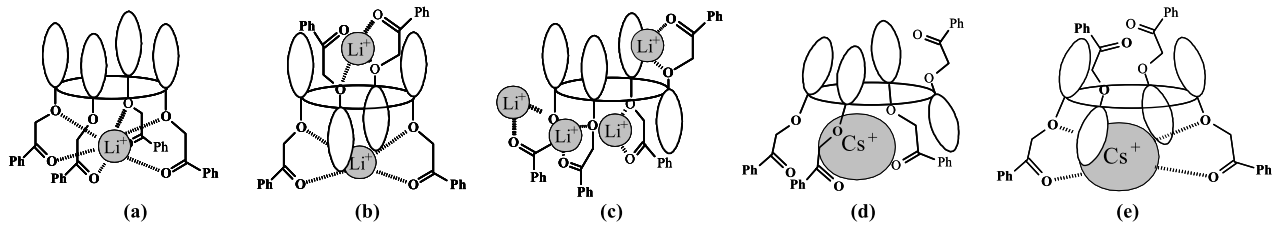


Figure 5. The possible structures of thiacalix[4]arene conformer complexes with Li^+ and Cs^+: (a) *cone*-Li^+, (b) 1,3-*alt*-Li^+, (c) *paco*-Li^+, (d) *paco*-Cs^+, (e) 1,3-*alt*-Cs^+. Small ellipses denote 4-*tert*-butylphenyl fragments.

to achieve the ideal interatomic distance needed for complexation of large alkali cations. As a result the other two ligating groups on the opposite side of 1,3-*alternate* become closer to each other and thus the binding of second cation does not occur (Fig. 5e). The complex of *cone*-**1** with all cations studied slightly deviated from 1:1 stoichiometry. This may suggest that aromatic cavity of *cone* conformer can also participate in the binding of alkali metal cations.

Figure 6 shows the log K_{ex} of conformers versus alkali metal ions. *Cone*-**1** demonstrates the highest ability to extract for the Na^+ ion compared to other alkali metal ions using CH_2Cl_2 as the organic phase. By contrast, *paco*-**1** and 1,3-*alternate*-**1** extract larger metal cations such as K^+ more effectively. A similar dependence was shown for the conformers of **2**. To compare the extractability of conformers of **1** measured in the present work and **2** determined earlier by Miano et al.[12] the *E%* values were calculated for **1** under the same extraction condition. The data obtained are summarized in Table 1. Their comparison is presented on Figure 7. One can see that the conformers of **1** generally exhibited better *E%* and selectivity than those of **2**. However, *paco*-**1** and -**2** are dramatically distinguished by their extraction properties. While *paco*-**2** shows a small *E%* for all alkali metal ions, the derivative containing phenylcarbonyl groups exhibits high efficiency and selectivity with a preference for potassium ion. Although the behavior of *cone* and 1,3-*alternate* conformers of **1** and **2** is closely similar to the extractability of **1** exceeds that of **2** for all alkali metal ions. Thus, the replacement of the ethoxy group by phenyl leads to an increase in the extraction efficiency of thiacalix[4]arene derivatives.

Several factors may be considered to rationalize this effect. These are: (i) donor ability of carbonyl groups, (ii) macrocycle lipophilicity, (iii) steric requirements. For quantitative estimation of the donor ability of investigated ligating groups the Lewis basicity values of acetophenone and ethyl acetate were used as model compounds. Among empirical scales of basicity the calorimetric scales of Gutmann[25] DN or ΔH^0_{SbCl5} (donor number) and Maria and Gal[26] $\Delta H°_{BF3}$ were chosen. They characterize directly the energy of donor–acceptor interactions and define as the enthalpy change for the formation of the 1:1 adduct between Lewis acid (antimony pentachloride or boron trifluoride) and electron pair donor compound. The data summarized in the review of IUPAC Commission on physical organic chemistry devoted to the scales of solvent parameters[25] indicate that ethoxycarbonyl group interacts more strongly than the phenylcarbonyl one with both hard and soft Lewis acids. $\Delta H°_{SbCl5}$ of acetophenone and ethyl acetate are equal to −62.8 and −71.5 kJ/mol, respectively.[27] The same relative order of donicity was observed for hard Lewis acids like BF_3. The values of $\Delta H°_{BF3}$ for acetophenone and ethyl acetate are −74.52 and −75.55 kJ/mol, respectively.[27]

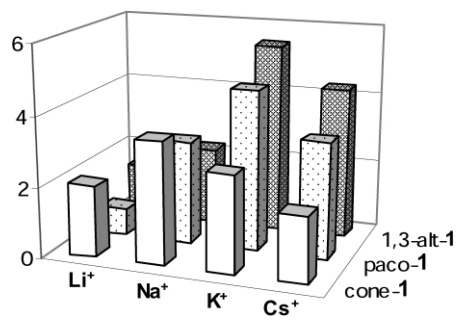


Figure 6. The extraction constants of the conformers (log K_{ex}) of **1** versus alkali metal ions.

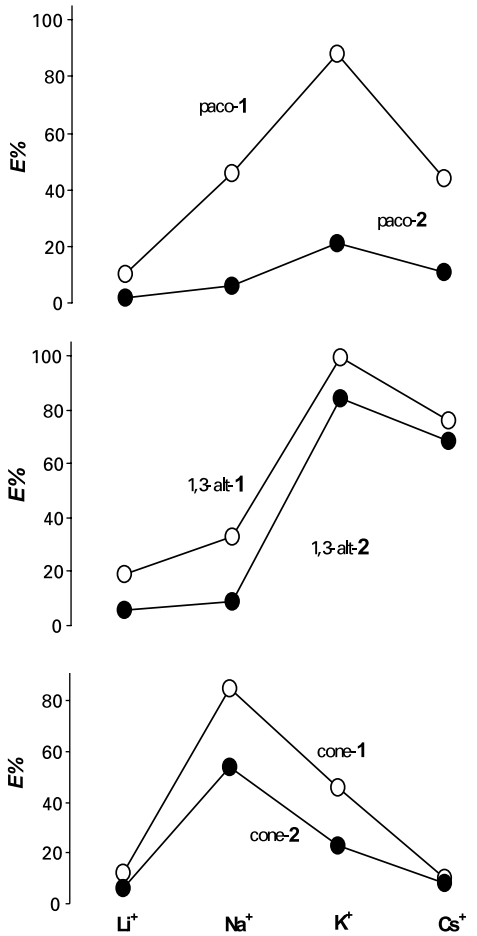


Figure 7. The percent extraction (*E%*) by three conformers of **1** and **2**, determined at the same extraction conditions (see the footnote of Table 1).

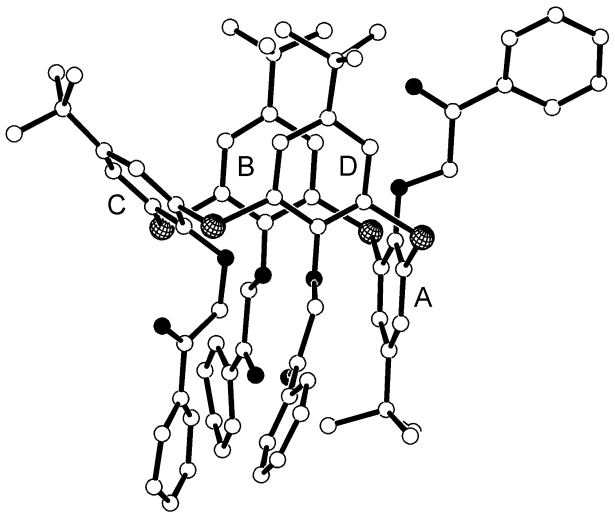


Figure 8. X-ray structure of *paco*-**1**. H atoms are omitted for clarity.

So, the increasing extractability of **1** with respect to **2** cannot be ascribed to the change of donor ability of the ligating group.

There is no doubt that the replacement of ethoxy groups by phenyl groups increases the receptor's lipophilicity. Moreover, the dependences of *E*% versus alkali metal ion for *cone* and 1,3-*alternate* conformers (Fig. 7) closely reproduce each other although the extraction degree of all ions by the conformers of **1** is greater than **2**. This fact could be considered as confirmation of the receptor lipophilicity effect that should be constant for different conformers.

The influence of steric requirements clearly appears in the case of the *paco* conformer. Significant differences of percent extraction and selectivity indicate that the spatial structures of *paco*-**1** and *paco*-**2** are quite different. Obviously, the planar and large CH_2–C(O)Ph moieties make the cavity less flexible and more preorganized than in the case of CH_2–C(O)OEt substituents. The ethoxy substituents are smaller and more flexible. As result they are not able to fix a definite spatial arrangement where carbonyl groups project into the cavity. Indeed, X-ray structure analysis of *paco*-**2**[13] as well as *cone*-**2**[12] indicates that the (ethoxycarbonyl)methoxy groups seem to be rather randomly arranged. Suitable monocrystals of *paco*-**1** were obtained from CH_2Cl_2–hexane mixture (1:9) and investigated by X-ray diffraction. *Paco*-**1** crystallized in a monoclinic form, space group $P2_1/n$ (Fig. 8). No solvent molecules were present in the lattice.

In *paco*-**1**, the dihedral angles of the four aromatic rings **A**–**D** with S main plane are 89.0(2), 82.5(2), 40.3(3) and 80.5(2), correspondingly. So, the opposite rings **B** and **D** are practically parallel to each other. Moreover, $PhC(O)CH_2$– moieties attached to these rings make interplanar angles of 88.2(5) and 83.6(4) with them.

Unlike *paco*-**2**[13] the two opposite substituents at the narrow rim of *paco*-**1** have their double bonded oxygen atom oriented *endo* whereas the third one directs out of macrocycle molecular cavity. Thus, the carbonyl groups form a spatial arrangement that looks like that in the 1,3-*alternate* conformation and preorganization of ion binding centers in the both mentioned conformations of **1** is similar. Additionally, the correlation (r^2=0.997) between log K_{ex} values of *paco* and 1,3-*alternate* conformers of **1** was observed for the investigated alkali metal ions with the exception of the sodium ion.

$$\log K_{ex}(1,3\text{-}alt\text{-}\mathbf{1}) = 1.04 \log K_{ex}(paco\text{-}\mathbf{1}) + 0.76 \qquad (6)$$

The deviation of sodium ion from the common dependence (higher extractability of *paco* with respect to 1,3-*alternate*) indicates that only in this case can the third carbonyl group of *paco*-**1** participate in the ion binding.

In most investigations of the ligand binding ability by extraction method *E*% values are only measured and discussed. This is only sufficient for correct analysis of 'structure–property' relationships if the stoichiometry is not significantly changed within the host–guest complexes studied. Data obtained for Li^+ ion (Table 1) indicate clearly that the extraction constants K_{ex} and percent extraction *E*% lead to different conclusions about the extractability order of thiacalix[4]arene conformers. According to *E*% the order is 1,3-*alternate*>*cone*≫*paco*, whereas the thermodynamic parameter K_{ex} shows: *cone*>1,3-*alternate*≫*paco*. The essential change in complex stoichiometry is the reason for these contradictory regularities. In the case of the other ions studied the conclusions made on the basis of either K_{ex} or *E*% are in agreement because complex stoichiometry does not significantly change. Using the determined thermodynamic values we can conclude that *cone* conformer extracts small alkali ions Li^+ and Na^+ best, but 1,3-*alternate*—K^+ and Cs^+.

It is interesting to note that the selectivity of alkali metal ion extraction does not completely correspond to the template effect observed in the synthesis of corresponding conformers. Sodium and caesium ions promote the formation of *cone* and 1,3-*alternate* due to strong and selective host-guest complexation with the corresponding conformer. So, the thermodynamic stability of the forming complex is a principal factor controlling the result of these reactions. In the case of potassium ions both *partial cone* and 1,3-*alternate* conformers bind this ion quite strongly. Although 1,3-*alt*-**1** binds potassium ions more strongly than *paco*-**1** the main product of the reaction in the presence of K_2CO_3 is *partial cone*. This may be a result of kinetic control of the reaction. According to general considerations[28] the *cone* to 1,3-*alternate* interconversion occurs via preliminary formation of the *partial cone* conformer due to the rotation of one phenyl ring. This conformation is stabilized by strong interaction with the potassium ion (log K_{ex}=4.61) and further inversion of second phenyl group does not take place. Thus, reaction terminates at the formation of *paco*-**1**.

3. Conclusion

Among four possible conformers, the *cone*, *partial cone* and 1,3-*alternate* conformers of thiacalix[4]arene tetra-substituted at the narrow rim bearing four ketone groups have been synthesized using the template effect of alkali metal ions. Ionophoric properties of isolated and structurally

characterized macrocycles were investigated by the ion-pair extraction method.

Our results show that the stoichiometries of complexes (ligand/ion ratio) forming in the organic phase range from 1:1 to 1:4 and depend on some factors: (i) the size complementarity of ion and cavity formed by four ligating moieties at the narrow rim; (ii) allosteric effect. Thermodynamic extraction parameters ($\log K_{ex}$) demonstrate that the *cone* conformer exhibits the highest extractability towards the Na^+ ion compared to other alkali metal ions, whereas *paco* and 1,3-*alternate* conformers extract more effectively the larger K^+ ion. The higher ability and selectivity of conformers of **1** compared to those of **2** for alkali metal extraction. These macrocycles therefore have perspectives for application as ionophores in ion selective sensors.

4. Experimental

4.1. General procedure for the preparation of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(benzoyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (1)

Parent thiacalix[4]arene TCA (1 g, 1.4 mmol) was suspended in dry acetonitrile (50 ml) containing anhydrous M_2CO_3 (M=Na, K or Cs) (8.3 mmol) and α-bromoacetophenone (1.65 g, 8.3 mmol). The reaction mixture was refluxed under nitrogen for 40 h. The reaction was monitored by TLC. After cooling, the reaction mixture was treated in different ways.

In the case of Na_2CO_3 and K_2CO_3, the solution was evaporated to dryness and the solid residue was extracted by chloroform. After concentration of the chloroform solution the addition of acetonitrile led to the fractional crystallization of pure conformational isomers: Na_2CO_3: 1.12 g, 68% of *cone*-**1** and 0.11 g, 7% of *paco*-**1**; K_2CO_3: 1.24 g, 75% of *paco*-**1**.

In the case of Cs_2CO_3 after filtration the solid residue and filtrate were treated separately. The solid residue was extracted by chloroform. The addition of acetonitrile to the concentrated extract gave 1,3-*alt*-**1** (0.66 g, 40%). To remove unreacted α-bromoacetophenone the filtrate was evaporated to dryness. The treatment of the obtained viscous oil with acetonitrile gave solid disubstituted derivative **3** (0.20 g, 15%). *Paco*-**1** was isolated from the filtrate (0.11 g, 7%).

4.1.1. *Cone*-1. Colorless crystals, mp 130–131°C ν_{max}, cm^{-1} (in KBr): 2968 (CH) and 1710 (CO); δ (400 MHz, $CDCl_3$) 1.13 (36H, s, Bu^t), 6.09 (8H, s, OCH_2CO), 7.35 (8H, m, *m*-PhH), 7.37 (8H, s, ArH), 7.55 (4H, m, *p*-PhH), 7.97 (8H, d, J=7.4 Hz, *o*-PhH). Found: C, 72.30%; H, 6.28%; S, 10.90%. Calcd for $C_{72}H_{72}O_8S_4$: C, 72.45%; H, 6.08%; S, 10.74%.

4.1.2. Partial *cone*-1. Colorless crystals, mp 217–219°C. ν_{max}, cm^{-1} (in KBr): 2960 (CH) and 1708 (CO); (400 MHz, $CDCl_3$) 1.13 (18H, s, Bu^t), 1.32 (9H, s, Bu^t), 1.37 (9H, s, Bu^t), 5.36 (2H, d, J=15.9 Hz, OCH_2CO), 5.43 (2H, s, OCH_2CO), 5.48 (2H, d, J=15.9 Hz, OCH_2CO), 5.92 (2H, s, OCH_2CO), 7.19 (2H, d, J=2.4 Hz, ArH), 7.53 (2H, d, J=2.4 Hz, ArH), 7.62 (2H, s, ArH), 7.86 (2H, s, ArH), 7.34–7.59 (12H, m, *m*- and *p*-PhH), 7.92 (4H, d J=7.3 Hz, *o*-PhH), 7.98 (2H, J=8.2 Hz, *o*-PhH), 8.01 (2H, d, J=9.0 Hz, *o*-PhH). Found: C, 72.40%; H, 6.19%; S, 10.79%. Calcd for $C_{72}H_{72}O_8S_4$: C, 72.45%; H, 6.08%; S, 10.74%.

4.1.3. 1,3-*Alternate*-1. Colorless crystals, mp 228–230°C ν_{max}/cm^{-1} (in KBr): 2967 (CH) and 1709 (CO); (400 MHz, $CDCl_3$) 1.15 (36H, s, Bu^t), 5.33 (8H, s, OCH_2CO), 7.39 (8H, s, ArH), 7.45 (8H, m, *m*-PhH), 7.55 (8H, m, *m*-PhH), 7.93 (8H, d, J=7.4 Hz, *o*-PhH). Found: C, 72.32%; H, 6.27%; S, 10.86%. Calcd for $C_{72}H_{72}O_8S_4$: C, 72.45%; H, 6.08%; S, 10.74%.

All isomers of compound **1** showed an intense (100%) peak in the MALDI-TOF-MS spectrum at m/z 1193 (the molecular mass spectra were recorded on FINNIGAN DYNAMO mass spectrometer with 1,8,9-trihydroxyantracene as a matrix).

4.2. NMR Spectrometry

^{1}H NMR spectra of samples in $CDCl_3$ (4 mg in 0.5 ml) were recorded in Bruker MSL 400 and WM 250 NMR spectrometers. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases. 1D ^{1}H NMR spectra. Size 32 K, pulse length 2.8 ms (30°), 16 acquisitions. 2D COSY Spectra. Sequence: D1-90-t1-90-t2; relaxation delay D_1=0.5 s; 90° pulse 8.5 ms. 2D ROESY Spectrum. Sequence: D1-90t1-Spin lock -t2, d_1=3 S, spin lock 0.8 s 90° pulse 28 ms; TPPI-mode, N_S=16, D_S=2, T=298 K, matrix 512×512.

4.3. X-Ray structure determination

The X-ray diffraction data for crystal *paco*-**1** were collected on a CAD4 Enraf-Nonius automatic four-circle difractometer (graphite monochromator, Cu K_α radiation (1.54184 Å), ω scan method, $\theta \leq 57.3°$). Twenty five centered reflections gave a refined unit cell of dimensions a=17.648(4), b=22.243(4), c=19.040(7) Å, β=108.80(2)°, V=7075.2 Å^3, Z=4, ρ=1.07 g cm^{-3}. A total of 6043 reflections were measured, of which 3777 were unique with $I>3\sigma$. The stability of crystals and of experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. No significant decay was observed. Corrections for Lorentz and polarization effects were applied. The structure was solved in the uniquely assignable space group $P2_1/n$ by direct methods and difference Fourier syntheses using SIR program[29] and MolEN package.[30] All non-hydrogen atoms were refined anisotropically, H-atoms were located in ΔF maps and were included into structure factor calculations with fixed positional and thermal parameters. The final R values were R=0.057, R_ω=0.066 for 3777 unique reflections with $F^2 \geq 3\sigma$. All calculations were carried out on a DEC Alpha Station 200 computer, all figures were made using the program PLATON.[31]

Crystallographic data (excluding structure factors) for the structure *paco*-**1** in this paper have been deposited with the

Cambridge Crystallographic Data Centre as supplementary publication number CCDC 183412. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. Extraction study

The alkali picrates were prepared from aqueous solutions of picric acid and metal hydroxides. Aqueous picrate solution (4 ml, 2.27×10^{-4} M) containing 0.1 M metal hydroxide and 4 ml of a 1.3×10^{-1}–2×10^{-4} M solution of thiacalixarene derivatives **1** in CH_2Cl_2 were shaken for 60 min at room temperature (22°C). The absorbances A_i and A_0 of the aqueous phases after and before extraction were measured at 355 nm. The percent extraction was calculated as ratio $100(A_0-A_i)/A_0$. Extraction experiments were performed at the different ligand concentration. The log K_{ex} and n values were determined from the plot of $\log(\alpha/1-\alpha)$ versus $\log[L]_{org}$.

Acknowledgements

This work was supported by the RFBR (02-03-32934, 02-03-32280), joint program of CRDF and the Russian Ministry of Education 'Basic Research and Higher Education' (REC-007) and the program of Russian Academy of Science 'Nanomaterials and Supramolecular Systems'.

References

1. *Calixarenes A Versatile Class of Macrocyclic Compounds*; Vicens, J., Bohmer, V., Eds.; Kluwer Academic: Dordrecht, 1991.
2. Gutsche, C. D. In *Calixarenes Revisited. Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; RSC: London, 1998.
3. *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College: London, 2000.
4. Pochini, A.; Ungaro, R. *Comperehensive Supramolecular Chemistry*; Vogtle, F., Ed.; Elsevier: Oxford, 1996; Vol. 2, pp 103–147.
5. *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluver Academic: Netherlands, 2001.
6. Kumagai, H.; Hagesawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971–3972.
7. Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, J.; Pansanel, J.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 2311–2314.
8. Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437–1443.
9. Iki, N.; Morohashi, N.; Narumi, F.; Miyano, S. *Bull. Chem. Soc. Jpn* **1998**, *71*, 1597–1603.
10. Iki, N.; Morohashi, N.; Kabuto, C.; Miyano, S. *Chem. Lett.* **1999**, 219–220.
11. Biluk, A.; Hall, A. K.; Harrowfield, J. M.; Hosseini, M. W.; Skeleton, B.; White, A. H. *Inorg. Chem.* **2001**, *40*, 672–686.
12. Iki, N.; Narumi, F.; Fujimoto, T.; Morohashi, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2745–2750.
13. Akdas, H.; Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1999**, *40*, 2113–2116.
14. Lhotak, P.; Stastny, V.; Zlatuskova, P.; Stibor, I.; Michlova, V.; Tkadlecova, M.; Havlicek, M.; Sykora, J. *Collect. Czech. Chem. Commun.* **2000**, *65*, 757–771.
15. Lhotak, P.; Himl, M.; Pakhomova, S.; Stibor, I. *Tetrahedron Lett.* **1998**, *39*, 8915–8918.
16. Antipin, I. S.; Stoikov, I. I.; Gubaidullin, A. T.; Litvinov, I. A.; Weber, D.; Habicher, W. D.; Konovalov, A. I. *Tetrahedron Lett.* **1999**, *40*, 8461–8464.
17. Weber, D.; Gruner, M.; Stoikov, I. I.; Antipin, I. S.; Habicher, W. D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1741–1744.
18. Lamartine, R.; Bavoux, G.; Vocauson, F.; Martin, A.; Senlis, G.; Perrin, M. *Tetrahedron Lett.* **2001**, *42*, 1021–1024.
19. Danil de Namor, A. F.; Sueros Velarde, F. J.; Casal, A. R.; Pugliose, A.; Goitia, M. T.; Montero, T.; Lopez, F. F. *J. Chem. Soc. Faraday Trans.* **1997**, *93*, 3955–3959.
20. Danil de Namor, A. F.; Goitia, M. T.; Casal, A. R.; Velarde, F. J.; Gonzalez, M. I. B.; Villanueva-Salas, J. A.; Zapata-Ormachea, M. L. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3633–3638.
21. Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, L.; Ugozzoli, F. *J. Incl. Phenom.* **1988**, *6*, 119–134.
22. Ikeda, A.; Suzuki, Y.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **1998**, *54*, 2497–2508.
23. Asfari, Z.; Lamare, V.; Dozol, J. F.; Vicens, J. *Tetrahedron Lett.* **1999**, *40*, 691–694.
24. Budka, J.; Lhotak, P.; Michlova, V.; Stibor, I. *Tetrahedron Lett.* **2001**, *42*, 1583–1586.
25. Gutmann, V. *Coordination Chemistry in Non-Aqueous Solvents*; Springer: New York, 1971.
26. Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296–1304.
27. Abboud, J.-L. M.; Notario, R. *Pure Appl. Chem.* **1999**, *71*, 645–718.
28. Van Veggel, F. C. J. M. In *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College: London, 2000; pp 11–36.
29. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Viterbo, D. *Acta Crystallogr. A* **1991**, *47*, 744–748.
30. Straver, L.; Schierbeek, A. J. *MolEN Structure Determination System*; Nonius BV, 1994; Vols. 1 and 2.
31. Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2000.