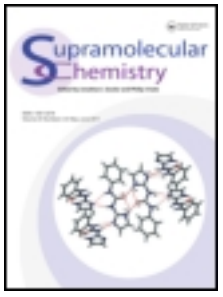

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Adamantane-bearing benzylamines and benzylamides: novel building blocks for supramolecular systems with finely tuned binding properties towards β-cyclodextrin

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Novel building blocks for the synthesis of supramolecular components based on adamantane-bearing benzylamines were prepared. The binding properties of these amines and the corresponding acetamides towards β-cyclodextrin (β-CD) were studied using mass spectrometry, NMR spectrometry, isothermal titration calorimetry and semi-empirical calculations. It was found that all of the examined guests predominantly formed 1:1 inclusion complexes in an enthalpy-driven manner with association constants of the order of 10^2–$10^3\ M^{-1}$. Stronger binding to the β-CD cavity was observed for guests with a longer spacer between the adamantane and benzene moieties and/or a 1,4-disubstituted benzene ring.

Keywords: adamantane; amines; cyclodextrins; binding properties; host–guest systems

1. Introduction

Many examples of host–guest systems based on the interactions between adamantane-bearing guests and β-cyclodextrin (β-CD) can be found in the recent literature. The geometric and electronic properties of both the host and guest components play important roles in the complexation process. The non-polar adamantyl moiety, $C_{10}H_{15}$, consists of three fused cyclohexane rings in a classical chair conformation and has an almost ideal spherical shape with an atom-to-atom diameter of 7.2 Å. β-CD is a macrocycle composed of seven glucopyranoside units in the $^4C_1$ conformation connected *via* α-1,4-glycosidic bonds. Its geometry is usually described as bottomless cap or doughnut with a wide secondary rim (occupied by secondary OH groups at the C2 and C3 positions) and a narrow primary rim (occupied by primary OH groups at the C6 positions). The hydrophobic cavity is lined with H5, H3 and glycosidic O-atoms and has an internal diameter of approximately 6.5 Å (*1*).

Although there are rare instances of the binding of some guests on the CD portal (*2*) or outside the CD cone (*3*), we are unaware of any demonstration of such binding modes for adamantane-based guests. Owing to the lipophilic character of both the adamantane scaffold and the CD cavity, in conjunction with their complementary geometries, adamantane and β-CD primarily form inclusion complexes in solution, with the adamantane cage more or less buried inside the CD cavity.

These interactions have been used to construct cyclic or linear supramolecular co-polymers consisting of β-CD dimers and homo-ditopic adamantane-based guest dimers (*4*). In addition, the formation of hydrogels from adamantane-based hetero-ditopic units and β-CD has been described (*5*). Comb-shaped assemblies based on a CD-modified polyacrylate backbone with reversibly grafted adamantane-terminated polyacrylate chains have been studied (*6*). The hydrophilic β-CD duplex has been used for the non-covalent cross-linkage of adamantane-grafted chitosan (*7*). The interactions between ditopic adamantane guests and tritopic β-CD hosts (*8*), as well as the aggregation of functionalised dendrons leading to tubular vesicles, have been studied (*9*). The formation of microcapsules for the pH-driven drug release based on the interaction between CD-grafted dextran and 1-adamantyl-grafted poly(aspartic amide) has been described (*10*). Furthermore, the interactions between the chains of modified dextran and poly[methyl vinyl ether-*alt*-(maleic anhydride)] (*11*), poly(ethylene glycol) (*12*), polyacrylate (*13*) or hyaluronic acid (*14*) have been studied, and the developed systems have then been used for the formation of multilayer films (*15*). Because of the strong binding between the adamantane scaffold and β-CD, simple adamantane derivatives (mostly $AdNH_2$ or AdCOOH, Ad = 1–adamantyl) are used to control supramolecular aggregation (*16*). Although the above-mentioned papers primarily describe the results of basic binding behaviour studies, it is easy to imagine future applications including

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drug delivery and controlled release, viscosity control and sensors. Some very interesting examples of the interactions between the adamantane cage and β-CD on a macroscopic scale have recently been published (*17*). In addition, some immunosorbents based on the interactions between modified polymers have already been developed for chromatographic applications (*18a*) and solid phase extraction material (*18b*).

Furthermore, the ability of the adamantane moiety to form inclusion complexes with β-CD is frequently used in drug design to produce novel biologically active adamantylated compounds with enhanced transport properties and/or cytotoxicity (*19*). However, a reduction of the desired biological activity has been clearly documented when the introduced adamantane scaffold lacked a sufficiently long spacer between adamantane and the active site of the drug (*20*).

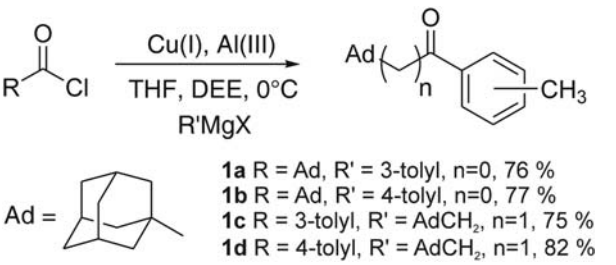
It should be noted that approximately one-half of the papers mentioned above describe guest components based on $AdNH_2$. Other frequently used adamantane building blocks are AdOH, $AdCH_2OH$, 2-(1-adamantyl)ethylamine, $AdCH_2COOH$ and 1-(1-adamantyl)-2-bromoethanone. It is reasonable to suppose that the electronic and steric properties of the linkage between adamantane and, for example, polymer backbone or pharmacophore can significantly affect binding to the CD cavity. For these reasons, novel adamantane building blocks are required. Considering the appropriate amino derivatives that are widely used as adamantane building blocks, we describe in this paper a convenient synthetic method for benzylamines that bear an adamantane moiety, which can be used for the synthesis of fine-tuned components for supramolecular assemblages or drug modification. Thermodynamic data of the host–guest interactions of the corresponding acetamides with β-CD based on calorimetric and NMR titrations, as well as the complex geometry, are discussed.

2. Results and discussion

2.1. Chemistry

The starting materials for this study, ketones **1a**–**d**, were prepared in satisfactory yields according to a previously described procedure (*21*) using acyl chlorides and the corresponding Grignard reagents in the presence of a catalytic amount of metal halide (Scheme 1).

Radical bromination of ketones **1** using 1.0 equiv. of *N*-bromosuccinimide (NBS) in dry tetrachloromethane at 80–85°C for the required time (monitoring by TLC) provided bromoketones **2** in approximately 70% yield. The reaction was initiated with a catalytic amount of benzoyl peroxide and irradiation with a tungsten lamp. In all cases, the starting material was not consumed completely when 1.0 equiv. of NBS was used. However, the addition of up to 1.2 equiv. of brominating agent did not increase the yield of product **2** significantly. Higher amounts of NBS led to the formation of undesired geminal dibromoderivatives.

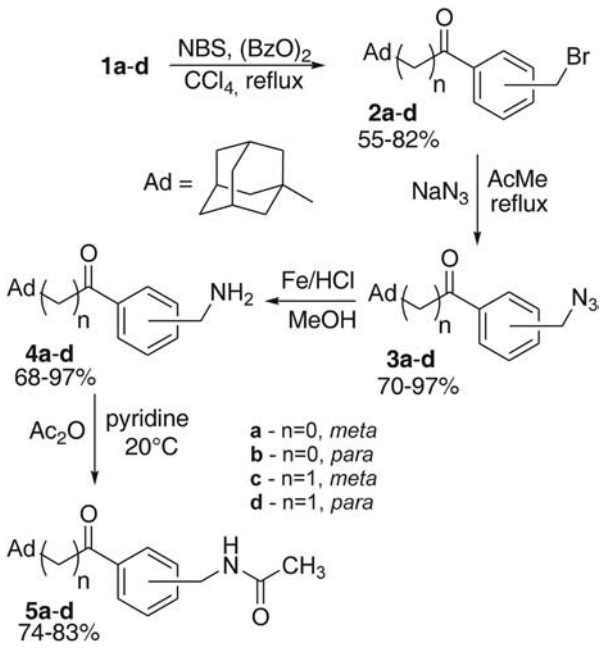


Scheme 1. Synthesis of starting ketones.

In the second step, bromoketones **2** were treated with sodium azide (10.0 equiv.) in dry acetone according to the conditions described by Seong (*22*), and the desired azidoketones **3** were isolated in good to excellent yield.

Several types of reducing agents [e.g. triphenylphosphine (*23*), triethylphosphite (*24*), propane-1,3-dithiol (*25*), zinc in acetic acid (*26*), $FeCl_3$/NaI in MeCN (*27*), complex hydrides (*28*), $FeSO_4/NH_3$ in MeOH (*29*) and Na_2S in MeOH (*30*)] under various reaction conditions were unsuccessfully utilised for the preparation of benzylamines **4**. Finally, compounds **4a**–**d** were smoothly prepared *via* the reaction of the corresponding azidoketones **3** with carbonyl iron powder as a reducing agent in a methanol:hydrochloric acid solution at room temperature. The benzylamines **4b**–**d** were isolated either as the free bases after adjusting the pH and extracting or as the hydrochlorides *via* treatment of the methanol solution of the corresponding amine with dry gaseous hydrogen chloride. Compound **4a** was isolated in excellent yield (97%) as a free base, but attempts to isolate the corresponding hydrochloride resulted in a colourless liquid. Moreover, the free base of compound **4a** was rather unstable, in contrast to benzylamines **4b**–**d**, and began to solidify within a few minutes at room temperature. This instability of amine **4a**, together with some difficulties accompanying the isothermal titration calorimetry (ITC) experiments with amines **4** (see discussion below), led us to transform amines **4** into the corresponding acetamides **5**. In addition, the adamantylated amines **4** were intended to be linked to the final supramolecular components *via* an amide bond, which is better mimicked by amides **5**. Amides **5** were prepared *via* the smooth reaction of amines **4** with acetic anhydride in pyridine at room temperature. The entire synthetic pathway is depicted in Scheme 2.

The ability of the prepared amines **4** and amides **5** to form supramolecular complexes with β-CD and the properties of the complexes were further studied. Qualitative ESI-MS analysis was used to detect the supramolecular aggregates in solution and to study their



Scheme 2. Reaction pathway leading to adamantylated amides.

fragmentation in the gas phase. The thermodynamic parameters of the complexation reactions were determined using NMR and ITC titrations, and the spatial arrangement of the aggregates was studied through 2D NMR spectrometry and theoretical calculations.

2.2. Mass spectrometry

The individual guests **4** and **5**, as well as their equimolar mixtures with β-CD, were studied in the gas phase with a mass spectrometer equipped with an electrospray ionisation source (ESI-MS). The pseudomolecular ions $[M + H]^+$ predominated in the first-order mass spectra of all of the examined guests. In the case of amine **4c** and all the examined amides **5a**–**d**, the signals of the proton associates were accompanied by signals at an *m/z* ratio twice as high minus unity (Table 1). We assigned these signals to H-bonded dimers associated with a single proton. Subsequent analyses of the ligand–cyclodextrin mixtures revealed that the protonated guest, a sodium adduct of β-CD and the protonated 1:1 host–guest aggregates were present in the gas phase. With amide **5a**, an additional aggregate of the amide with β-CD and Na^+ was observed and successfully trapped. As illustrated for the equimolar mixture of amide **5d** with β-CD in Figure 1(a), some further minor signals were observed and assigned to the products of either host or guest cleavage during the ESI process. In accordance with the well-known dissimilar stabilities of $[\beta\text{-CD} + H]^+$ and $[\beta\text{-CD} + Na]^+$, the corresponding aggregates of **5**·β-CD with H^+ and with Na^+ displayed markedly different fragmentation patterns during treatment under collision-induced dissociation (CID) conditions. Although the positive ion $[\mathbf{5}\cdot\beta\text{-CD} + H]^+$ lost the neutral amide **5** to produce the singly positively charged ion $[\beta\text{-CD} + H]^+$, which subsequently released four glucose units to produce signals at *m/z* 973, 811, 649 and 487 as demonstrated with further tandem mass spectrometry (Figure 1(b)), the sodium adduct $[\mathbf{5}\cdot\beta\text{-CD} + Na]^+$ lost the neutral amide **5** to yield solely the sodium adduct of β-CD at *m/z* 1157, and further fragmentation products were not detected. In addition, the supramolecular aggregates of amides **5** were also observable in the negative-ion mode (Figure 1(c)). In this case, the ions $[\beta\text{-CD} - 2H]^{2-}$, $[\mathbf{5}-H]^-$, $[\beta\text{-CD} - H]^-$ and $[\mathbf{5}\cdot\beta\text{-CD} - H]^-$ were usually observed. The fragmentation of the supramolecular aggregate $[\mathbf{5}\cdot\beta\text{-CD} - H]^-$ led exclusively to the release of neutral amide **5** to yield the $[\beta\text{-CD} - H]^-$ ion (Figure 1(d)). The MS data obtained clearly demonstrate that all of the studied amides **5** and amines **4b**–**d** form 1:1 supramolecular aggregates with β-CD in methanol–water solution, which were successfully transferred and detected in the gas phase using ESI.

Table 1. Important signals observed in the positive-ion mode ESI mass spectra.

	Exact mass							
	Ligand analysis						Mixture analysis	
	Single + H		Dimer + H		Single + Na		β-CD + amine +H	
Compound	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
4b	270.2	270.1	539.4	–	292.2	–	1404.6	1404.6
4c	284.2	284.1	567.4	567.4	306.2	306.0	1418.6	1418.5
4d	284.2	284.1	567.4	–	306.2	–	1418.6	1418.6
5a	312.2	312.1	623.4	623.3	334.2	334.1	1446.6	1446.5
5b	312.2	312.2	623.4	623.5	334.2	334.2	1446.6	1446.8
5c	326.2	326.3	651.4	651.5	348.2	348.2	1460.6	1460.7
5d	326.2	326.3	651.4	651.5	348.2	348.3	1460.6	1460.7

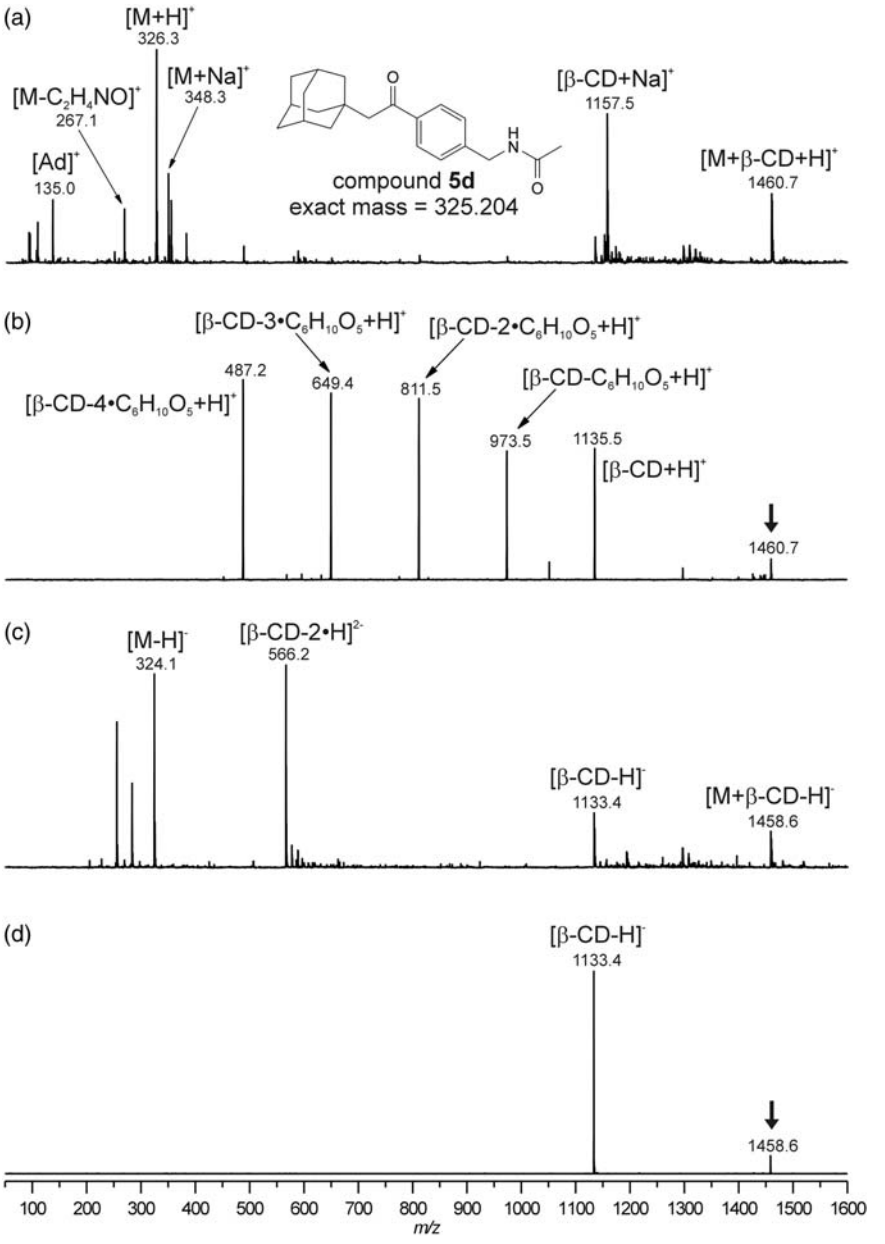


Figure 1. ESI-MS spectra of the mixtures of **5d** and β-CD in the positive-ion (a) and negative-ion (c) mode; ESI-MS/MS spectra of ions at *m/z* 1460 (b) and 1458 (d). Precursor ions are marked with a bold downward arrow.

2.3. Binding thermodynamics

NMR spectrometry was used to determine the stoichiometry of the complexes and the binding constants *K*. All of the examined host–guest systems follow the fast exchange mode on the NMR timescale. The complexation-induced shifts (CIS) were clearly seen in the spectra of the host–guest systems in a D_2O:[D_6]DMSO mixture. As it is shown for amide **5d** in Figure 2 (left), the complexation caused a deshielding of the adamantane hydrogen atoms at positions 2, 3 and 4 (for atom numbering, see Figure 3) and a shielding of hydrogen atoms at positions 5, 8 and 9. Nevertheless, the NMR data were often compromised by the very small CIS of the signals of the shielded H-atoms and overlapping of the signals of the deshielded H-atoms. Therefore, all of the NMR titration data are based only on the unambiguously observed signal of the H-atom at position 3. The stoichiometry of the studied complexes was estimated using the Job method (*31*) as applied to the NMR data. The prepared amides **5** form 1:1 complexes with β-CD under the experimental conditions, as clearly demonstrated for amide **5d** in Figure 2 (right).

Considering the 1:1 stoichiometry of the studied complexes, the NMR titration data were fitted to the theoretical rectangular hyperbola (Equation (1)), and the

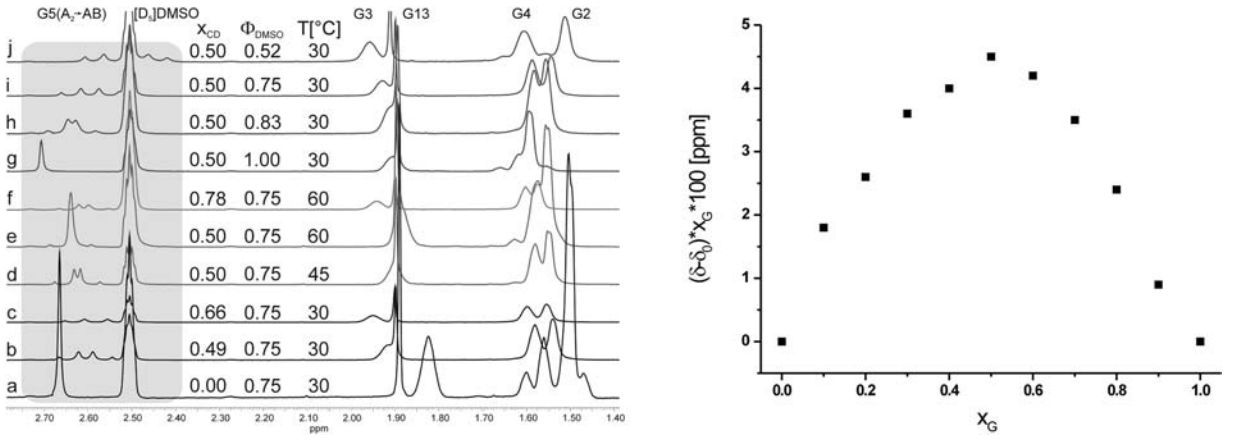


Figure 2. Stacking plot of a portion of the ^{1}H NMR spectra (left) and Job plot (right) for amide **5d** and β-CD mixture. Significant parameters [x_{CD} (molar fraction of CD), Φ_{DMSO} (volume fraction of DMSO) and temperature] are given above each line. Signals of the host and guest nuclei are labelled as H for β-CD and G for guest. The assignment of signals corresponds with the atom numbering in Figure 3.

values of CIS_{max} and K were obtained using a standard least squares regression process (for further details, see Section 4).

$$CIS = \frac{CIS_{max} \cdot K \cdot c_{\beta\text{-CD}}}{1 + K \cdot c_{\beta\text{-CD}}}. \quad (1)$$

The calculated K values are listed in Table 2. It should be noted that satisfactory fits to a theoretical model were not accomplished for amines **4**. We attributed this failure to the formation of higher order aggregates within the wide range of initial concentrations in the studied solutions. The only successful NMR titration was done with amine **4d**. The comparison of the binding constant value for amine **4d** and the corresponding amide **5d** implies a marginal role of the free amino group in complex stabilisation *via* hydrogen bonding. Further thermodynamic parameters were obtained from ITC experiments. Standard treatment of the ITC data for amides **5a**–**c** (using a one-binding-site model with three parameters, n, K and ΔH) did not lead to

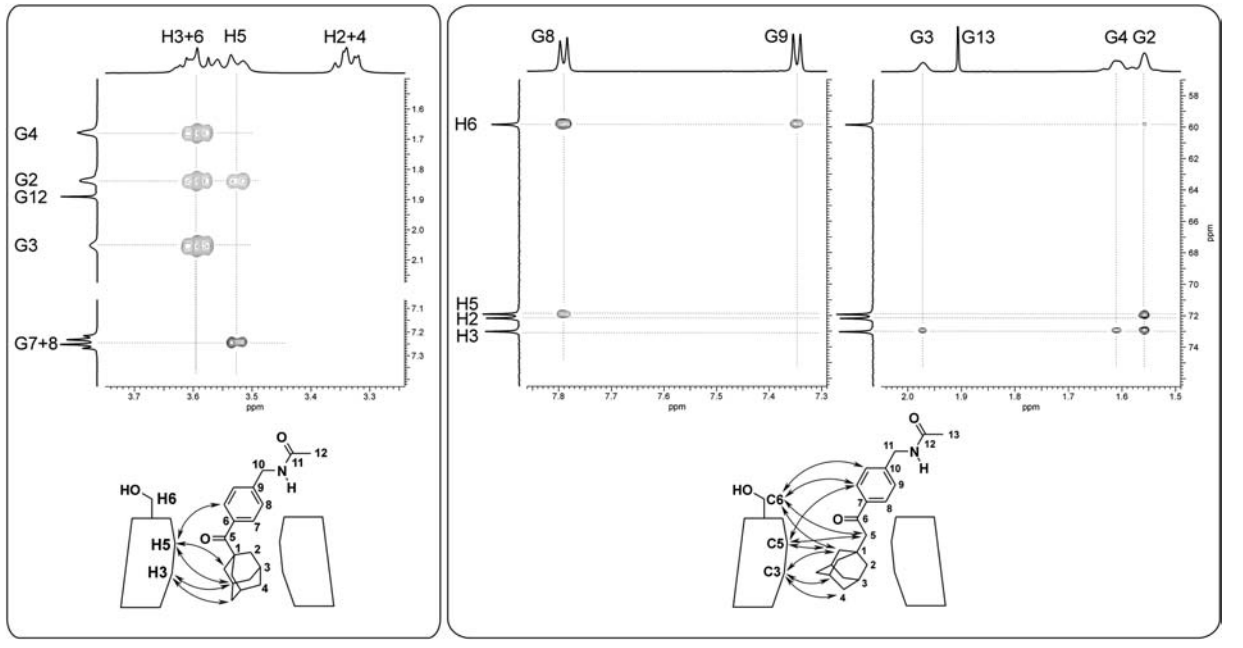


Figure 3. A portion of the ROESY spectrum of a 1:1 mixture of guest **5b** with β-CD (left frame) and a portion of the gs-HMQC-ROESY spectrum of a 1:1 mixture of guest **5d** with β-CD (right frame). Signals of the host and guest nuclei are labelled as H for β-CD and G for guest.

Table 2. Thermodynamic parameters of complexations.

Compound	NMR	ITC			
	K (M^{-1})	K (M^{-1})	$-\Delta H$ (kJ mol^{-1})	$-\Delta S$ (J mol^{-1} K)	n
5a	538 ± 70	128 ± 4	26.3 ± 0.6	46	1[a]
5b	767 ± 75	258 ± 9	28.1 ± 0.7	46	1[a]
5c	1206 ± 107	219 ± 5	31.0 ± 0.4	59	1[a]
5d	1721 ± 34	329 ± 3	35.2 ± 0.2	67	1[a]
5d	–	329 ± 20	35.3 ± 4	68	1.00 ± 0.09
5d[b]	439 ± 30	–	(28)[c]	(34)[c]	–
4d	1142 ± 128	–	–	–	–

Note: $T = 303$ K.
[a] The stoichiometry was predicted to be 1:1 using the ITC data treatment parameter $n = 1$.
[b] $T = 333$ K.
[c] See Section 4.

satisfactory results. Only iteration of the data for compound **5d** converged to reasonable values. However, we have previously shown predominantly 1:1 stoichiometry using NMR data under essentially the same conditions as those used for the calorimetric titrations. Therefore, we decided to fix the iteration parameter at $n = 1$. Thus, we obtained the thermodynamic parameters given in Table 2. Comparison of the thermodynamic parameters obtained for amide **5d** with and without a fixed n (Table 2) suggests that the presumption of 1:1 aggregates was justified. The slightly higher entropy loss in the case of amides **5c** and **5d** can be attributed to the more constrained guest conformation inside the CD cavity. These data allow us to conclude that all of the examined guests bind in an enthalpy-driven manner. The elongation of the spacer between the adamantane moiety and the benzene ring leads to the formation of more stable aggregates. Further fine tuning of the binding strength can be accomplished by choosing appropriate substitution on the benzene ring. The *para*-substituted amides form more stable complexes; *meta*-substituted amides form less stable complexes.

The common simple adamantane derivatives, independently on their charge, displayed association constants with β-CD around 10^4. Typically, for $AdCOO^-$ and $AdNH_3^+$, K was estimated to be of 1.6×10^4 and $8.3 \times 10^3\,M^{-1}$, respectively (*32*). For compounds with the adamantane cage linked to some bulkier moiety or polymer backbone, weaker binding was reported. For example, *N*-(1-adamantyl)pyridinium bromide binds the β-CD with $K = 1.9 \times 10^3\,M^{-1}$ (*4a*). Nevertheless, these values were obtained in pure or buffered water. Owing to low solubility of our ligands in water, we carried out all titrations in H_2O:DMSO (1:3, v:v) mixture in which the contribution of hydrophobic effect is significantly weakened. We carried out calorimetric titration of $AdNH_2$·HCl in phosphate buffer (pH 7.00) and in H_2O:DMSO mixture to be able to estimate the solvent influence on the K value. The respective association constants are 1.5×10^4 and $2 \times 10^2\,M^{-1}$. As can be seen, the binding is of two orders stronger in water. We believe that this trend is applicable also for our new ligands to sound their binding strength towards β-CD in water similar to other conventional adamantane derivatives.

When carrying out the NMR titration of amide **5d** with β-CD, we observed a large separation between the signals of the initially enantiotopic hydrogen atoms at position 5 (for C-atom numbering, see Figure 3) with an increased proportion of β-CD as the spin system was changed from A_2 to AB (Figure 2(a)–(c)). We attempted to understand the nature of this phenomenon by carrying out additional measurements. Increasing the temperature led to coalescence at approximately 60°C (Figure 2(d),(e)). However, when we increased the proportion of β-CD, while concomitantly holding the mixture at 60°C, the signal split again (Figure 2(f)). Finally, lines g–j in Figure 2 demonstrate the increased signal separation observed with increasing proportions of water in the mixed solvent. All of these observations suggest that the signal splitting could be attributed to the amount of complexed amide in the mixture. We postulate that amide **5d** (similar but significantly smaller signal splitting was also observed with amide **5c**) predominantly adopts a particular conformation within the β-CD cavity, which belongs to the C_1 symmetry point group and is fixed *via* interactions with β-CD. In such a situation, the hydrogen atoms at carbon 5 become non-equivalent due to the adjacent strongly anisotropic carbonyl group (see the calculated model in Figure 4). These observations clearly indicate that particular guest conformations may be locked inside a suitable cavity *via* weak van der Waals interactions and/or a steric hindrance.

2.4. Complex geometry

Owing to geometrical properties of the β-CD cavity (i.e. wider secondary rim, narrower primary rim and central constriction caused by H3 and H5 H-atoms), there are four principal arrangements of an inclusion complex of adamantane guest with β-CD. The adamantane cage can

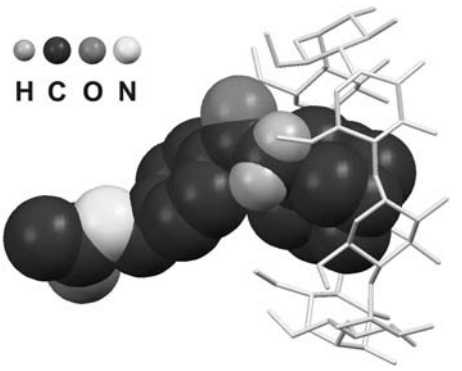


Figure 4. A calculated model of the **5d**·β-CD inclusion complex. H-atoms are omitted for clarity with the exception of AdC**H**$_2$, which were commented in the text.

occupy secondary (S) or primary (P) rim and in both cases, the residue of the guest molecule can either thread the cavity in a pseudorotaxane manner (I – interior) or protrude to the outer environment (E – exterior) (*33*, *34*). As the adamantane cage better fits the wider secondary rim, the positioning of adamantane-based guest molecule in the primary rim has been rarely reported. Although the host–guest complex of 1-adamantylammonium and modified β-CD with the PE geometry was observed only when the secondary rim was blocked by the positively charged aminogroup (*33*), the PI arrangement has not been reported to the best of our knowledge. The adamantane-based guests with long non-polar substituent adopt predominantly the SI geometry (*34*, *35c*). However, when the SI arrangement was obstructed by either host (e.g. the cyclodextrins are frequently linked to the polymer backbone *via* C6 carbon) or guest (e.g. two adamantane cages linked with a short spacer) form, the preferable geometry was reported to be of SE (*4a*,*b*, *35*).

Although the distinguishing of S and P binding mode is reasonable from a geometrical point of view, it should be noted that the adamantane cage is usually deeply buried into the CD cavity with the centre of gravity of 10 adamantane carbons being close to the best plane of seven etheric oxygen atoms of β-CD. In addition, the analyses of NOE data including only adamantane H-atoms can be rather confused by means of significant sterically driven deviation of the three-folded axes of adamantane substituent from the seven-folded axes of cyclodextrin ring.

The 2D NMR ROESY spectra indicate that all of the examined amides **5** interact with the β-CD unit predominantly by inclusion within the internal cavity. We clearly observed interactions between the inner H-atoms at carbons 3 and 5 with adamantane H-atoms 2, 3 and 4. The additional cross-peaks that relate to interactions between the aromatic guest H-atoms and the H-atoms at position 5 in CD indicate that the aromatic part of the guest molecule protrudes from the primary rim of cyclodextrin. A partial ROESY spectrum of an equimolar mixture of amide **5b** with β-CD and a schematic drawing of the suggested complex geometry including the observed interactions is depicted in Figure 3 (left). Furthermore, we attempted to support this arrangement by applying a 2D ^{1}H–^{13}C gs-HMQC-ROESY experiment. As Figure 3 (right) shows for amide **5d**, the interactions between CD carbon 3 and the amide H-atoms 2, 3 and 4, between CD carbon 5 and the amide H-atoms 2 and 8 and between CD carbon 6 and the amide H-atoms 2, 8 and 9 were clearly observed. These data led us to suggest a very similar arrangement for the **5d**·β-CD complex (Figure 3, right) as that discussed above for amide **5b**.

Finally, the geometry of the inclusion complexes was calculated in a manner described previously (*34*). The particular amide was positioned stepwise along the seven-fold axis of β-CD to simulate threading the guest molecule through the CD cavity. The geometries were initially optimised using a semi-empirical PM3 method, and single point energies were subsequently calculated at DFT level of theory. The arrangement with the maximum difference between the energy of the complex and sum of the energies of the guest and host calculated separately was considered to be the closest to the predominant actual complex geometry. A typical result obtained for amide **5d** is depicted in Figure 4. The calculated geometry agrees well with the experimental data.

3. Conclusion

In conclusion, we described a convenient synthetic method leading to versatile adamantane-bearing building blocks, which could be subsequently used to prepare components for supramolecular systems. In addition to full characterisation of all of the novel compounds by spectral methods, we studied the binding behaviour of four guests towards β-CD using mass spectrometry, NMR and calorimetric titrations. The association constants were found to be of the order of 10^{2}–10^{3} M^{-1}, and a relationship between the guest structure and the binding strength was clearly observed. Binding of the guest into the β-CD cavity was improved with a longer non-polar spacer separating the adamantane scaffold from the rest of the molecule and/or a 'linear' arrangement (i.e. *para* substitution of the central benzene ring) of the guest molecule.

4. Experimental section

4.1. General

All solvents, reagents and starting compounds (except those mentioned below) were of analytical grade, purchased from commercial sources and used without further purification. Adamantane-1-carbonyl chloride and 3-methylbenzoyl chloride were prepared according to a previously published procedure (*21*). Melting points were

measured on a Kofler block and are uncorrected. Elemental analyses (C, H and N) were determined with a Thermo Fisher Scientific Flash EA 1112. Retention times were determined using TLC plates (Alugram Sil G/UV from Macherey-Nagel) and petroleum ether/ethyl acetate was used as the mobile phase. Four systems of mobile phases were used (v/v): system a (1/1); system b (4/1); system c (8/1) and system d (16/1). NMR spectra were recorded at 25°C on a Bruker Avance 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) and a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^{1}H) and 75.77 MHz (^{13}C). ^{1}H and ^{13}C NMR chemical shifts were referenced to the signal of the solvent [^{1}H: δ(residual $CHCl_3$) = 7.27 ppm, δ(residual [D_5]DMSO) = 2.50 ppm; ^{13}C: $\delta(CDCl_3) = 77.23$ ppm, δ([D_6]DMSO) = 39.52 ppm]. The mixing time for the NOESY experiment was adjusted to 700 ms and the spin-lock for ROESY was adjusted to 400 ms. The 2D ^{1}H–^{13}C gs-HMQC–ROESY spectrum (*36*) was measured at resonance frequencies of 600.15 MHz (^{1}H) and 150.67 MHz (^{13}C). The HMQC step was adjusted for $^1J_{H-C} = 145$ Hz with a subsequent ROESY spin-lock of 400 ms. The spectrum was recorded in phase-sensitive mode using the echo–antiecho protocol (*37*). NMR titration experiments were carried out as follows. The solution of guest was titrated with stock solution of β-CD. Complexation-induced shifts (CIS) were calculated as $CIS = |\delta_{observed} - \delta_{free\ guest}|$. According to Benesi–Hildebrand approach, CIS values were plotted against total concentration of β-CD ($c_{\beta\text{-CD}}$) and data were fitted to a theoretical rectangular hyperbole (Equation (1)) *via* the routine least square regression process using MicroCal Origin software. The CIS_{max} describes coordinate of horizontal asymptote with the meaning of chemical shift of particular ^{1}H in the complexed guest molecule ($CIS_{max} = |\delta_{complexed\ guest} - \delta_{free\ guest}|$) and K (an association constant) is the slope for the CIS = 0. For further details, see (*31*) and references therein. The values of ΔH and ΔS were calculated from NMR data using the van't Hoff equation with $-\Delta H/R$ as the slope and $\Delta S/R$ as the intercept of the straight line obtained from linear regression of the plot of $\ln K$ versus $1/T$. The IR spectra were recorded with a Mattson 3000 FT-IR using a KBr disc. GC-MS analyses were run on a Shimadzu QP-2010 instrument using a Supelco SLB-5 ms (30 m, 0.25 mm) column with He as the carrier gas in constant linear flow mode (38 cm s^{-1}), 100°C for 7 min, 25°C min^{-1} to 250°C, then held for the required time. Only the peaks with relative abundances exceeding 5% are listed. The electrospray mass spectra were recorded with an Esquire LC ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an ESI source. Sample solutions were prepared immediately before each experiment by mixing β-CD and the individual amine:amide (8.8 μM in methanol:water, 1:1, v/v). Clear mixtures were introduced into the ion source at a flow rate of 3 μl/min *via* a metal capillary held at high voltage (±3.5 kV). The other instrumental conditions were as follows: the drying gas temperature was 250°C, the drying gas flow was 5 l/min, and the nebuliser pressure was 41.37 kPa. Nitrogen was used for nebulisation and drying. The nozzle-skimmer potential and octopole potential were modified and optimised before each experiment. The tandem mass spectra were collected using CID with He as the collision gas after isolation of the required ions. The ITC measurements were carried out in a DMSO:H_2O (3:1, v/v) solvent mixture using a VP-ITC MicroCal instrument at 30°C. The concentrations of the host in the cell and the guest in the microsyringe were approximately 0.9–1.5 and 9–17 mM, respectively. The raw experimental data were analysed with MicroCal ORIGIN software. The heats of dilution were taken into account for each guest compound. The data were fitted to a theoretical titration curve using the 'one set of binding sites' model.

4.2. *General procedure for ketones 1 preparation*

Ketones **1a–d** were prepared from the corresponding Grignard reagent and acyl chloride in the presence of a catalyst (*21*). In all cases, the desired product and a Grignard dimer as a co-product were observed. The dimers were separated from the mixture by column chromatography (system b). The spectral data for ketones **1b** (yield 77%) and **1a** (yield 76%) correspond with the literature (*21*, *38*).

4.2.1. *2-(1-Adamantyl)-1-(4-methylphenyl)ethanone (**1d**)*

Compound **1d** was isolated as colourless crystals in the yield of 82%. M.p. 62–64°C, R_f 0.37 (system d), anal. calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01%; found C, 84.87%; H, 8.95%. ^{1}H NMR ($CDCl_3$): d 1.66 (m, 12H, CH_2(Ad)), 1.95 (m, 3H, CH(Ad)), 2.41 (s, 3H, $PhCH_3$), 2.69 (s, 2H, CH_2CO), 7.24 (d, J = 7.9 Hz, 2H, Ph), 7.85 (d, J = 8.0 Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): d 21.7(CH_3), 28.9(CH), 37.0(CH_2), 43.2(CH_2), 51.3(C), 128.7(CH), 129.3(CH), 136.7(C), 143.6(C), 200.0(CO) ppm. IR (KBr): 3066(w), 3027(w), 2899(s), 2846(s), 1659(s), 1604(s), 1571(w), 1449(m), 1323(m), 1308(m), 1268(s), 1183(m), 1152(w), 1119(m), 1017(w), 975(w), 842(w), 813(m), 761(m), 582(w) cm^{-1}. GC-MS (EI, 75eV); *m/z* (%): 41(11), 55(6), 65(14), 67(6), 77(9), 79(13), 91(47), 92(8), 93(9), 105(7), 119(100), 120(9), 135(11), 253(46), 254(9), 268(M^+, 8).

4.2.2. *2-(1-Adamantyl)-1-(3-methylphenyl)ethanone (**1c**)*

Compound **1c** was isolated as colourless liquid in the yield of 75%. R_f 0.17 (system a), anal. calcd for $C_{19}H_{24}O$: C, 85.03%; H, 9.01%; found C, 85.22%; H, 8.92%. ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 12H, CH_2(Ad)), 1.95 (m, 3H,

CH(Ad)), 2.42 (s, 3H, PhC**H**$_3$), 2.71 (s, 2H, COC**H**$_2$), 7.30–7.35 (m, 2H, Ph), 7.73–7.76 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 21.6(CH_3), 28.9(CH), 34.1(C), 37.0(CH_2), 43.2(CH_2), 51.4(CO**C**H$_2$), 125.9(CH), 128.4(CH), 129.0(CH), 133.6(CH), 138.4(C), 139.2(C), 200.6(CO) ppm. IR (KBr): 2902(s), 2847(s), 2674(w), 2657(w), 1671(s), 1602(w), 1584(w), 1450(m), 1343(w), 1317(w), 1267(s), 1237(w), 1190(w), 1151(w), 1098(w), 1041(w), 804(w), 777(w), 754(m), 693(m) and 607(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 41(8), 55(5), 65(11), 67(5), 77(7), 79(11), 91(43), 92(8), 93(9), 119(100), 120(9), 134(5), 135(17), 250(5), 253(15), 268(M$^+$, 24) and 269(5).

4.3. General procedure for the synthesis of benzylbromides 2a–d

The corresponding ketone **1** (47.1 mmol) was dissolved in 100 ml of dry tetrachloromethane, and NBS (8.54 g, 48.0 mmol) was added in one portion to this solution. The reaction was initiated by the addition of a catalytic amount of benzoyl peroxide and irradiation with a tungsten lamp. The mixture was stirred and refluxed for 8 h, and the reaction progress was monitored by TLC during this time. After this period, the succinimide was filtered off, and the filtrate was evaporated under vacuum. The desired product was obtained after purification of the crude product by column chromatography (system c).

4.3.1. 1-Adamantyl-[3-(bromomethyl)phenyl] methanone (2a)

Compound **2a** was isolated as colourless liquid in the yield of 80%. The oily material slowly crystallised at − 15°C. M.p. 48–50°C, R_f 0.42 (system c), anal. calcd for $C_{18}H_{21}BrO$: C, 64.87%; H, 6.35%; found C, 64.78%; H, 6.21%. ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 6H, CH_2(Ad)), 2.01 (m, 6H, CH_2(Ad)), 2.09 (m, 3H, CH(Ad)), 4.50 (s, 2H, C**H**$_2$Br), 7.34–7.50 (m, 3H, Ph), 7.54 (s, 1H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3(CH), 33.0(CH), 36.7(CH_2), 39.3(CH_2), 47.2(C), 127.1(CH), 127.9(CH), 128.6(CH), 130.8(CH), 137.9(C), 140.4(C), 209.8(CO) ppm. IR (KBr): 2905(s), 2850(s), 2678(w), 2657(w), 1664(s), 1598(w), 1452(m), 1344(w), 1276(m), 1214(m), 1194(w), 1175(m), 1104(w), 1004(m), 802(w), 763(w), 733(w), 695(m), 625(w), 568(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 41(8), 55(6), 67(8), 77(7), 79(22), 81(6), 89(7), 90(10), 91(10), 93(18), 107(10), 118(5), 135(100), 136(11) and 332(M$^+$, $<$1).

4.3.2. 1-Adamantyl-[4-(bromomethyl)phenyl] methanone (2b)

Compound **2b** was isolated as colourless crystals in the yield of 72%. M.p. 60–62°C, R_f 0.49 (system c), anal. calcd for $C_{18}H_{21}BrO$: C, 64.87%; H, 6.35%; found C, 64.59%; H, 6.23%. ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 6H, CH_2(Ad)), 2.02 (m, 6H, CH_2(Ad)), 2.09 (m, 3H, CH(Ad)), 4.50 (s, 2H, C**H**$_2$Br), 7.42 (d, J = 7.9 Hz, 2H, Ph), 7.54 (d, J = 7.9 Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3(CH), 32.7(CH_2), 36.7(CH_2), 39.3(CH_2), 47.2(C), 127.8(CH), 128.8(CH), 139.7(C), 139.9(C), 209.6(CO) ppm. IR (KBr): 2924(s), 2905(s), 2852(s), 2658(w), 1669(s), 1605(w), 1453(w), 1403(w), 1274(m), 1243(m), 1226(m), 1176(w), 1108(m), 988(m), 951(w), 930(w), 846(w), 788(w), 683(w), 619(m), 595(w) and 557(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 43(6), 67(5), 77(5), 79(13), 89(6), 93(13), 107(8), 118(15), 135(100), 136(11) and 332(M$^+$, $<$1).

4.3.3. 2-(1-Adamantyl)-1-[3-(bromomethyl)phenyl] ethanone (2c)

Compound **2c** was isolated as colourless liquid in the yield of 82%. R_f 0.45 (system c), anal. calcd for $C_{19}H_{23}BrO$: C, 65.71%; H, 6.68%; found C, 65.58%; H, 6.65%. ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 12H, CH_2(Ad)), 1.94 (m, 3H, CH(Ad)), 2.71 (s, 2H, C**H**$_2$CO), 4.52 (s, 2H, C**H**$_2$Br), 7.42 (t, J = 7.6 Hz, 1H, Ph), 7.56 (d, J = 7.6 Hz, 1H, Ph), 7.86 (t, J = 7.6 Hz, 1H, Ph), 7.95 (s, 1H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.8(CH), 32.8(CH_2), 34.1(C), 36.9(CH_2), 43.1(CH_2), 51.4(CH_2), 128.5(CH), 128.9(CH), 129.1(CH), 133.3(CH), 138.4(C), 139.4(C), 199.6(CO) ppm. IR (KBr): 2901(s), 2846(s), 1673(s), 1600(w), 1449(m), 1312(w), 1168(w), 1216(w), 1143(w), 1094(w), 807(w), 762(w) and 692(s) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 41(12), 55(7), 65(5), 67(9), 77(11), 79(21), 81(6), 89(14), 90(31), 91(26), 92(9), 93(16), 105(7), 107(8), 118(21), 119(26), 133(8), 135(40), 136(5), 196(19), 198(20), 253(11), 267(100), 268(21), 346(M$^+$, 3) and 348(M$^+$ + 2, 3).

4.3.4. 2-(1-Adamantyl)-1-[4-(bromomethyl)phenyl] ethanone (2d)

Compound **2d** was isolated as colourless crystals in the yield of 55%. M.p. 85–88°C, R_f 0.22 (system d), anal. calcd for $C_{19}H_{23}BrO$: C, 65.71%; H, 6.68%; found C, 65.48%; H, 6.52%. ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 12H, CH_2(Ad)), 1.96 (m, 3H, CH(Ad)), 2.71 (s, 2H, C**H**$_2$CO), 4.51 (s, 2H, C**H**$_2$Br), 7.48 (d, J = 8.6 Hz, 2H, Ph), 7.93 (d, J = 8.6 Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9(CH), 32.4(CH_2), 34.2(C), 37.0(CH_2), 43.2(CH_2), 51.5(CH_2), 129.1(CH), 129.3(CH), 138.9(C), 142.5(C), 199.7(CO) ppm. IR (KBr): 2900(s), 2846(m), 2672(w), 2657(w), 1670(s), 1604(w), 1571(w), 1446(w), 1411(w), 1346(w), 1322(w), 1286(w), 1262(m), 1204(w), 1179(w), 1152(w), 1094(w), 1015(w), 977(w), 861(w), 816(w), 782(w), 709(w), 667(w) and 601(m) cm^{-1}. GC-MS (EI, 75 eV);

m/z (%): 40(5), 41(41), 43(6), 51(6), 53(15), 55(24), 63(11), 64(5), 65(24), 66(5), 67(26), 69(6), 77(35), 78(12), 79(59), 80(8), 81(17), 89(33), 90(78), 91(92), 92(24), 93(41), 104(16), 105(20), 107(16), 118(70), 119(100), 120(9), 133(22), 134(21), 135(45), 136(5), 169(6), 197(20), 199(19), 253(43), 254(9), 267(89) and 268(21).

4.4. General procedure for the synthesis of azides 3a–d

The appropriate bromide (2.72 mmol) was dissolved in 10 ml of dry acetone, and sodium azide (1.77 g, 27.2 mmol) was added to this solution in one portion. The reaction mixture was refluxed under an Ar atmosphere until TLC indicated the complete disappearance of the starting material (6–8 h). Subsequently, the mixture was diluted with water and extracted six times with diethyl ether. The combined organic layers were dried over sodium sulphate. Evaporation of the solvent under vacuum followed by purification *via* column chromatography (system c) provided the desired product.

*4.4.1. 1-Adamantyl-[3-(azidomethyl)phenyl]methanone (**3a**)*

Compound **3a** was isolated as colourless liquid in the yield of 73%. R_f 0.24 (system d), anal. calcd for $C_{18}H_{21}N_3O$: C, 73.19%; H, 7.17%; N, 14.23%; found C, 73.08%; H, 7.32%; N, 14.17%. ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 6H, CH_2(Ad)), 2.01 (m, 6H, CH_2(Ad)), 2.09 (m, 3H, CH(Ad)), 4.39 (s, 2H, C**H**$_2$N$_3$), 7.41–7.51 (m, 4H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.3(CH), 36.7(CH_2), 39.3(CH_2), 47.2(C), 54.7(CH_2), 126.9(CH), 127.0(CH), 128.7(CH), 129.8(CH), 135.7(C), 140.6(C) and 205.2(CO) ppm. IR (KBr): 2905(s), 2851(s), 2678(w), 2659(w), 2098(s), 1672(s), 1601(w), 1584(w), 1452(m), 1344(m), 1273(m), 1245(m), 1194(w), 1172(m), 1104(w), 999(m), 972(w), 935(w), 887(w), 803(w), 782(w), 732(w), 711(w) and 650(w) cm^{-1}.

*4.4.2. 1-Adamantyl-[4-(azidomethyl)phenyl]methanone (**3b**)*

Compound **3b** was isolated as colourless crystals in the yield of 70%. M.p. 35–36°C, R_f 0.45 (system c), anal. calcd for $C_{18}H_{21}N_3O$: C, 73.19%; H, 7.17%; N, 14.23%; found C, 73.36%; H, 7.26%; N, 13.95%. ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 6H, CH_2(Ad)), 2.02 (m, 6H, CH_2(Ad)), 2.09 (m, 3H, CH(Ad)), 4.39 (s, 2H, C**H**$_2$N$_3$), 7.35 (d, J = 7.9 Hz, 1H, Ph), 7.58 (d, J = 7.9 Hz, 1H, Ph) ppm. ^{13}C NMR: δ 28.4(CH), 36.8(CH_2), 39.3(CH_2), 47.2(C), 54.6(CH_2), 128.8(CH), 128.0(CH), 137.8(C), 139.7(C) and 204.8(CO) ppm. IR (KBr): 2910(s), 2851(s), 2098(s), 1657(s), 1605(w), 1452(w), 1428(w), 1408(w), 1344(w), 1295(w), 1270(w), 1233(w), 1173(w), 1103(w), 987(w), 950(w), 927(w), 834(w), 799(w), 738(w) and 685(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 55(8), 67(10), 77(14), 79(21), 81(6), 91(6), 93(20), 107(10), 118(7), 135(100), 136(10), 239(10), 267(M^+–N_2, 2) and 295(M^+, 1).

*4.4.3. 2-(1-Adamantyl)-1-[3-(azidomethyl)phenyl] ethanone (**3c**)*

Compound **3c** was isolated as colourless crystals in the yield of 97%. The analytical sample was further crystallised from hexane. M.p. 60–62°C, R_f 0.22 (system d), anal. calcd for $C_{19}H_{23}N_3O$: C, 73.76%; H, 7.49%; N, 13.58%; found C, 73.65%; H, 7.23%; N, 13.78%. ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 12H, CH_2(Ad)), 1.94 (m, 3H, CH(Ad)), 2.72 (s, 2H, C**H**$_2$CO), 4.42 (s, 2H, C**H**$_2$N$_3$), 7.44–7.52 (m, 2H, Ph) and 7.89–7.92 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9(CH), 34.1(C), 37.0(CH_2), 43.1(CH_2), 51.5(CH_2), 54.6(CH_2), 128.0(CH), 128.5(CH), 129.2(CH), 132.4(CH), 136.1(C), 139.6(C) and 199.9(CO) ppm. IR (KBr): 2905(s), 2847(s), 2099(s), 1673(s), 1602(w), 1449(m), 1344(w), 1311(w), 1266(m), 1189(w), 1148(w), 1095(w), 979(w), 925(w), 806(w), 757(w), 723(w), 695(m), 695(w), 649(w) and 610(w) cm^{-1}.

*4.4.4. 2-(1-Adamantyl)-1-[4-(azidomethyl)phenyl] ethanone (**3d**)*

Compound **3d** was isolated as colourless solid in the yield of 77%. M.p. 25–27°C, R_f 0.33 (system b), anal. calcd for $C_{19}H_{23}N_3O$: C, 73.76%; H, 7.49%; N, 13.58%; found C, 73.82%; H, 7.12%; N, 13.55%. ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 12H, CH_2(Ad)), 1.95 (m, 3H, CH(Ad)), 2.72 (s, 2H, C**H**$_2$CO), 4.42 (s, 2H, C**H**$_2$N$_3$), 7.40 (d, J = 8.3 Hz, 2H, Ph), 7.96 (d, J = 8.3 Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9(CH), 34.2(C), 36.2(CH_2), 43.2(CH_2), 51.5(CH_2), 54.5(CH_2), 128.2(CH), 127.1(CH), 138.9(C), 140.4(C), 199.8(CO) ppm. IR (KBr): 2903(s), 2847(s), 2099(s), 1671(s), 1608(m), 1573(w), 1504(w), 1450(w), 1412(w), 1345(w), 1287(w), 1262(m), 1209(w), 1178(w), 1149(w), 1014(w), 978(w), 915(w), 851(w), 813(w) and 764(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 41(16), 51(7), 53(5), 55(9), 67(12), 76(6), 77(39), 78(6), 79(26), 81(8), 91(21), 92(9), 93(20), 103(6), 104(28), 105(13), 107(9), 132(100), 133(11), 135(32), 252(6), 253(23), 264(9), 280(6), 281(M^+–N_2, 75) and 282(16).

4.5. General procedure for the synthesis of benzylamines 4a–d

The corresponding azide (1.88 mmol) was dissolved in 20 ml of methanolic HCl (1–2 M), and iron powder (203 mg, 3.64 mmol) was added to this solution in one portion. The reaction mixture was stirred at room temperature, and another portion of carbonyl iron (3.64 mmol) was added until

the starting material had completely disappeared (according to TLC). The solvent was then removed under vacuum, 30 ml of 7% NaOH (water solution) was added, and the water layer was extracted with diethyl ether (5 × 10 ml). The collected organic portions were washed with brine (3 × 10 ml), dried over sodium sulphate and evaporated under vacuum. The purified product (column chromatography, system d) was generally isolated as a colourless liquid, which was subsequently converted to the hydrochloride.

4.5.1. 1-Adamantyl-[3-(aminomethyl)phenyl]methanone (**4a**)

Compound **4a** was isolated as colourless liquid in the yield of 97%. R_f 0.25 (system a). GC-MS (EI, 75 eV); *m/z* (%): 41(5), 67(8), 77(11), 79(19), 91(5), 93(18), 106(10), 107(12), 134(14), 135(100), 136(11), 241(22), 252(7) and 269(M^+, 2).

4.5.2. 1-Adamantyl-[4-(aminomethyl)phenyl]methanone hydrochloride (**4b**)

Compound **4b** was isolated as colourless crystalline powder in the yield of 68%. M.p. 200–204°C, R_f (free base) 0.79 (MeOH:$CHCl_3$, 3:1, v:v), anal. calcd for $C_{18}H_{24}ClNO$: C, 70.69%; H, 7.91%; N, 4.58%; found C, 70.48%; H, 7.85%; N, 4.32%. ^{1}H NMR ([D_6]DMSO, 2.50 ppm): δ 1.69 (m, 6H, CH_2(Ad)), 1.90 (m, 6H, CH_2(Ad)), 2.01 (m, 3H, CH(Ad)), 4.05 (s, 2H, C**H**$_2$$NH_3$), 7.57 (m, 4H, Ph) and 8.52 (s, 3H, NH_3) ppm. ^{13}C NMR ([D_6]DMSO, 39.5 ppm): δ 27.2(CH), 35.7(CH_2), 38.1(CH_2), 41.5(CH_2), 45.8(C), 126.8(CH), 128.4(CH), 135.8(C), 138.7(C) and 208.5(CO) ppm. IR (KBr): 3034(w), 2906(s), 2849(w), 1733(w), 1690(s), 1613(w), 1595(w), 1493(m), 1452(m), 1382(w), 1343(w), 1273(w), 1240(m), 1178(w), 1103(w), 1070(w), 989(m), 931(w), 849(m) and 636(m) cm^{-1}. GC-MS (free base) (EI, 75 eV); *m/z* (%): 79(18), 81(5), 89(7), 91(5), 93(16), 105(5), 106(6), 107(10), 134(21), 135(100), 136(11), 252(10) and 269(M^+, 2).

4.5.3. 2-(1-Adamantyl)-1-[3-(aminomethyl)phenyl] ethanone hydrochloride (**4c**)

Compound **4c** was isolated as a pale yellow crystalline powder in the yield of 91%. M.p. 163–167°C, R_f (free base) 0.27 (system a), anal. calcd for $C_{19}H_{26}ClNO$: C, 71.34%; H, 8.19%; N, 4.38%; found C, 71.12%; H, 8.08%; N, 4.53%. ^{1}H NMR ($CDCl_3$): δ 1.60 (m, 12H, CH_2(Ad)), 1.88 (s, 3H, CH(Ad)), 2.64 (s, 2H, C**H**$_2$CO), 4.18 (s, 2H, C**H**$_2$$NH_2$), 7.36 (t, J = 7.6 Hz, 1H, Ph), 7.71 (d, J = 7.6 Hz, 1H, Ph), 7.79 (d, J = 7.6 Hz, 1H, Ph) and 8.09 (m, 1H, Ph), 8.63 (bs, 3H, NH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9(CH), 34.2(C), 36.9(CH_2), 43.5(CH_2), 51.5(CH_2), 129.2(CH), 129.3(CH), 133.6(CH), 134.0(CH), 139.3(C) and 200.7(CO) ppm. IR (KBr): 3340(w), 2901(s), 2847(m), 1671(s), 1600(w), 1451(m), 1317(m), 1267(m), 1190(w), 1148(w), 807(w), 757(w), 695(m) and 469(m) cm^{-1}. GC-MS (free base) (EI, 75 eV); *m/z* (%): 41(6), 55(5), 67(6), 77(21), 79(19), 91(10), 93(11), 104(8), 105(11), 106(22), 107(7), 118(19), 119(5), 134(100), 135(27), 253(14), 266(67) and 267(14).

4.5.4. 2-(1-Adamantyl)-1-[4-(aminomethyl)phenyl] ethanone hydrochloride (**4d**)

Compound **4d** was isolated as a colourless crystalline powder in the yield of 85%. M.p. 220–222°C, R_f (free base) 0.24 (MeOH:$CHCl_3$, 3:1, v:v), anal. calcd for $C_{19}H_{26}ClNO$: C, 71.34%; H, 8.19%; N, 4.38%; found C, 71.48%; H, 8.13%; N, 4.72%. ^{1}H NMR ([D_6]DMSO, 2.50 ppm): δ 1.58 (m, 12H, CH_2(Ad)), 1.88 (m, 3H, CH(Ad)), 2.74 (s, 2H, C**H**$_2$CO), 4.08 (s, 2H, C**H**$_2$$NH_3$), 7.65 (s, 2H, Ph), 7.98 (s, 2H, Ph) and 8.66 (bs, 3H, NH_3) ppm. ^{13}C NMR ([D_6]DMSO, 39.5 ppm): δ 28.0(CH), 33.4(C), 36.2(CH_2), 41.6(CH_2), 42.2(CH_2), 50.4(CH_2), 128.3(CH), 129.0(CH), 138.2(C), 138.9(C), 199.3(CO) ppm. IR (KBr): 2901(s), 2847(s), 2674(w), 2611(w), 1670(s), 1611(m), 1450(m), 1417(w), 1264(m), 1218(w), 1179(w), 1121(w), 1100(w), 1009(w), 983(w), 915(w), 825(w), 668(w) and 587(w) cm^{-1}. GC-MS (free base) (EI, 75 eV); *m/z* (%): 41(8), 55(7), 67(7), 77(15), 79(19), 89(20), 91(15), 92(5), 93(12), 104(7), 105(24), 106(15), 107(6), 134(100), 135(24), 253(62), 254(12), 266(42) and 267(10).

4.6. General procedure for the synthesis of acetamides 5

The corresponding benzylamine **4** (0.9 mmol) was dissolved in 45 ml of pyridine, and 0.15 ml of acetic anhydride was added to this solution. The mixture was stirred for 12 h at room temperature and then poured onto crushed ice. The water layer was extracted with diethyl ether (5 × 10 ml), and the combined organic layers were dried over sodium sulphate and evaporated under vacuum. The desired acetamide **5** was obtained after purification of the crude product by column chromatography (system a).

4.6.1. N-[3-(1-adamantylcarbonyl)benzyl]acetamide (**5a**)

Compound **5a** was isolated as a colourless crystalline powder in the yield of 83%. M.p. 105–110°C, R_f 0.31 (system a), anal. calcd for $C_{20}H_{25}NO_2$: C, 77.14%; H, 8.09%; N, 4.50%; found C, 76.95%; H, 8.18%; N, 4.22%. ^{1}H NMR ($CDCl_3$): δ 1.74 (m, 6H, CH_2(Ad)), 1.98–2.07 (m, 12H, CH_2 (Ad) + CH(Ad) + CH_3CO), 4.42 (d, J = 5.6 Hz, 2H, C**H**$_2$NH), 6.10 (bs, 1H, NH), 7.34–7.43 (m, 4H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ 23.4(CH_3), 28.3(CH), 36.7(CH_2), 39.3(CH_2), 43.6(CH_2), 47.1(C), 126.1(CH), 126.5(CH), 128.4(CH), 129.7(CH), 138.6(C), 140.3(C), 170.2(NHCO) and 210.4(CO) ppm. IR (KBr):

3250(s), 3074(s), 2905(s), 2851(s), 2678(w), 2658(w), 1679(s), 1642(s), 1563(s), 1440(m), 1373(m), 1349(w), 1299(m), 1274(m), 1249(m), 1193(w), 1172(w), 1101(w), 1032(m), 996(m), 896(w), 790(m), 733(w), 705(m), 689(w), 640(w) and 496(w) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 43(5), 67(6), 77(5), 79(14), 93(13), 106(5), 107(9), 135(100), 136(9), 178(5), 311(M^+, 9).

4.6.2. *N-[4-(1-adamantylcarbonyl)benzyl]acetamide (**5b**)*

Compound **5b** was isolated as a colourless crystalline powder in the yield of 55%. M.p. 114–117°C, R_f 0.30 (system a), anal. calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50; found C, 77.42; H, 7.93; N, 4.37. ^{1}H NMR ($CDCl_3$): δ 1.69–1.79 (m, 6H, CH_2(Ad)); 1.99 (m, 6H, CH_2(Ad)); 2.04 (s, 3H, $COCH_3$); 2.07 (m, 3H, CH(Ad)); 4.44 (d, $J = 5.6$ Hz, 2H, PhC**H**$_2$NH); 6.08 (bs, 1H, NH); 7.28 (d, $J = 7.9$ Hz, 2H, Ph); 7.51 (d, $J = 7.9$ Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 23.3$ (CH_3), 28.3 (CH), 36.7 (CH_2), 39.3 (CH_2), 43.5 (CH_2), 47.1 (C), 127.4 (CH), 127.8 (CH), 138.9 (C), 140.7 (C), 170.3 (NHCO) and 209.8 (CO) ppm. IR (KBr): 3250 (s), 3085 (s), 2904 (s), 2848 (s), 2658 (m), 1686 (s), 1646 (s), 1612 (m), 1548 (s), 1452 (s), 1421 (m), 1406 (w), 1375 (m), 1344 (w), 1292 (s), 1273 (s), 1237 (s), 1180 (m), 1122 (m), 1099 (m), 989 (s), 931 (m), 837 (w), 742 (s), 687 (m), 641 (s), 595 (s) and 495 (s) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 43(6), 67(7), 79(20), 89(5), 91(5), 93(15), 107(10), 135(100), 176(8), 311(M^+, 9).

4.6.3. *N-[3-(1-adamantylmethylcarbonyl)benzyl] acetamide (**5c**)*

Compound **5c** was isolated as a colourless crystalline powder in the yield of 74%. M.p. 115–120°C, R_f 0.30(system a), anal. calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30; found C, 77.24; H, 8.28; N 4.57. ^{1}H NMR ($CDCl_3$): δ 1.59–1.70 (m, 12H, CH_2(Ad)); 1.94 (m, 3H, CH(Ad)); 2.04 (s, 3H, $COCH_3$); 2.69 (s, 2H, AdC**H**$_2$CO); 4.48 (d, $J = 5.3$ Hz, 2H, PhC**H**$_2$NH); 6.17 (bs, 1H, NH); 7.37–7.48 (m, 2H, Ph) and 7.81–7.83 (m, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 23.3$ (CH_3), 28.9 (CH), 34.2 (C), 37.0 (CH_2), 43.2 (CH_2), 43.6 (CH_2), 51.5 (CH_2), 127.5 (CH), 127.9 (CH), 129.0 (CH), 132.4 (CH), 139.0 (C), 139.4 (C), 170.4 (NHCO) and 200.3 (CO) ppm. IR (KBr): 3251 (s), 3077 (s), 2990 (w), 2905 (s), 2846 (s), 2674 (w), 2660 (w), 1672 (s), 1644 (s), 1600 (m), 1553 (s), 1437 (s), 1371 (m), 1290 (m), 1251 (m), 1026 (m), 803 (w), 760 (m), 582 (w) and 515 (m) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 43(18), 55(5), 67(11), 73(5), 77(23), 79(33), 81(8), 89(8), 90(7), 91(18), 43(18), 92(6), 93(22), 104(3), 105(18), 105(35), 107(17), 118(26), 119(11), 134(13), 135(100), 136(11), 148(20), 149(9), 172(7), 176(73), 177(8), 190(10), 253(93), 254(19), 266(65), 267(14) and 325(M^+, 5).

4.6.4. *N-[4-(1-adamantylmethylcarbonyl)benzyl] acetamide (**5d**)*

Compound **5d** was isolated as a colourless crystalline powder in the yield of 43%. M.p. 84–88°C, R_f 0.27 (system a), anal. calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30; found C, 77.38; H, 8.41; N 3.98. ^{1}H NMR ($CDCl_3$): $\delta = 1.59$–1.70 (m, 12H, CH_2(Ad)); 1.94 (m, 3H, CH(Ad)); 2.04 (s, 3H, $COCH_3$); 2.68 (s, 2H, AdC**H**$_2$CO); 4.47 (d, $J = 5.9$ Hz, 2H, PhC**H**$_2$NH); 6.16 (bs, 1H, NH); 7.32 (d, $J = 8.3$ Hz, 2H, Ph) and 7.88 (d, $J = 5.9$ Hz, 2H, Ph) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 23.3$ (CH_3), 28.9 (CH), 34.2 (C), 37.0 (CH_2), 43.2 (CH_2), 43.5 (CH_2), 51.5 (CH_2), 127.8 (CH), 129.0 (CH), 138.3 (C), 143.5 (C), 170.3 (NHCO) and 200.5 (CO) ppm. IR (KBr): 3261 (s), 3079 (s), 2903 (s), 2844 (s), 2673 (w), 2655 (w), 1652 (m), 1609 (m), 1561 (s), 1426(m), 1371 (s), 1350 (w), 1286 (s), 1263 (s), 1214 (m), 1100 (m), 1027 (s), 983 (m), 915 (w), 813 (m), 771 (m), 623 (w), 585 (s) and 511 (m) cm^{-1}. GC-MS (EI, 75 eV); *m/z* (%): 41(8), 43(16), 77(14), 79(20), 93(13), 105(17), 106(15), 135(17), 176(55), 253(10), 266(100) and 267(22).

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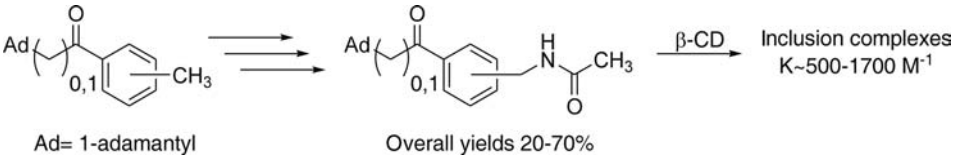

Michal Rouchal, Alena Matelová, Fabiana Pires de Carvalho, Robert Bernat, Dragan Grbić, Ivo Kuřitka, Martin Babinský, Radek Marek, Richard Čmelík and Robert Vícha

Adamantane-bearing benzylamines and benzylamides: novel building blocks for supramolecular systems with finely tuned binding properties towards β-cyclodextrin

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