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Synthesis of Adamantyl-Containing Compounds - Structure Elements of Rotaxanes and Supramolecular Polymers

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Abstract. This manuscript deals with the synthesis of various Adamantane derivatives as objects of supramolecular chemistry, in particular, supramolecular Cyclodextrine polymers (SCP) and Rotaxanes. One of the structural elements of the SCP and Rotaxanes are linear molecules modified by the end-blockers. A considerable volume of adamantyl group allows Adamantane derivatives to create locking groups in Rotaxanes, and a high affinity for β-Cyclodextrine to create supramolecular polymers.

Keywords: Adamantane, Cyclodextrine, Isocyanate, supramolecular polymer, urea.

1 Introduction

In the last decades there was a rapid development of new scientific area –supramolecular chemistry [1], which focuses on various supramolecular interactions. Among such supramolecular complexes supramolecular polymers, Rotaxanes and pseudorotaxanes are of the highest interest. In recent years, new areas of research on Cyclodextrin complexes with various Adamantane derivatives were outlined to produce Polymeric Rotaxanes, supramolecular oligomeric and Polymeric Rotaxanes with unique structure and properties [2].

One of the important components for the assembly of such supramolecular structures is barbell-like molecules such as diadamantyl compounds of formula Ad-X-Ad, where, Ad – adamantyl; X – hydrocarbon- or heteroatomic spacer. In the case of supramolecular polymers development such compounds could be considered as guest-monomers.

On the other hand, from the all cavity-containing compounds only α- and β- Cyclodextrines are best for rapid, selective and reversible bonding of Adamantane fragment [3], which allows them to be used for supramolecular polymers development [4-10].

It is necessary to mention that Adamantane chemistry is rapidly developing [11-16] and the amount of adamantyl-containing compounds as well as methods of its synthesis are continuously increasing. Direct synthesis of Adamantane derivatives can be interesting for supramolecular chemistry, however it is not actively developing at this current state of time.

In this case, given research is devoted to the synthesis of 1,3-diadamantyl disubstituted urea and diurea, which can be used as guest-monomers for assembling supramolecular Cyclodextrin polymers as well as guests in Rotaxanes development.

2 Material and Methods

2.1 General

All reagents and solvents were obtained from commercial suppliers and were used without further purification. All reactions, unless otherwise described, were performed under an inert atmosphere of dry nitrogen. Melting points were determined on an OptiMelt melting point apparatus. ^{1}H NMR spectra were recorded at 500 MHz “Bruker DRX500”. Mass spectra were measured with Agilent Technologies

GC 7820A Series / MSD 5975 Series. Elemental analyses were determined on Perkin Elmer 2400 series II analyzer at Volgograd State Technical University, Russia.

1-Isocyanato-3,5-dimethyladamantane (IV). First step. 6.9 g (0.058 mol) thionyl chloride was added to 10 g (0.048 mol) 3,5-dimethyladamantane-1-carboxylic acid (I) , which was then maintained at its bp for 90 min. Excess of thionyl chloride was distilled. Second step. 3,5-Dimethyladamantane-1-carbonyl chloride (II) acquired on first step was added dropwise to the boiling suspension of 3.15 g (0.048 mol) sodium azide at 88 g (0.96 mol) anhydrous toluene. Reaction mixture was maintained at its bp for 60 min. Then it was cooled, filtered and the excess of solvent was distilled. Crude product was purified by distillation in vacuum to afford transparent liquid (9.3 g, 95% yield). Bp 127°C/8 mm Hg. IR, ν, cm^{-1}: 2278 (NCO). MS (ESI) m/z: 205 (3%, $[M]^+$), 163 (100%, $[Ad(CH_3)_2]^+$).

2.2 General Procedure for the Synthesis of Diadamantyl Diureas V-XIII from Adamantine Amines and Diisocyanates

To the 1-aminoadamantane hydrochloride or (adamantan-1-yl)methanamine hydrochloride (1 mmol) in DMF (10 mL), corresponding diisocyanate (0.5 equiv) and triethylamine (1 equiv) was added at 0°C. The reaction mixtures were allowed to slowly warm to room temperature overnight. The reaction mixtures were poured into water, and the resulting precipitates were collected and washed with 1 N HCl solution followed by water. The crude product was purified by silica gel chromatography.

1,1-(Methylenebis(4,1-phenylene))bis(3-methyl(adamantane-1-yl)urea) (V). The general method above was used with (adamantan-1-yl)methanamine hydrochloride and bis(4-isocyanatophenyl)methane to afford a white solid (0.27 g, 93% yield). Mp 280.8-281.3°C. MS (ESI) m/z: 582 (36%, $[M+1]^+$). ^1H NMR (DMSO-d_6): 7.26-7.00 (dd, J = 130 Hz, 8H, aromatic), 6.04-6.01 (t, J = 7.5 Hz, 2H, 2NH), 3.73 (s, 2H, CH_2), 2.77-2.76 (d, J = 5 Hz, 4H, $2CH_2$).

1,2-(Ethylene)bis[(adamant-1-yl)urea] (VI). The general method above was used with 1-aminoadamantane hydrochloride to afford a white solid (0.2 g, 98% yield). Mp 240.4-241.0 MS (ESI) m/z: 414 (1.1%, $[M+1]^+$). Anal. ($C_{24}H_{38}N_4O_2$) C 69.55%, H 9.29%, N 13.46%.

1,2-(Ethylene)bis{[(adamant-1-yl)methyl]urea} (VII). The general method above was used with (adamantan-1-yl)methanamine hydrochloride to afford a white solid (0.21 g, 99% yield). Mp 211.0-212.3 °C. MS (ESI) m/z: 443 (0.9%, $[M+1]^+$). Anal. ($C_{26}H_{42}N_4O_2$) C 70.53%, H 9.57%, N 12.67%.

1,4-(Tetramethylene)bis[(adamant-1-yl)urea] (VIII). The general method above was used with 1-aminoadmantane hydrochloride to afford a white solid (0.43 g, 98% yield). Mp 251.1-253.4°C.^1H NMR (DMSO-d_6): δ 5.62-5.59 (t, J = 7.6 Hz, 2H), 5.42-5.41 (s, J = 13.4 Hz, 2H), 2.91-2.89 (dd, J = 33 Hz, 8H), 1.97-1.28 (m, 30H). MS (ESI) m/z: 443 (0.7%, $[M+1]^+$). Anal. ($C_{26}H_{42}N_4O_2$) C 70.45%, H 9.56%, N 12.61%.

1,4-(Tetramethylene)bis{(adamant-1-yl)methyl]urea} (IX). The general method above was used with (adamantan-1-yl)methanamine hydrochloride to afford a white solid (0.20 g, 99% yield). Mp 176.7-179.2°C.^1H NMR (DMSO-d_6): δ 7.66-7.63 (t, J = 13 Hz, 4H), 3.01-2.98 (d, 8H), 1.95-1.33 (m, 34H). MS (ESI) m/z: 470 (3.1%, $[M]^+$). Anal. ($C_{28}H_{46}N_4O_2$) C 71.45%, H 9.87%, N 11.87%.

1,6-(Hexamethylene)bis[(adamant-1-yl)urea] (X). The general method above was used with 1-aminoadmantane hydrochloride to afford a white solid (0.23 g, 98% yield). Mp 221.3-221.9°C. MS (ESI) m/z: 470 (0.8%, $[M+1]^+$). Anal. ($C_{28}H_{46}N_4O_2$) C 71.45%, H 9.86%, N 11.91%.

1,6-(Hexamethylene)bis{[(adamant-1-yl)methyl]urea} (XI). The general method above was used with (adamantan-1-yl)methanamine hydrochloride to afford a white solid (0.23 g, 96% yield). Mp 218,4-219,4°C. MS (ESI) m/z: 499 (3.5%, $[M+1]^+$). Anal. ($C_{30}H_{50}N_4O_2$) C 72.26%, H 10.06%, N 11.18%.

1,8-(Octamethylene)bis[(adamant-1-yl)urea] (XII). The general method above was used with 1-aminoadmantane hydrochloride to afford a white solid (0.47 g, 96% yield). Mp 256.3-257.8°C.^1H NMR (DMSO-d_6): δ 5.57-5.54 (t, J = 16 Hz, 2H), 5.38-5.36 (d, J = 20 Hz, 2H), 2.92-2.72 (m, 16H), 1.98-0.96 (m, 30H). MS (ESI) m/z: 499 (0.4%, $[M+1]^+$). Anal. ($C_{30}H_{50}N_4O_2$) C 72.30%, H 10.09%, N 11.31%.

1,8-(Oktamethylene)bis{[(adamant-1-yl)methyl]urea} (XIII). The general method above was used with (adamantan-1-yl)methanamine to afford a white solid (0.25 g, 98% yield). Mp 163.9-164.2°C.^1H NMR (DMSO-d_6): δ 5.68-5.65 (t, J = 3.5 Hz, 4H), 2.97-2.68 (m, 16H), 1.94-1.24 (m, 34H). MS (ESI) m/z: 527 (3.0%, $[M+1]^+$). Anal. ($C_{32}H_{54}N_4O_2$) C 73.02%, H 10.22%, N 10.54%.

2.3 General Procedure for the Synthesis of Adamantyl Ureas XIV and XV from 1-Isocyanato-3,5-Dimethyladamantane (IV) and Amines

To the 1-isocyanato-3,5-dimethyladamantane (1 mmol) in DMF (10 mL) corresponding amine (1 equiv) was added. The reaction mixtures were allowed to slowly warm to room temperature overnight. The reaction mixtures were poured into water, and the resulting precipitates were collected and washed with 1 N HCl solution followed by water. The crude product was purified by silica gel chromatography.

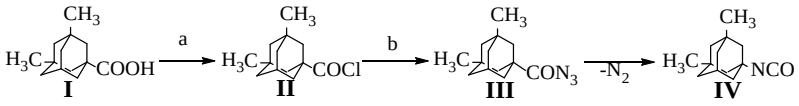
1-((-Adamantan-1-yl)methyl)-3-(3,5-dimethyladamantan-1-yl)urea (**XIV**). The general method above was used with (adamantan-1-yl)methanamine to afford a white solid (0.35 g, 96% yield). Mp 185.8-186.4°C. MS (ESI) m/z: 370 (15.0 %, $[M]^+$), 163 (41.0%, $[Ad(CH_3)_2]^+$), 135 (53.0%, $[Ad]^+$). Anal. ($C_{24}H_{38}N_2O$) C 77.78%, H 10.32%, N 7.54%.

1-((2-cyanoadamantan-2-yl)methyl)-3-(3,5-dimethyladamantan-1-yl)urea (XV). The general method above was used with (adamantan-1-yl)methanamine to afford a white solid (0.35 g, 96% yield). Mp 185.8-186.4°C. MS (ESI) m/z: 370 (15.0 %, $[M]^+$), 163 (41.0%, $[Ad(CH_3)_2]^+$), 135 (53.0%, $[Ad]^+$). Anal. ($C_{24}H_{38}N_2O$) C 77.78%, H 10.32%, N 7.54%.

3 Results and Discussion

As a starting material for the synthesis of disubstituted urea and diurea 1-isocyanato-3,5-dimethyladamantane, received by convenient method from the corresponding Acyl Azide on Curtius rearrangement [14] was used.

In the first step 3,5-dimethyladamantane-1-carboxylic acid (I) was treated by Thionyl Chloride to give 3,5-dimethyladamantane-1-carbonyl chloride (II). In the second step Carbonyl Chloride II was introduced into the exchange reaction with Sodium Azide in Toluene at its boiling temperature for 2 hours and gave the corresponding 3,5-dimethyladamantane-1-carbonylazide (III), which is then refluxed in Toluene without isolation until the complete allocation of Nitrogen. Azide undergone Curtius rearrangement into the 1-isocyanato-3,5-dimethyladamantane (IV), which was purified by vacuum distillation to yield up to 95% of the original acid:

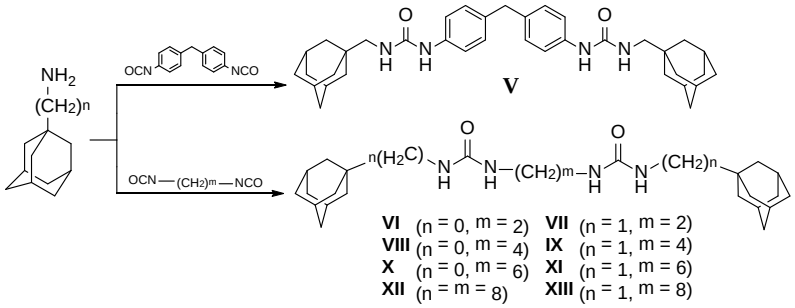


Scheme 1. Method for the preparation of 1-isocyanato-3,5-dimethyladamantane. a. $SOCl_2$, benzene, rt, 1h; b NaN_3, toluene, 110℃, 2h.

Methods described in the literature on the Curtius reaction involve the step of isolation and desiccation of the intermediate Azide, followed by its heating [17]. Heating of large amounts of Azide, even at low temperature with the strict observance of safety is potentially an explosive process.

We have improved the process as follows: the stages of formation of the Azide and its rearrangement have been combined into one step and held it in a single reactor. The acid chloride was added dropwise to a boiling suspension of Sodium Azide in Toluene. Thus, acid azide did not accumulate, and after the formation immediately rearranges into the Isocyanate. The amount of the acid azide was controlled by accounting of the Nitrogen evolved. Reaction rate was controlled by the chloride admission.

Synthesis of symmetric adamantyl-containing diurea was performed by the reaction of adamantyl-containing amines with Adamantane Isocyanates and symmetric diisocyanates with the 2:1 ratio:

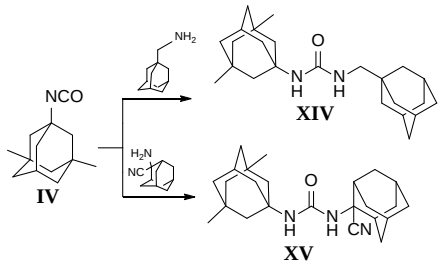


Scheme 2. Preparation of the ureas VI-XIII from (adamantan-1-yl)methanamine. Conditions: DMF, rt, 8h.

Reactions were carried out in DMF for 8 hours at room temperature. Adamantyl-containing diurea formed were poorly soluble in DMF, which facilitated their isolation and purification. Synthesis of the compounds V-XIII almost completely ended after 4 hours in DMF at room temperature with 94% yield.

Synthesis of unsymmetric adamantyl-containing urea XIV and XV was carried out by the reaction of Isocyanate IV with adamantyl-containing amines, with an amine group in the nodal, or in the bridge position: (adamantan-1-yl)methanamine and 2-aminoadamantane-2-carbonitrile, at an equimolar ratio of the initial reagents.

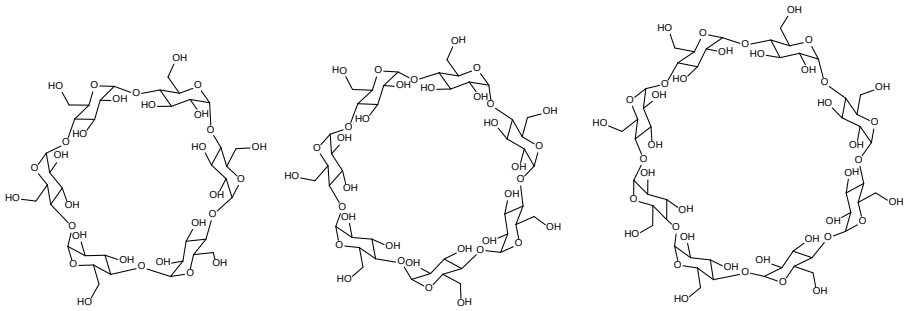
Those reactions also were carried out in DMF for 4 hours at room temperature. Adamantyl-containing urea produced was also poorly soluble in DMF, which resulted in the crystallization from the solution during the reaction. Yield reached 96%. All synthesized ureas and diureas V-XV, are white solids with high mp.



Scheme 3. Ureas synthesized from novel 1-isocyanato-3,5-dimethyladamantane. Conditions: DMF, rt, 4h.

It should be noted that the structure of the ureas and diureas are characterized by different length of the spacer, the presence of aliphatic and aromatic fragments, various amount of urea groups, as well as different structures of the adamantyl group (hub and bridge position, the presence or absence of substituents, different distance from the urea bonds). Moreover, the structure of the adamantyl group will influence the binding energy in the Cyclodextrine cavity, thereby determining the properties of the resulting supramolecular complexes.

New "host-guest" inclusion complexes of the diadamantyl-containing diureas with β-Cyclodextrine, which can form inclusion compounds with small molecules that are partially or fully included in the hydrophobic cavity of the Cyclodextrine were obtained. Using the method of complexation with Cyclodextrines should solve the problem of the water solubility of hydrophobic compounds, such as drugs, which eliminates the necessity of chemical modification of the drug introducing hydrophilic residues which can interfere with the membrane transport of the medicine. Cyclodextrines - are cyclic oligosaccharides consisting of several glucopyranose units, linked by α-1,4-glycosidic bonds. Due to the presence of a hydrophobic cavity, CDs possess the ability to form "host-guest" inclusion complexes. Depending on the number of Glucopyranose residues (6, 7 or 8), α-, β- and γ-Cyclodextrines are differentiated:



Scheme 4. α-, β- and γ-Cyclodextrinesas shown from left to right.

An important factor of complexation is the ratio of Cyclodextrin cavity size and "guest" molecule size. Adamantyl group is a spherical group with a diameter of 7 Å, which perfectly matches the β-Cyclodextrin cavity (see Fig. 1).

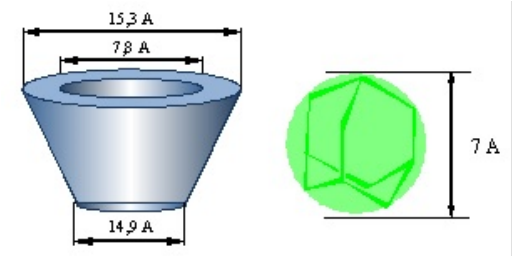


Figure 1. Comparison of the sizes of β-Cyclodextrin and Adamantane molecules.

Inclusion complexes of β-Cyclodextrin with adamantyl-containing ureas were obtained by traditional methods: by the co-grinding and co-precipitation method.

The co-grinding method: In a mortar β- Cyclodextrine (β- CD) was mixed with distilled water in a 1:1 ratio. The appropriate adamantyl-containing urea was added to the resulting suspension and trituration was continued in a mortar with pestle by adding a solvent and drying to a consistency of "thick cream" for 4 hours. The resulting suspension was placed in a desiccator overnight for drying. The dried mixture was triturated and washed with Ethyl alcohol and dried under a vacuum to constant weight.

The co-precipitation method: The aqueous solution of β-Cyclodextrine was heated to 70°C, a sample of adamantyl-containing urea was added under stirring, and stirring continued for 10 hours. As a result, the turbidity disappears with time, indicating the formation of an inclusion complex. The resulting solution was evaporated and the residue was washed with Ethanol and dried under a vacuum.

The choice of water as the solvent was made due to the fact that the driving force of molecular interaction of "guests" with β-Cyclodextrine cavity are hydrophobic interactions, thereby adamantyl-containing urea tends to avoid contact with the polar solvent molecules and occupy the cavity of the "host", which contributes to the formation of the complex. Co-precipitation complexes were isolated as white crystals (see Fig. 2).

Complexes were analyzed by ^{1}H NMR spectroscopy. The spectra along with the signals of protons of diureas represent proton signals of β-Cyclodextrin. Strong field displacement of H-3 and H-5 proton signals of β-Cyclodextrin was detected in the ^{1}H NMR spectra which indicates the formation of the internal inclusion complex.

Previously, Compound X was investigated as a human soluble Epoxide Hydrolase inhibitor [12]. IC_{50} of Compound X was reported to be 0.6 nM but it was insoluble in water and a phosphate buffer (0.1M Sodium Phosphate, pH 7.4) and barely soluble in DMSO. We decided to compare the inhibitory activity of Compound X and the activity of its complex with Cyclodextrin. IC_{50} of complex is 44.3 nM but it has good solubility in a phosphate buffer.

Figure 2. Crystals of the compound X complex with – Cyclodextrin acquired by the co-precipitation method.

4 Conclusion

Adamantyl-containing ureas and diureas, obtained by the reaction of Isocyanates with amines, can be used as molecular components for the synthesis of supramolecular complexes, in particular, Rotaxanes or as monomers for supramolecular Cyclodextrin polymers that were synthesized. Moreover, complexes of adamantyl-containing ureas with Cyclodextrin are water soluble and could be used for the drug delivery.

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