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^{13}C, ^{15}N and ^{113}Cd NMR and Molecular Orbital Studies of Novel Bile Acid *N*-(2-aminoethyl)amides and Their Cd^{2+}-complexes

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Abstract. Lithocholic acid *N*-(2-aminoethyl)amide (**1**) and deoxycholic acid *N*-(2-aminoethyl)amide (**2**) have been prepared and characterized by ^{1}H, ^{13}C and ^{15}N NMR. The accurate molecular masses of **1** and **2** have been determined by ESI MS. The formation of the Cd^{2+}-complexes (**1+Cd** and **2+Cd**) in CD_3OD solution have been detected by ^{1}H, ^{13}C, ^{15}N and ^{113}Cd NMR. The ^{13}C NMR chemical shift assignments of **1** and **2** and their Cd^{2+}-complexes are based on DEPT-135 and z-GS $^{1}H,^{13}C$ HMQC experiments as well as comparison with the assignments of the related structures. The ^{15}N NMR chemical shift assignments of the ligands and their Cd^{2+}-complexes are based on z-GS $^{1}H,^{15}N$ HMBC experiments. ^{13}C NMR chemical shift differences between **1** and its 1:1 Cd^{2+}-complex based on *ab initio* calculations at Hartree-Fock SCI-PCM level using 3-21G(d) basis set are in agreement with the experimental shift changes observed on Cd^{2+}-complexation.

Key words: bile acid amides, Cd^{2+}-complexes, ^{13}C, ^{15}N and ^{113}Cd NMR

1. Introduction

Bile acids possessing a hydroxy substituted steroidal framework and a flexible carboxylic acid side chain have been used as suitable building blocks in tailoring supramolecular hosts [1]. Consequently, the structural diversity and the variety of the molecular recognition properties of these steroidal hosts are increasing rapidly [2]. It has also been shown that significant advantages are achieved when hydroxyls are replaced by amino functionalities in constructing synthetic reseptors, novel amphiphiles and scaffolds for the assembly of combinatorial libraries [3]. Further, it is also known that bile acids generally exist in bile in the form of amino acid conjugates [4].

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Therefore, in order to tailor bile acid conjugates suitable for specific recognition of (cat)ions it is reasonable to introduce amino moieties into these structures. An approach is to attach diaminoalkanes to the carboxyl functionality of the bile acid and study the complex formation properties of these derivatives towards metal cations such as Cd^{2+}.

From the biochemical point of view it is interesting that cadmium can replace zinc and calcium in many biologically important molecules. Advantages of cadmium in comparison with zinc and calcium are that cadmium is much easier to detect by NMR and there exist good review articles on recent achievements in this area of chemistry [5]. This offers an efficient scope to investigate these nitrogen containing structures. Our present work is a continuation of our recent investigation on Ag^{+}-cation complexation with the molecular clefts derived from isomeric pyridine carboxylic acids and lithocholic acid ethane-1,2-diol diester [6]. As an example of the specificity of the complex formation among these compounds the above mentioned pyridine derivatives did not show a clear complexation tendency with Cd^{2+}-cation differing from the amine derivatives studied in this work.

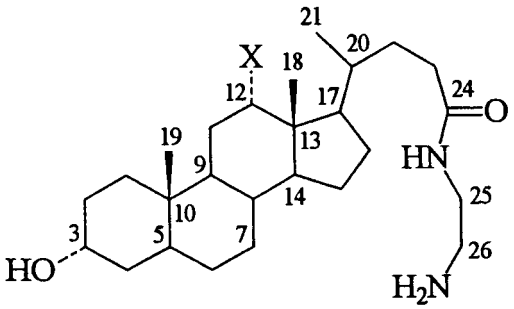
2. Experimental

2.1. COMPOUNDS

Lithocholic acid (3α-hydroxy-5β-cholan-24-oic acid) and deoxycholic acid (3α, 12α-dihydroxy-5β-cholan-24-oic acid) were 98% products from Aldrich. Their *N*-(2-aminoethyl)amides **1** and **2** were prepared by a reaction of their methyl esters with 1,2-diaminoethane in methanol [7]. The reaction mixture was evaporated to dryness. The products were purified by repeated washing with chloroform. The yields were almost quantitative. All attempts to prepare symmetrical diamides failed. The Cd^{2+}-complexation experiments of **1** and **2** were done by i) adding an equimolar amount of $Cd(NO_3)_2{\cdot}4H_2O$ to a 0.1 M solution of the ligands in CD_3OD and ii) then adding $Cd(NO_3)_2{\cdot}4H_2O$ to the solution until the ^{113}Cd NMR signal of solvated Cd^{2+}-cation was clearly visible and finally the solution was saturated by the salt. 1-Hexanoic acid *N*-(2-aminoethyl)amide used as a model compound was prepared via the reaction of 1-hexanoyl chloride (prepared from the acid by $SOCl_2$ treatment) and 1,2-aminoethane [8].

2.2. NMR AND MS

All ^{1}H,^{13}C and ^{113}Cd NMR experiments were carried out with a Bruker Avance DRX 500 NMR spectrometer equipped with a 5 mm diameter broad band direct probehead working at 500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C and 110.94 MHz for ^{113}Cd, respectively. The ^{13}C NMR chemical shift assignments are based on our previous studies on related structures [9], DEPT-135 and ^{1}H, ^{13}C HMQC [10, 11] experiments. The ^{1}H, ^{15}N HMBC experiments [12] have been run with a Bruker Avance DRX 500 or DPX 250 NMR spectrometer equipped with a 5 mm



Scheme 1. Structures and numbering of **1** (X=H) and **2** (X=OH).

diameter broad band inverse probehead and using z-gradient selection working at 500.13/250.13 MHz for ^{1}H and 50.70/25.35 MHz for ^{15}N, respectively.

In ^{1}H NMR experiments the spectral width was 2500 Hz, the number of data points 32 K and the number of scans 8 with a flip angle of 30°. The FIDs were apodized by an exponential window function of point resolution prior to FT. The ^{1}H NMR chemical shifts are referenced to the residual signal of partly deuterated solvent, $\delta(CD_2{}^{1}H) = 3.31$ ppm.

In proton composite pulse decoupled (Waltz-16) ^{13}C NMR experiments the spectral width was 27 000 Hz, the number of data points 65 K and the number of scans 1000 with a flip angle of 30°. The FIDs were apodized by an exponential window function of the point resolution prior to FT. The ^{13}C NMR chemical shifts are referenced to the signal of solvent, $\delta(^{13}CD_3) = 49.0$ ppm.

^{113}Cd NMR experiments were done without proton decoupling. The spectral width was 67 000 Hz, the number of data points 65 K and number of scans varied from 10 000 to 50 000. The FIDs were apodized by an exponential window function of 50–100 Hz prior to FT. The ^{113}Cd NMR chemical shifts are referenced to the signal of external 0.1 M aqueous $Cd(ClO_4)_2$ in a 1 mm diameter capillary tube inserted coaxially inside the NMR tube, $\delta(^{113}Cd) = 0.0$ ppm.

In $^{1}H,^{13}C$ HMQC experiments the dimension of the f_1-axis (^{1}H) was 2500 Hz/256 points and that of the f_2-axis (^{13}C) was 9000 Hz/512 points. 64 scans were accumulated for every f_2-increment (f_1-spectrum). Shifted sinebell window functions were used along both axes prior to FT.

In $^{1}H,^{15}N$ HMBC experiments the dimension of the f_1-axis (^{1}H) was 2500 Hz/256 points and that of the f_2-axis (^{15}N) was 22 500 Hz/512 points. A 50 ms delay was used for the evolution of long-range couplings. 64 scans were accumulated for every f_2-increment. Sinebell window functions were used along both axes prior to FT. The ^{15}N NMR chemical shifts are referenced to the signal of external ^{15}N-enriched nitromethane in a 1 mm diameter capillary tube inserted coaxially inside the NMR tube, $\delta(^{15}N) = 0.0$ ppm.

The molecular masses of compounds **1** and **2** were determined by electro-spray ionization using a Bruker (Bruker Daltonics, Billerica, USA) BioAPEX^{TM}47e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 4.7

Tesla, 160 mm bore superconducting magnet (Magnex Scientific Ltd, Abingdon, UK), Infinity^{TM} cell and electrospray source (Analytica of Branford Inc., Branford, CT, USA). Sample solutions were continuously introduced to the interface sprayer through a glass microliter syringe at a flow rate of 40 μl/h under atmospheric pressure. A 50:50:1 mixture of methanol:water:acetic acid was used as a solvent, the sample concentration being 1 pM/μl. Under these conditions only protonated molecules were observed.

The measurements were made in the broad band mode with a resolution of $\geq$25000. The instrument was calibrated using sodium trifluoroacetate as external calibrant [13]. For accurate mass measurement a single scan was collected otherwise the spectra represented the average of 16 scans. The average precision of the accurate mass measurements was better than 5 ppm for six measurements.

Compound **1**: $[M + H]^+$, $C_{26}H_{47}N_2O_2$, calculated mass 419.3632, measured mass 419.3628, mass deviation 1.2×10^{-4}. Melting point 162–165 °C. Compound **2**: $[M + H]^+$, $C_{26}H_{47}N_2O_3$, calculated mass 435.3581, measured mass 435.3579, mass deviation 2.3×10^{-4}. Melting point 119–121 °C.

2.3. MOLECULAR ORBITAL CALCULATIONS

The geometry of compound **1** was initially fully optimized at the PM3 [14] level on a Silicon Graphics O2 workstation by using SPARTAN software [15]. After that the side chain of **1** with and without Cd^{2+}-cation in methanol was optimized at the *ab initio* Hartree-Fock (HF) level using the 3-21G(d) basis set and Self-Consistent Isodensity Polarized Continuum model (SCI-PCM) on a Silicon Graphics Origin 200 workstation by Gaussian 94 software [16]. Finally, the optimized substructures in methanol were used to compute ^{13}C NMR chemical shift changes on complex formation.

3. Results and Discussion

The scheme describes the structures and numbering of lithocholic and deoxycholic acid *N*-(2-aminoethyl)amides **1** and **2** derived from methyl litho- or deoxycholate and 1,2-diaminoethane [7]. Tables I and II show the ^{13}C, ^{15}N and ^{113}Cd NMR chemical shifts (δ/ppm) measured in CD_3OD for **1**, **2**, **1 + Cd** and **2 + Cd**. The z-gradient selected ^{1}H,^{15}N HMBC contour map of **1** produced with a Bruker Avance DPX 250 spectrometer for saturated CD_3OD solutions at 30 °C using 100 ms delay for evolution of long-range couplings is described in Figure 1. Table III contains the experimental and calculated ^{13}C NMR chemical shift changes ($\Delta\delta$/ppm) of **1** on Cd^{2+}-complexation. These calculations have been done at *ab initio* HF SCI-PCM level using 3-21G(d) basis set and limited only to one case (**1**) owing to their very CPU-time invasive character.

Table I. ^{13}C NMR chemical shifts (ppm from CD_3OD δ = 49.0 ppm) of lithocholic acid *N*-(2-aminoethyl)amide **1** and deoxycholic acid *N*-(2-aminoethyl)amide **2** and their cadmium complexes, **1 + Cd** and **2 + Cd**

	$\delta(^{13}C)$/ppm			
Carbon	**1**	**2**	**1 + Cd**	**2 + Cd**
1[a]	36.52	36.46	36.18	36.39
2	31.22	31.10	30.82	31.00
3	72.37	72.52	72.30	72.48
4[a]	37.20	37.24	36.78	37.15
5	43.53	43.64	43.18	43.54
6[b]	28.38	28.42	28.05	28.36
7[b]	27.67	27.48	27.35	27.42
8[c]	37.23	37.46	36.90	37.38
9	41.88	34.83	41.52	34.75
10	35.68	35.31	35.34	35.23
11	21.97	29.94	21.66	29.85
12	41.54	73.99	41.18	73.93
13	43.91	47.57	43.57	47.50
14	57.91	49.29	57.51	49.18
15	25.29	24.87	25.00	24.85
16[b]	29.26	28.66	28.92	28.62
17	57.43	48.07	57.03	47.98
18	12.57	13.22	12.30	13.22
19	24.01	23.73	23.72	23.70
20[c]	36.86	36.87	36.56	36.84
21	18.94	17.71	18.65	17.70
22[d]	34.15	34.15	33.80	34.06
23[d]	33.26	33.26	32.72	33.02
24	176.98	177.14	178.33	178.41
25	43.02	43.03	40.36	42.84
26	42.03	42.04	42.08	41.53

[a,b,c,d]Assignments may be interchanged.

3.1. NMR SPECTROSCOPY

The formation of Cd^{2+}-complexes in solution is detected unambiguosly by their ^{113}Cd NMR chemical shifts (Table II) which differ significantly from that of the salt itself, $Cd(NO_3)_2 \cdot 4H_2O$, in CD_3OD. The latter is shifted upfield (shielded) from the shift of the reference [0.1 M aqueous $Cd(ClO_4)_2$], $\delta(^{113}Cd)$ = 0 ppm, while those of

Table II. ^{15}N NMR chemical shifts (ppm from ext. neat CH_3NO_2, δ = 0.0 ppm) and ^{113}Cd NMR chemical shifts (ppm from ext. aqueous 0.1 M $Cd(ClO_4)_2$, δ = 0.0 ppm) of **1** and **2** and their Cd^{2+}-complexes

Compound	Solvent	$\delta(^{15}N/ppm)$		$\delta(^{113}Cd/ppm)$
		NH_2	NHCO	
1	$CDCl_3$	−362.0	−268.0	–
1[a]	CD_3OD	−364.0	−263.7	–
1 + Cd[b]	CD_3OD	−370.3	−263.0	92
2[a]	CD_3OD	−364.2	−263.8	–
2 + Cd[b]	CD_3OD	−360.0	−263.6	84

[a]Saturated solution; [b] solution saturated with $Cd(NO_3)_2{\cdot}4H_2O$.

Table III. Experimental and calculated ^{13}C NMR chemical shift changes ($\Delta\delta$/ppm) of **1** on complex formation with Cd^{2+}-cation

Carbon	$\Delta\delta$/ppm	
	Exp.	Calc.
22	+0.35	+0.47
23	+0.54	+0.71
24	−1.35	−3.50
25	+2.66	+1.98
26	−0.05	−0.12

the complexes are strongly deshielded (Table II). In the ^{13}C NMR chemical shifts there also exist some changes observed on $Cd(NO_3)_2{\cdot}4H_2O$ addition but not so clear as those detected by ^{113}Cd NMR. The most significant changes take place in the ^{13}C NMR chemical shifts of C-24 (carbonyl) and C-25 (methylene carbon next to NH). The ^{13}C NMR chemical shifts of the hydroxyl bearing carbon C-12 in **2** and **2 + Cd** do not differ significantly supporting the above reasoning that the Cd^{2+}-cation does not complex with that site of the molecule.

^{113}Cd NMR experiments are also useful in observing the complexation strengths between **1** and **2**. Deoxycholic acid derivative **2** complexed Cd^{2+}-cation remarkably easier than the lithocholic acid derivative **1**. At a weighed 1:1 stoichiometric ratio of the ligand:$Cd(NO_3)_2{\cdot}4H_2O$, the ratio of complexed and free cadmium was 1:10 for **1** and 7:10 for **2**, respectively. This difference between **1** and **2** can be explained by solvent effects and/or differences in molecular self-association

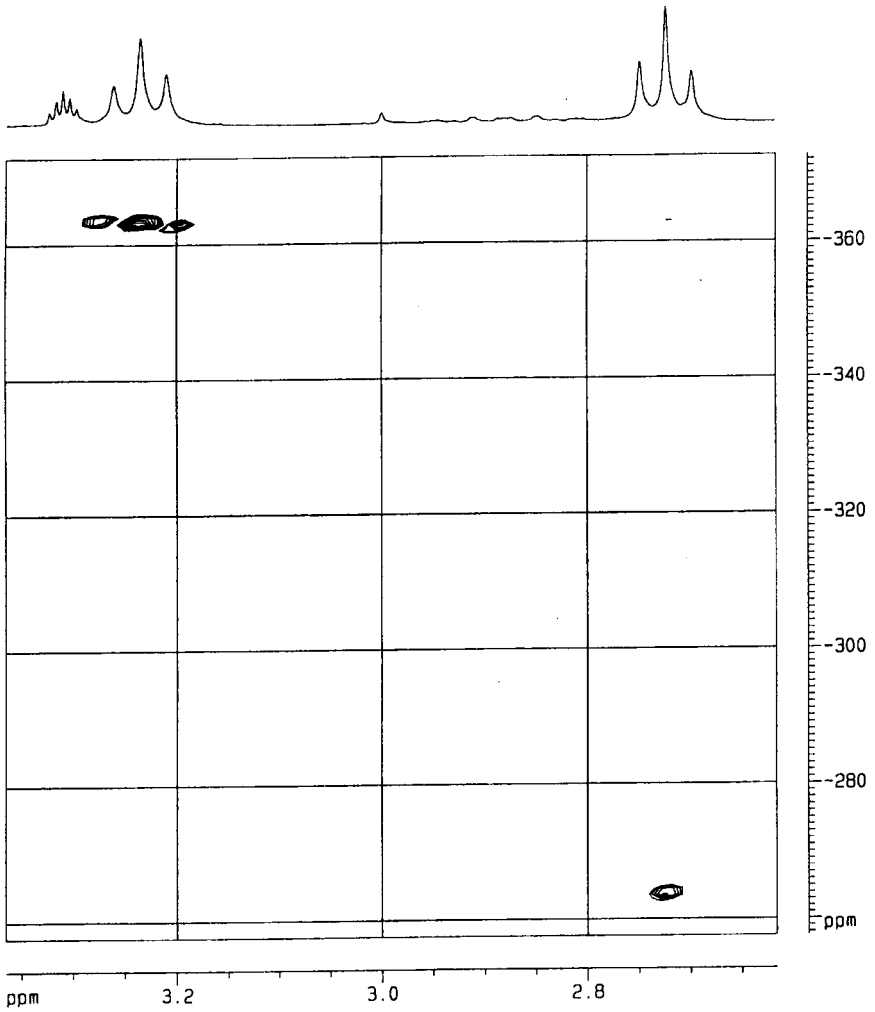


Figure 1. z-GS ^{1}H, ^{15}N HMBC contour map of **1**.

properties (aggregate formation) which are typical for bile acid amine conjugates [17].

The ^{113}Cd NMR chemical shifts for **1 + Cd** and **2 + Cd** are 92 and 84 ppm, respectively, when the solutions of their ligands are saturated by $Cd(NO_3)_2 \cdot 4H_2O$ (Table II). These values suggest that at these conditions the Cd^{2+}:ligand molar ratio is 1:1 otherwise the ^{113}Cd NMR chemical shifts of the complexes should be much more deshielded, as observed for $[Cd(en)3]^{2+}$ type complexes [18]. This different behavior is understandable taking into account the larger size of the bile acid derived ligands **1** and **2** when compared with those of diaminoalkanes. It indicates that in addition to the bile acid amide ligand there must be solvent molecules coordinated with Cd^{2+}-cation in these complexes to satisfy the coordination de-

mands of cadmium. That was one reason why the computationally heavy SCI-PCM model was used in the present theoretical calculations. Unfortunately, all attempts to measure samples at lower temperatures to slow down the chemical exchange and to see whether various complexed forms are present as in the case of pyridine complexes in ethanol at -90 °C [18] failed owing to sample precipitation and the poor quality of the spectra.

The ^{15}N NMR chemical shifts of NH_2-nitrogens also show some changes upon Cd^{2+}-complexation. Unfortunately, there are no reference data so far on the ^{15}N NMR of cadmium complexes. The different complexation strengths and opposite signs of the ^{15}N NMR chemical shift changes of N-1 in **1** and **2** upon complexation suggest that the bile acid moiety also has some influence on the complex formation, probably by differences in the self-association behavior of bile acid amine conjugates as proposed before. On the other hand, the sensitivity of the ^{15}N NMR chemical shifts on solvent and concentration effects does not suggest more far reaching conclusions. In any case the amide bond formation causes a very strong deshielding effect on the nitrogen-15 chemical shift as reported before for example in the case of dipeptides [19].

In order to deepen the insight into the the role of bile acid moieties in the Cd^{2+}-complex formation NMR experiments with model compounds have also been performed. First, 0.1 M deoxycholic acid in CD_3OD was saturated by $Cd(NO_3)_2 \cdot 4 H_2O$ and the ^{13}C NMR spectrum of this mixture was recorded. Any significant changes in the ^{13}C NMR chemical shifts of deoxycholic acid, however, were not observed. The variation in the chemical shifts of C-3, C-7 and C-24 (possible sites for complexation) was less than 0.1 ppm. In agreement with this ^{13}C NMR experiment, ^{113}Cd NMR showed only the signal of the solvent complexed Cd^{2+}-cation. The solubility of lithocholic acid in methanol was so small that experiments with bile acids was limited only to deoxycholic acid. Second, 0.1 M 1-hexanoic acid *N*-(2-aminoethyl)amide was saturated by $Cd(NO_3)_2 \cdot 4H_2O$ and the ^{13}C NMR spectrum of this solution was recorded. Now, clear changes were observed in the chemical shifts of the C=O-group as well as in the CH_2-signals of the ethyl amino moiety as in the case of bile acid amides. The $\Delta\delta$-values were -0.27 (**C**=O), +1.08 (NH**C**H_2) and +0.40 ppm (**C**H_2NH_2), respectively.

These experiments reveal that the complexation site in bile acid amides must also be the $CONH(CH_2)_2NH_2$-moiety and the 3α-OH and 12α-OH-substituents are not directly involved in the complexation. On the other hand, owing to some differences in the ^{13}C NMR chemical shift changes between bile acid and 1-hexanoic acid amides, there can be some forms where the bile acid aggregation can stabilize the Cd^{2+}-complexes formed. However, the verification of all possible forms in this kind of dynamic system by NMR alone is a very tedious task and beyond the scope of this work. Unfortunately, all attempts to grow single crystals for X-ray diffraction studies failed.

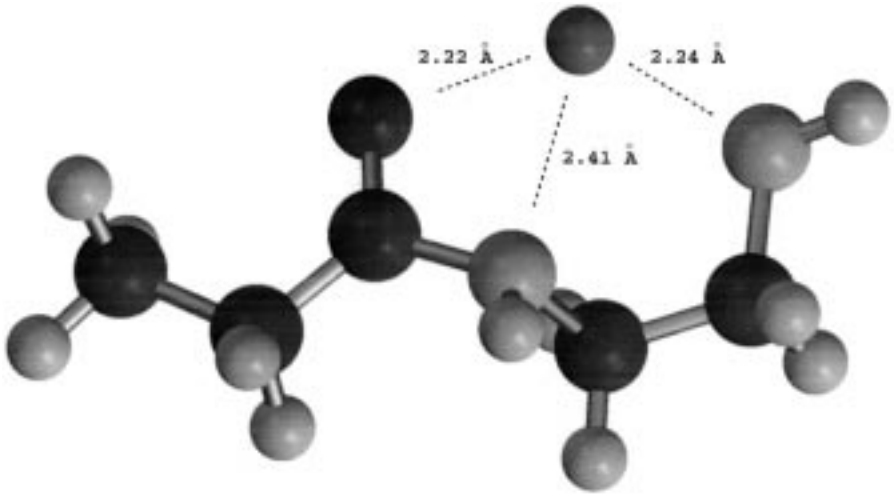


Figure 2. The energetically most stable partial structure for **1**:**Cd**$^{2+}$-complex.

3.2. MO CALCULATIONS

As mentioned above the final optimizations of the structures of ligand **1** and the complex **1 + Cd** have been done at *ab initio* HF SCI-PCM level using the 3-21G(d) basis set. Calculations were limited only to one case owing to their very CPU-time invasive character: it is reasonable to assume that an additional hydroxyl at the 12α-position in **2** does not markedly influence the complexation behavior of Cd^{2+} with the —$CONH(CH_2)_2NH_2$ moiety. This hypothesis is also supported by NMR experiments as mentioned before. Figure 2 illustrates the energetically most favourable three-coordinated structure of Cd^{2+}-cation with the above mentioned fragment. This structure is also in agreement with the experimental NMR data because clear changes are also observed on the complexation in the ^{13}C NMR chemical shift of C-24. As mentioned before the ^{113}Cd NMR chemical shifts of the complexes suggest 1:1 stoichiometry. Therefore, the Cd^{2+}-complex with two bile acid derived ligands (1:2 stoichiometry) has not been considered as a potential structure to be studied and omitted from our theoretical calculations. Another reason is that those calculations would be very computational capacity and time consuming.

4. Conclusions

Multinuclear magnetic resonance methods can provide a versatile tool in characterizing the Cd^{2+}-complexes of bile acid amine conjugates. Especially useful is ^{113}Cd NMR which can be utilized in mimicking the complexation of the biochemically more important (non-toxic) Ca^{2+}- and Zn^{2+}-ions. Further, modern calculational methods with enormously increased computational power can predict ^{13}C NMR chemical shift changes at least qualitatively correctly.

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