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Article

Adjusting the structure of β-cyclodextrin to improve complexation of anthraquinone-derived drugs

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Abstract: β-cyclodextrin (CD) derivatives containing aromatic triazole ring were studied as potential carriers of drugs containing an anthraquinone moiety in the structure: anthraquinone-2-sulfonic acid (AQ2S), anthraquinone-2-carboxylic acid (AQ2CA) and a common anthracycline, daunorubicin (DNR). UV-Vis and voltammetry measurements were carried out to determine the solubilities and stability constants of the complexes formed and revealed the unique properties of the chosen CDs as effective pH dependent drug complexing agents. The stability constants of the drug complexes with the CDs containing triazole: βCDLip and βCDGAL were significantly larger than with the native βCD. The AQ2CA and AQ2S drugs are ill-soluble and their solubilities increased as the result of complex formation with βCDLip and βCDGAL ligands. AQ2CA, AQ2S were negatively charged at pH 7.4 and therefore they were less prone to form inclusion complex with the hydrophobic CD cavity than at pH 3 (characteristic of gastric juices) when they were protonated. βCDTriazole and βCDGAL ligands were found to form weaker inclusion complexes with the positively charged drug DNR at acidic pH (pH 5.5) than in the neutral medium (pH 7.4) when the drug dissociates to the neutral, uncharged form. This pH dependence is favorable for anti-tumor applications.

Keywords: cyclodextrins; anthraquinone-2-sulfonic acid; anthraquinone-2-carboxylic acid; daunorubicin; stability constant; solubility; inclusion complex

1. Introduction

Anthraquinone (AQ) derivatives constitute a large and diverse group, many of which have therapeutic properties and are used as chemotherapeutic,[1,2] antiviral,[3] immune-boosting [4] or anti-inflammatory agents.[5] They are considered as promising scaffolds for the development of antiviral drugs against SARS-CoV-2.[6, 7] They are also used as laxatives [8] for the treatment of malaria [9,10] and multiple sclerosis.[11] 6-methyl-1,3,8-trihydroxyanthraquinone (emodine) is investigated for the treatment of neurodegenerative diseases and was reported to inhibit the pathological aggregation of tau protein. It was shown to protect from beta-amyloid-induced or H_2O_2 induced cortical neuronal deaths. [12-15] The synthetic quinone anthraquinone-2-sulfonic acid (AQ2S, Scheme 1) studied in this work has a specially strong protective effect towards primary neurons and the neuroprotective mechanisms of AQ2S are related to caspase inhibition. [16] Another drug, anthraquinone-2-carboxylic acid (9,10-dihydro-9,10-dioxo-2-

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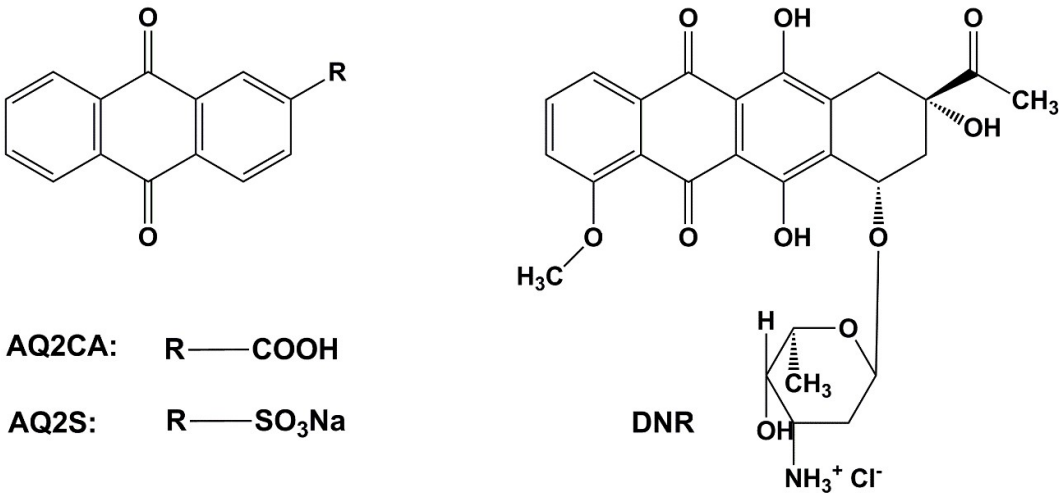
anthracenecarboxylic acid, (AQ2CA, Scheme 1) has been shown to alleviate various inflammatory and pain symptoms, including EtOH/HCl and acetylsalicylic acid (ASA) gastritis and to inhibit the expression of inflammatory genes and acts as potent anti-inflammatory ingredient in vivo, contributing to the regulation of the immune system.[17]



Scheme 1. Structure of anthraquinone-2-sulfonic acid (AQ2S), anthraquinone-2-carboxylic acid (AQ2CA) and daunorubicin (DNR).

Anthracyclines are a different anthraquinone derivatives group used to treat various types of cancer. The most popular representatives of anthracyclines daunorubicin (DNR, Scheme 1) and doxorubicin are among the most effective anti-cancer drugs so far. They are used, among others, in the treatment of acute lymphocytic and myeloid leukemias, lymphomas, bladder cancer, breast and brain cancer.[18-20] The cytostatic and cytotoxic effects of anthracyclines are explained by different mechanisms including their interaction with topoisomerase II which promotes growth arrest and apoptotic death of the tumor cells. It is also known that anthracyclines anthraquinone moiety intercalates between adjacent DNA base pairs which leads to the inhibition of DNA and RNA synthesis, especially in highly replicating cells.[21]

Despite the wide range of applications of anthraquinone-based pharmaceuticals, these drugs also have serious limitations as they have negative side effects during therapy. They have the ability to generate reactive oxygen species (ROS) in the presence of cytochrome P450 reductase, NADH dehydrogenase and xanthine oxidase, Scheme 2. The excess ROS cannot be detoxified, which causes oxidative stress, DNA damage and lipid peroxidation, triggering cell apoptosis. This is a minor process for cancer cells, but ROS also damages healthy tissues in the body. The most dangerous side effect of anthracycline is cardiotoxicity. [22]

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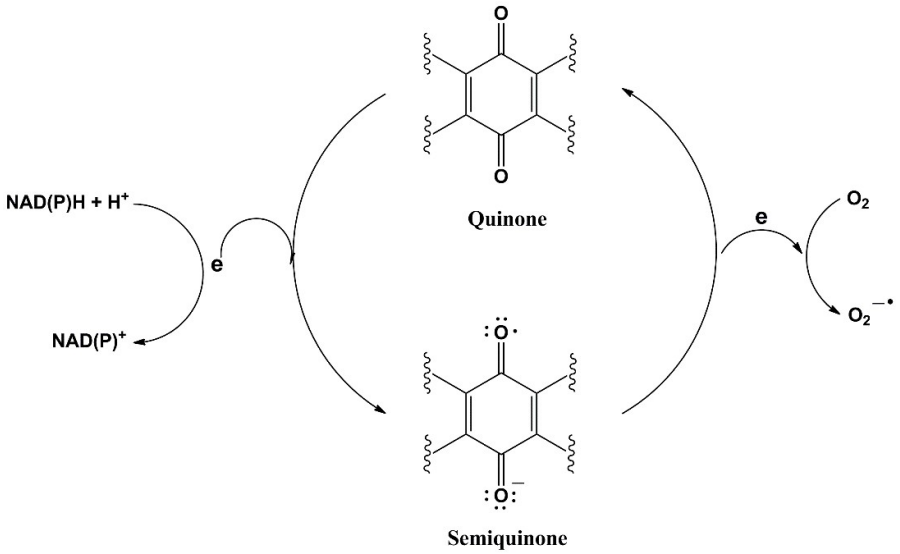
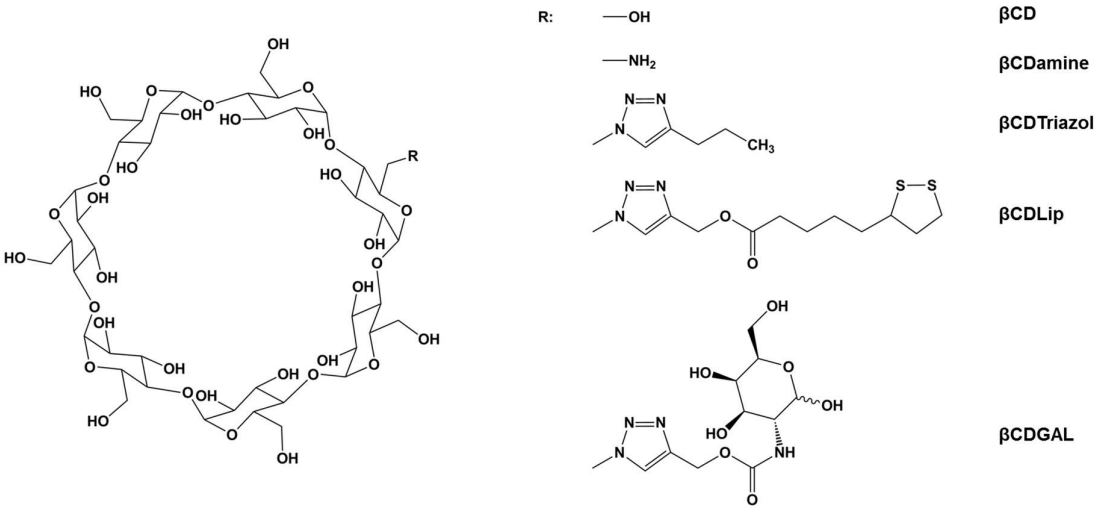


Scheme 2. Reactive oxygen species (ROS) production in the presence of NADH

Another disadvantage of anthraquinone - based drugs is their limited solubility in aqueous solutions.[23] The presence of hydrophilic substituents such as sugar substituents may improve solubility, however, changes also the therapeutic properties of these drugs. The solubility depends on the pH of the solution, leading to reduced absorption of drugs, and, thus, reduced bioavailability and therapeutic effect.[24]

These negative properties of anthraquinone derivatives, such as poor solubility, or production of reactive oxygen species, can be decreased by encapsulating the drug molecules in carriers [25, 26] e.g. binding them in the cavities of cyclic oligosaccharides, cyclodextrins (CD). The CD structure with its hydrophobic cavity allows formation of an inclusion complex with hydrophobic drugs (Scheme 3). Additionally, the presence of free hydroxyl groups outside the oligosaccharide ring allows CDs to be modified with substituents that influence the strength of drug binding.[27, 28]



Scheme 3. Structures of β cyclodextrin and its derivatives used in the present work.

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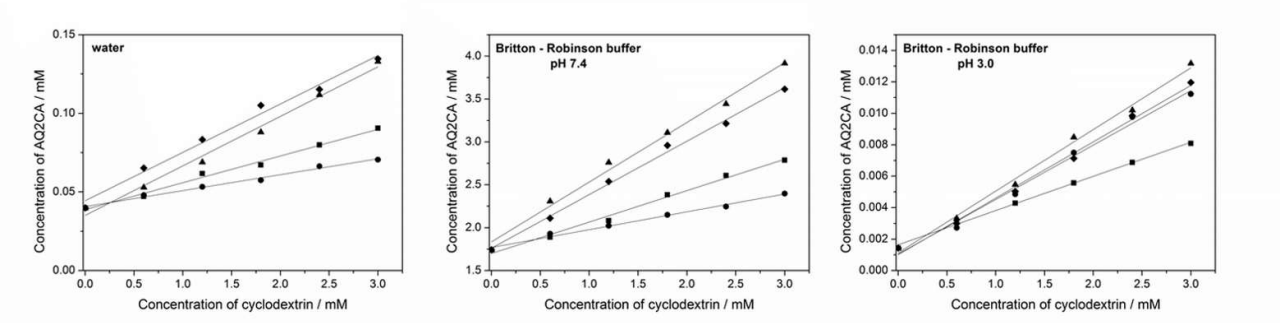
In this work we show that by using appropriate CD derivatives as carriers of anthraquinone-based drugs (Scheme 3) we can improve both the solubility of the drug and increase the strength of the complex with the drug paving the way to decreasing of the unwanted side effects of these drugs connected with ROS production, membrane permeability and solubility limitations.

2. Results and Discussion

2.1. Tuning β cyclodextrin structure to improve the solubilities of the AQ2CA and AQ2S drugs

Anthraquinone-2-carboxylic acid (AQ2CA) is a poorly water-soluble drug ($S_{AQ2CA\ in\ water}$ = 3.98×10^{-5} M). The solubility of AQ2CA in Britton-Robinson buffer, pH 7.4 is 1.74×10^{-3} M) while in acidic solution (Britton-Robinson buffer pH 3.0), it is significantly lower (S_{AQ2CA} = 1.43×10^{-6} M). Improvement in aqueous solubility of AQ2CA, would improve the biological availability of the drug. Such drug solubilisation effect was achieved by complexation using appropriate CD derivatives. The phase solubility method developed by Higuchi and Connors, was employed to quantify the solubilisation ability of cyclodextrins.[29] The solubility values of AQ2CA in water, BR buffer at pH 7.4 (pH corresponding to the physiological conditions) and at pH 3.0 with addition of CDs was determined. The pH characteristic for the body fluids (pH 7.4) and for gastric juices (pH 3) were chosen for these measurements. The solubility diagrams (Figure 1) show that the solubility of anthraquinone-2-carboxylic acid increases linearly with the increase of cyclodextrins concentration (correlation coefficient >0.99) up to 3 mM. According to Higuchi and Connors classification [29], the phase solubility diagrams for anthraquinone-2-carboxylic acid with various cyclodextrin concentrations can be classified as A_L type. The diagrams, with linear correlation and a slope lower than one, were characteristic for 1:1 complexation between the guest (AQ2CA) and host (cyclodextrin) molecules and suggest that well-soluble AQ2CA-CD complex was formed in the solution. The most spectacular increase in solubility was obtained in the presence of βCDLip and βCDGAL (almost tenfold increase in solubility at pH 3.0).



(**a**) (**b**) (c)

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Figure 1. Phase solubility diagrams of the inclusion complexes of AQ2CA with: βCD (■), βCDamine (●), βCDLip (◊) and βCDGAL (▲) in (a) water, Britton-Robinson buffer at pH (b) 7.4 and (c) 3.0.

The stability constant of AQ2CA-cyclodextrin complex (1:1) was calculated from the linear plot of the phase solubility diagrams using Equation 1. The K_s, corresponding slopes and correlation coefficients of the phase solubility diagrams, are presented in Table 1.

Table 1. Solubility increase (%) of AQ2CA, stability constant (K_s), slope and correlation coefficient (R^2) obtained from the AQ2CA-cyclodextrin phase solubility diagrams in water, Britton-Robinson buffer at pH 7.4 and 3.0.

Water			
Cyclodextrin	Solubility[a] increase (%)	K_s [M^{-1}]	R^2
βCD	128	460 ± 45	0.9911
βCDamine	77	280 ± 30	0.9900
βCDLip	238	800 ± 40	0.9880
βCDGAL	234	840 ± 45	0.9896
Britton-Robinson buffer pH 7.4			
Cyclodextrin	Solubility[b] increase (%)	K_s [M^{-1}]	R^2
βCD	60	350 ± 40	0.9913
βCDamine	38	160 ± 20	0.9906
βCDLip	108	940 ± 25	0.9961
βCDGAL	125	1300 ± 60	0.9932
Britton-Robinson buffer pH 3.0			
Cyclodextrin	Solubility[c] increase (%)	K_s [M^{-1}]	R^2
βCD	464	1480 ± 180	0.9965
βCDamine	683	2450 ± 200	0.9910
βCDLip	734	2520 ± 175	0.9940
βCDGAL	820	2760 ± 110	0.9945

[a] Solubility in water without CDs - 0.01 mg/ml

[b] Solubility in Britton-Robinson buffer pH 7.4 without CDs – 0.44 mg/ml

[c] Solubility in Britton-Robinson buffer pH 3.0 without CDs – 0.00036 mg/ml

The phase solubility diagrams (Figure 1) and the stability constant values (K_s) values reported in Table. 1, βCDLip and βCDGAL reflect enhanced solubilizing effect and larger stability constants of the complexes formed with these ligands. Complexes with βCD and βCDamine are weaker especially in neutral solutions. The stronger βCDLip and βCDGAL, effect is related to the presence of aromatic triazole ring in their structures, which contributes to the strengthening of the complex through proton-acceptor π-π interactions with the aromatic ring of the drug.[30] These results confirm the beneficial effect achieved thanks to appropriate modification of the cyclodextrin. Larger stability constants in the

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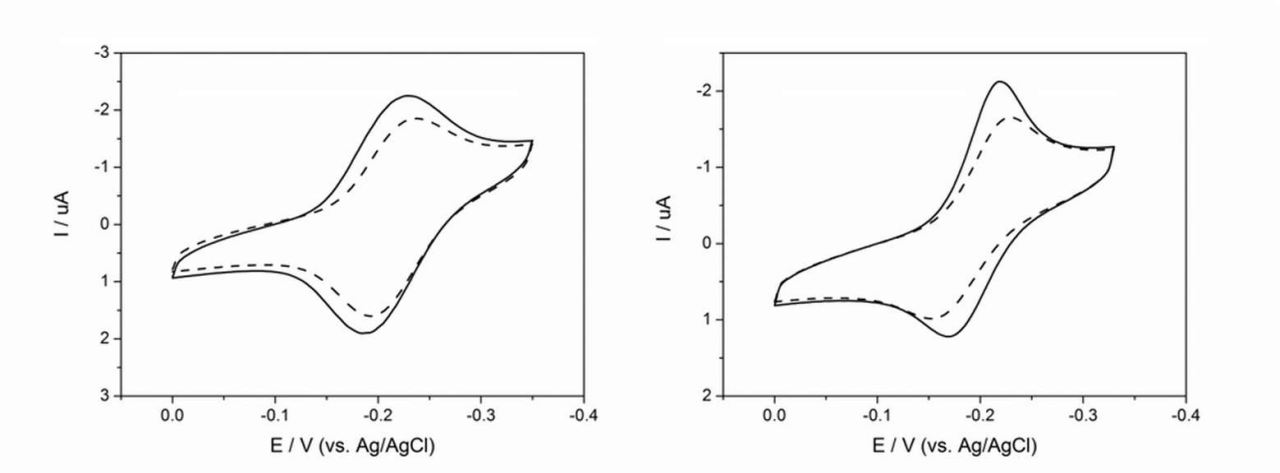
proton-rich environment (pH 3.0), are connected with the form of the drug. At pH 3.0, AQ2CA is in neutral (protonated) form, while at pH 7.4 it is anionic. The lower stability constants at pH 7.4 reflect the lower affinity of the charged drug molecule to the hydrophobic cavity of the cyclodextrin.

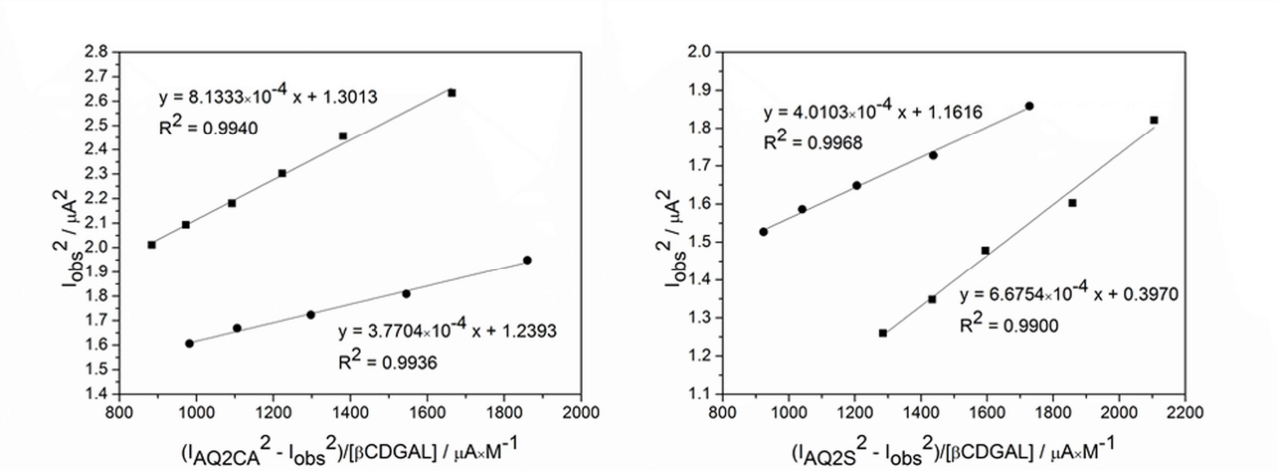
The stability constants of AQ2CA and another drug, AQ2S-cyclodextrin complexes were also determined by voltammetry using the Osa method (equation 2) in solutions of pH 3.0 and 7.4. The cyclic voltammograms for AQ2CA and AQ2S recorded in the absence and presence of βCDGAL are shown in Figure 2.



(**a**) (b)

Figure 2. Cyclic voltammograms of 2.5×10^{-5} M (a) AQ2CA and (b) AQ2S in the absence (solid line) and presence of 1.08×10^{-3} M βCDGAL (dashed line), recorded in BR buffer at pH 3.0. All potentials reported vs. silver/silver chloride (Ag/AgCl) electrode. Scan rate 100 mV s^{-1}.

The addition of cyclodextrin to the AQ2CA or AQ2S solution leads to a decrease in the voltammetric peak currents ascribed to smaller diffusion coefficient of the drug-cyclodextrin complex compared with that of the free drug. The dependencies of I^2_{obs} vs. $(I^2_{drug} - I^2_{obs})/[CD]$ for AQ2CA-CD and AQ2S-CD complexes at pH 7.4 and pH 3.0 obtained using the CV method are shown in Figure 3, respectively. The values of the stability constants for all of all complexes at pH 7.4 and 3.0 are exhibited in Table 2



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(**a**) (b)

Figure 3. Osa (equation 2) dependencies for (a) AQ2CA and (b) AQ2S in the presence of βCDGAL at pH 7.4 (■) and 3.0 (●). Reduction peak currents recorded were recorded using cyclic voltammetry at scan rate: 100 mV s^{-1}.

Table 2. Stability constants of AQ2CA and AQ2S complexes with β-cyclodextrin and its derivatives in Britton-Robinson buffer at pH 7.4 and 3.0.

Complex	**Stability constant K_s [M^{-1}]**	
	pH 7.4	pH 3.0
AQ2CA-βCD	315 ± 40	1 360 ± 180
AQ2CA –βCDamine	800 ± 70	2 860 ± 190
AQ2CA –βCDLip	935 ± 60	2 680 ± 230
AQ2CA –βCDGAL	1 250 ± 90	2 700 ± 150

Complex	**Stability constant K_s [M^{-1}]**	
	pH 7.4	pH 3.0
AQ2S -βCD	175 ± 30	840 ± 50
AQ2S -βCDamine	250 ± 45	3 040 ± 190
AQ2S -βCDLip	910 ± 40	2 085 ± 135
AQ2S -βCDGAL	1 450 ± 60	2 500 ± 120

The values of the stability constants of the AQ2CA-cyclodextrin complexes obtained by the cyclic voltammetry method are consistent with those obtained by UV-Vis spectroscopy. Moreover, both AQ2CA and AQ2S form more stable complexes with modified βCDs than with the native one, and the largest stability constants are also obtained at pH 7.4 and with βCDGAL. As mentioned above, strong proton-acceptor π-π interaction between the triazole ring of the cyclodextrin side group and the aromatic ring of drug molecule is responsible for the increased stability constants of the complexes. The stability constants depend on pH also for AQ2S and weaker binding at pH 7.4 is understood in terms of lower affinity of the charged form of the this drug for the hydrophobic CD cavity. The formation of strong inclusion complexes would increase solubility hence facilitate the delivery of the AQ2S and AQ2CA drugs and prevent the encapsulated drug from the generation of reactive oxygen species.

2.2. Determination of the stability constants of daunorubicin-cyclodextrin inclusion complexes at pH 7.4. and 5.5.

Due to the fact that the cancer cells environment is more acidic (pH 5.5) than that of healthy cells (pH 7.4), the carrier should be pH sensitive to allow the release of the DNR drug. The βCDs with triazole in the side chain were, therefore, now chosen to compare the stability constants of DNR-cyclodextrin complexes at these two values of pH. The same Osa (equation 2) dependencies are used to follow the changes of DNR reduction

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current in the absence and presence of the CDs. Osa dependencies of I^2_{obs} vs. (I^2_{DNR} - I^2_{obs})/[βCDGAL] for the two selected pH are shown in Fig 4.

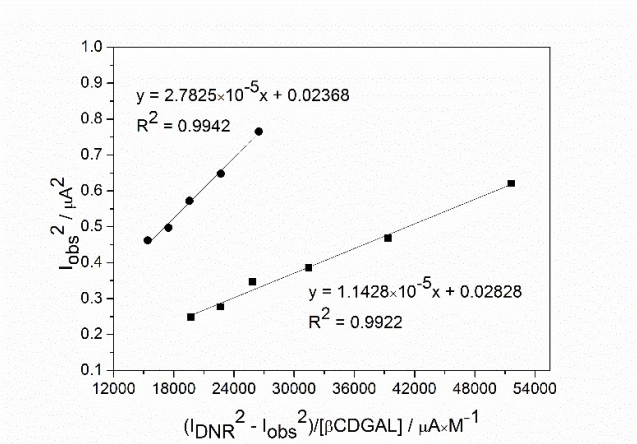

Figure 4. Osa (equation 2) dependencies for DNR in the presence of βCDGAL at pH 7.4 (■) and 5.5 (●).

The values of stability constants depicted in Table 3 show that modification of cyclodextrin with triazole linker increases the stability constants of DNR-CD complexes as in the case of AQ2CA and AQ2S. Exploiting the additional interaction between the drug aromatic ring and the triazole linker of cyclodextrin is, therefore, a general way of increasing the stability of the complexes. Daunorubicin - βCD derivatives are also sensitive to the pH change from 5.5 to 7.4.

Table 3. Stability constants of DNR complexes with β-cyclodextrin and its derivatives in Britton-Robinson buffer at pH 7.4 and 5.5.

Complex	**Stability constant $K_s \times 10^4$ [M^{-1}]**	
	pH 7.4	pH 5.5
DNR -βCD	0.097 ± 0.0035	0.078 ± 0.0030
DNR - βCDTriazol	1.10 ± 0.050	0.30 ± 0.020
DNR - βCDGAL	8.40 ± 0.55	3.72 ± 0.32

Interestingly, here the situation is different than in the case of AQ2CA and AQ2S. At pH 5.5, which is characteristic of the cancer cell environment, these cyclodextrins form weaker complexes with DNR than at physiological pH (pH 7.4). Smaller values of stability at lower pH (5.5) are now explained by the fact that DNR is in the cationic form at this pH since the pKa for DNR is 7.48 [31]. At higher pH the fraction of deprotonated hence neutral form of the drug is larger hence its binding to the hydrophobic cavity increases. Thus the difference in the charges of the anthraquinone drugs: DNR and AQ2CA (at acidic pH DNR is positively charged while AQ2CA is negative) is the reason of the different properties of their complexes at acidic and neutral pH. It may be noted that at pH 5.5, the proton-

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acceptor π-π interactions should be additionally weakened due to the interaction of protons with lone electron pairs present on the nitrogen atoms of the triazole linker.

Significantly high values of the stability constants of DNR inclusion complexes with βCDGAL at both pHs confirm the affinity of drug molecules for the cyclodextrin cavity. Moreover, the higher stability of the complex at physiological pH than at pH 5.5. is promising in view of cancer therapies. At higher pH the carrier encapsulates strongly DNR protecting it from oxygen radicals formation reactions while at lower pH corresponding to the cancer environment the release of the drug from the complex would be favorable.

Lower values of the stability constants of anthracycline complexes with βCDTriazole compared to βCDGAL may indicate some contribution of self-inclusion complex between the side substituents of the βCDTriazole derivative and the cavity of this cyclodextrin.

3. Material and Methods

3.1. Chemicals and reagents

All reagents were of high purity grade (≥97%). Anthraquinone-2-carboxylic acid (AQ2CA) and anthraquinone-2-sulfonic sodium salt (AQ2S) were purchased from Sigma Aldrich and used without further purification. Daunorubicin (DNR) hydrochloride salt was purches from AK Scientific. β-cyclodextrin (βCD) and 6-monodeoxy-6-monoamino-β-cyclodextrin hydrochloride (βCDamine) were obtained from Sigma-Aldrich. The synthesis of the lipoic acid derivative (βCDLip) [27], triazole (βCDTriazol) and galactosamine (βCDGAL) derivatives of β-cyclodextrin [28], were performed as previously described. Other compounds were purchased from Sigma-Aldrich. Buffers were prepared using water from a Milli-Q ultrapure water system. Britton-Robinson buffers (pH 7.4, 5.5 and 3.0) were prepared in the usual way by the addition of appropriate amounts of 0.2 M sodium hydroxide to 0.04 M solution of orthophosphoric acid, acetic acid and boric acid. The pH was controlled using a pH-Meter E2 (Mettler Toledo). All experiments were carried out at room temperature (25 ± 1ºC).

3.2. UV-Vis spectroscopy

UV-Vis measurements were performed using an Agilent Technologies Cary 60 UV-Vis Spectrophotometer. All UV-Vis spectra were measured in quartz cuvettes with a 1 cm optical path-length.

3.3. Voltammetry

Cyclic (CV) and square-wave (SWV) voltammetry were carried out on an EC Epsilon potentiostat (BASI). Electrochemical cell was kept in a Faraday cage. All electrochemical experiments were performed in a three-electrode arrangement with a glassy carbon electrode (BASi, 3 mm diameter) as the working electrode, a platinum foil as the counter electrode and silver/silver chloride (Ag/AgCl) electrode (BASi) in a saturated solution of KCl as the reference electrode. Before each electrochemical experiment, the surface of the glassy carbon electrode was polished using 0.05 μm alumina powder on a Buehler polishing cloth. After polishing, to remove traces of alumina from the electrode surface, the working electrode was rinsed with copious amounts of Milli-Q ultrapure water (resistivity 18.2 MΩ×cm).

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3.4. *Phase solubility diagrams*

Solubility studies of anthraquinone-2-carboxylic acid with three different cyclodextrins were carried out according to the Higuchi and Connors procedure [29]. The solutions of cyclodextrin in water, Britton-Robinson buffers (pH 7.4 and 5.5) were prepared in concentration range 0-3 mM. A constant amount of AQ2CA (3 mM) that exceeded its solubility was added into cyclodextrin solution. Molar ratios of AQ2CA:CD were: 1:0, 1:0.2, 1:0.4, 1:0.6, 1:0.8, 1:1. Three samples of each molar ratio were prepared. The suspensions were shaken for 24 hours at 25 ºC, after which equilibrium was reached. After 24h the concentration of dissolved drug monitored by UV-Vis spectroscopy did not change anymore, thus, the maximum of dissolved drug was achieved. Subsequently, the samples were filtered through a 0.45 μm filter and appropriately diluted. The aliquots of solutions were assayed for AQ2CA again by using UV-Vis spectroscopy in the 200-600 nm range with maximum absorbance value for TMZ at 335 nm. The apparent stability constant (K_s) for the complexes formed was calculated from the slope of the phase solubility diagram and the solubility of AQ2CA in water, Britton-Robinson buffer at pH 7.4 and 3.0 at 25 ºC. The stability constant of the inclusion complex was determined using the following equation:

$$K_s = \frac{Slope}{S_0(1-Slope)} \quad (1)$$

where K_s is the stability constant, S_0 is the solubility of AQ2CA in the absence of cyclodextrin and the slope is measured by UV-Vis spectroscopy and from the initial straight-line part of AQ2CA concentration vs. CD concentration plot.

3.5. *Evaluation of the stability constants of drug-cyclodextrin inclusion complexes by cyclic and square wave voltammetry*

For cyclic voltammetry experiments the concentration of AQ2CA and AQ2S were 2.5×10^{-5} M, whereas the concentration of βCD, βCDamine, βCDLip and βCDGAL varied from 2.5×10^{-4} to 1.08×10^{-3} M. Cyclic voltammetry (CV) was carried out at scan rate 100 mV s^{-1}. For SWV measurements, the concentration of DNR was 1.0×10^{-6} M, while the concentration of βCD, βCDTriazol and βCDGAL were increased in the range from 1.0×10^{-5} to 6.7×10^{-5} M. Before each SWV run, the electrode was additionally electrochemically cleaned by applying a negative potential (-1.0 V) for 40 s as described by Mora et. al. [32] The potential was varied beetwen -0.2 V and -0.9 V, at a frequency of 25 Hz, with an amplitude of 25 mV and a step of 2 mV. Prior to all electrochemical measurements, the buffer solutions were purged with purified argon for 15 min.

AQ2CA, AQ2S and DNR are an electroactive compounds. As a result of the potential change, they undergo reduction and oxidation reactions involving two electrons and two protons, Scheme 4.

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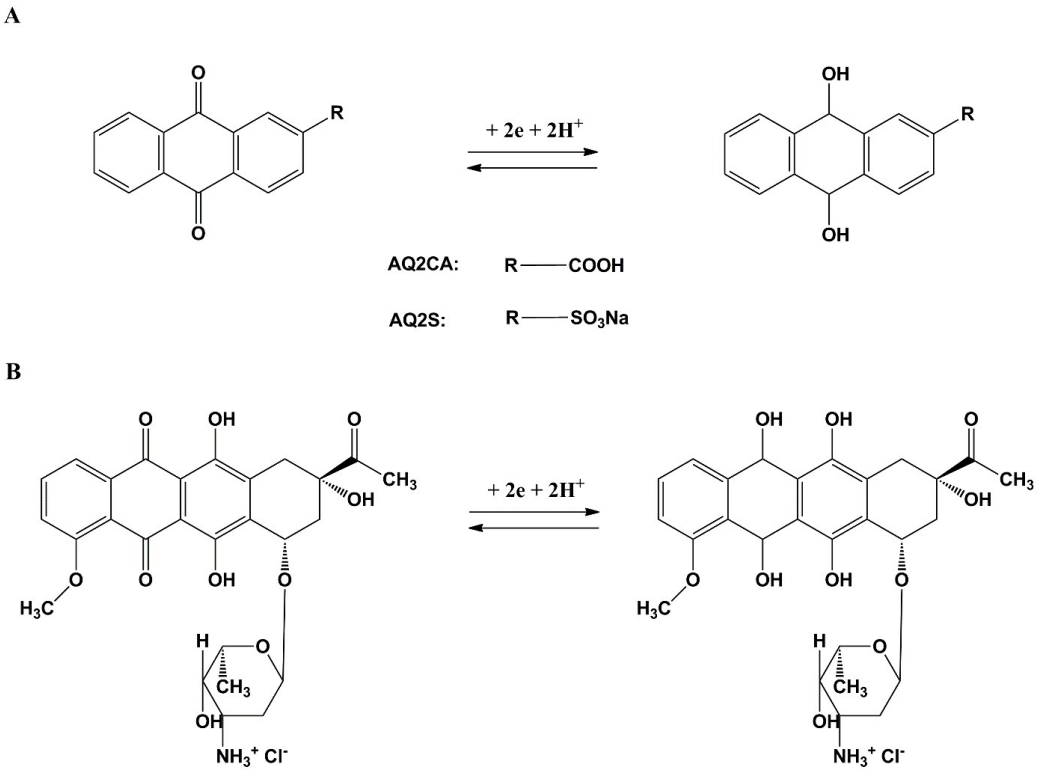

Scheme 4. Oxidation and reduction reaction of AQ2CA, AQ2S (A) and DNR (B)

Cyclic and square-wave voltammetry reduction peak currents were employed for the calculation of the drug-cyclodextrin complex formation constants based on the Osa equation [33]:

$$I_{obs}^2 = \frac{(I_{drug}^2 - I_{obs}^2)}{K_S \cdot [CD]} + I_{drug:CD}^2 \quad (2)$$

where I_{obs} is the observed reduction peak current of the quinone group of the drug, and I_{drug} and $I_{drug:CD}$ are the reduction peak currents for the free drug and inclusion complex, respectively. K_s is the complex formation constant, and [CD] is the concentration of the cyclodextrin. The value of K_s was calculated from the slope of the linear plot of I_{obs}^2 vs $(I_{drug}^2 - I_{obs}^2)/[CD]$.

4. Conclusions

β-cyclodextrin derivatives containing aromatic triazole ring in side arm are demonstrated to be suitable carriers of drugs which contain the anthraquinone moiety in the structure. Spectroscopic and voltammetry measurements show that AQ2CA and AQ2S form stable water inclusion complexes with cyclodextrin with 1:1 stoichiometries. The phase solubility diagrams for the AQ2CA-cyclodextrin inclusion complexes are classified as A_L type. The advantage of using the designed cyclodextrins to complex the

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drugs relies in the increased solubility of these ill-soluble drugs allowing delivery of larger doses of the drugs when they are encapsulated in the CD carriers. βCDLip and βCDGAL derivatives forms stronger inclusion complexes with AQ2CA and AQ2S than native βCD, due to the aromatic triazole linker, which is involved in direct $\pi-\pi$ interactions with these drugs. The AQ2CA and AQ2S drugs are anionic in neutral medium while at low pH they are protonated, hence neutral. This lead to the observed sensitivity of their CD complexes to changes of pH. At pH 3.0 (characteristic of gastric juices) the stability constants of complex with the neutral form of the drug were much larger than at physiological pH (7.4) when the drugs were in their anionic form and showed lower affinity for the hydrophobic cyclodextrin cavity. This is important in view of potential medical applications of these drugs complexed with βCDLip and βCDGAL derivatives.

βCDTriazole and βCDGAL derivatives also formed stronger inclusion complexes with anthracyclines compared to native βCD as shown on the example of DNR. Interestingly stronger inclusion complexes with DNR were, however, formed at higher pH (7.4) than at more acidic pH in the contrary to AQ2CA. This was due to the positive charge of DNR at lower pH which was less prone to form inclusion complex with the modified CDs. Such behaviour is therapeutically promising since at higher pH which corresponds to physiological pH of normal cells part of the drug molecules will be in the neutral form strongly bound to cyclodextrin. They will not be released from the carrier, therefore, they will not undergo negative side reactions. At pH 5.5, characteristic for the cancer cell environment the positively charged drug is released from the carrier free to intercalate into the DNA helices of the cancer cell.

Based on the results of our electrochemical and spectroscopic studies, it can be concluded that cyclodextrins modified with an aromatic triazole ring, especially βCDGAL, are promising carriers of drugs containing an anthraquinone skeleton in their structure. The formation of complexes with the anthraquinone group included in the cyclodextrin cavity improves the solubility of the drug but even more importantly it would protect the drug from unwanted side reactions such as the generation of reactive oxygen species which impedes the applications of these highly effective drugs.

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