Chinese Chemical Letters 26 (2015) 636–640

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Solubilization of organic compounds by arginine-derived polymers

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ARTICLE INFO

Article history:
Received 27 January 2015
Received in revised form 19 March 2015
Accepted 1 April 2015
Available online 20 April 2015

Keywords:
Arginine
Cation–π interaction
Drug solubilization

ABSTRACT

Poor aqueous solubility of drugs is one of the major challenges in the pharmaceutical science. In this study, a guanidinium-containing polymer based on arginine was designed and synthesized, and was evaluated as a solubility enhancing additive for three model organic compounds (coumarin, pyrene and doxorubicin). At a guanidinium group concentration of 100 mmol/L, the polymer could significantly increase the solubility of pyrene and doxorubicin by 6- and 11-fold respectively, much more effective than arginine (2- and 3-fold, respectively). In contrast, its effect on the solubility of coumarin was less effective than arginine. The solubilizing effect may be explained by the enhanced interaction between the guanidinium group in the polymer and the aromatic compounds.

1. Introduction

About 40% of marketed drugs and over 75% of drugs under development are poorly water-soluble, and this causes problems in drug development and their clinical use, representing one of the major challenges in the pharmaceutical science [1,2]. Current strategies to address this low solubility problem include co-crystals, solid dispersions, and nanosizing [3–5]. Most of these approaches can be explained with the "spring-and-parachute" concept that drugs are dissolved first and make a supersaturated solution in the gastrointestinal tract, and then the supersaturated state is maintained for an extended period of time to maximize the oral absorption [6]. Along the line with this concept, it is highly desirable to develop additives which can enhance the drug solubility in the aqueous solution, as they can be used to reduce the actual supersaturation level and hence prolong the supersaturation *in vivo*.

Among the studied solubilizing additives, arginine is an interesting example. Arginine is a natural amino acid with a zwitterionic head (NH_3^+–CHR–COO^-) and a guanidinium tail group, which are connected by a short aliphatic segment (*i.e.*, 3 methylene groups) in its molecule structure. The guanidinium group is a planar group with a high pK_a (12.5 for arginine in water [7]), thus it is positively charged in aqueous solutions at all physiologically relevant pH. Due to this special structure, the guanidinium group is capable of forming ionic bonds and hydrogen bonds with anionic and hydrogen-bond-active groups (including water), respectively, in the guanidinium plane [7,8]. However, the guanidinium group is poorly hydrated above and below the plane, and can form strong cation–π interaction with hydrophobic aromatic groups along the direction perpendicular to the guanidinium plane [9–13]. With this special structure, arginine has been used to suppress the aggregation of proteins, probably due to the interactions between the guanidinium groups and the protein surface residues [11,14–19]. Recently, it was reported that arginine can also increase the solubility of small aromatic compounds (*e.g.*, coumarin, benzyl alcohol, and alkyl gallates), but not of non-aromatic caffeine, suggesting that the solubilization effect is due to the cation–π interactions between the guanidinium group of arginine and the aromatic compounds [9,10,13,20].

However, one problem with arginine is that high concentration is often needed to be effective on drug solubilization. For example, 1 mol/L (174 mg/mL) arginine is needed to double the coumarin solubility [10]. We hypothesized that a polymer of arginine-derived monomers should have a high local concentration of guanidinium groups and may have stronger interaction with aromatic compounds (Fig. 1), *i.e.*, the aromatic plane may bind simultaneously with two guanidinium groups or a guanidinium group may interact with two aromatic compounds [21]. Here, we designed a guanidinium-containing polymer based on an arginine-derived monomer (Scheme 1), and compared with arginine for their effect on the solubility of three model compounds (*i.e.*, coumarin, pyrene and doxorubicin).

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http://dx.doi.org/10.1016/j.cclet.2015.04.009

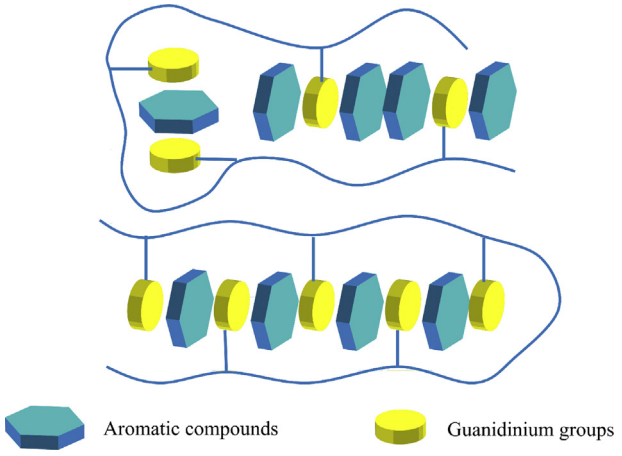


Fig. 1. Hypothesized interactions between aromatic compounds with the guanidinium side groups along the polymer chains.

2. Experimental

2.1. Materials

L-Arginine, methanol and coumarin were purchased from J&K Chemicals. Methacrylic anhydride, triethylamine (TEA), ammonium persulfate (APS) and *N*,*N*,*N*′,*N*′-tetramethyl ethylene diamine (TMEDA) were purchased from Alfa Aesar. 3-(Trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) and pyrene were purchased from Sigma-Aldrich. Doxorubicin hydrochloride (Dox·HCl) was purchased from Melone Pharma (Liaoning, China). Thionyl chloride ($SOCl_2$) was purchased from Aladdin. Dioxane and acetone were purchased from Beijing Chemical Company. Phosphate buffer saline (PBS) tablets were purchased from Amresco. All reagents were of analytical grade and used as received.

2.2. Synthesis of N-methacryl arginine (M-Arg, *I*)

M-Arg was prepared following the method in literature [22] with modifications. L-Arginine (2 g, 11.5 mmol) was dissolved in a mixed solvent of deionized water (20 mL) and dioxane (8.5 mL). Then TEA (4.5 mL, 32.3 mmol) was added and the solution was cooled with an ice/water bath. Methacrylic anhydride (3 mL, 18.9 mmol) was added dropwise over a period of 10 min under stirring. Then the ice/water bath was removed and the mixture was stirred overnight at room temperature. The product was precipitated in acetone (400 mL). The precipitates were then redissolved in water and precipitated again in acetone. The precipitation step was repeated two times. White powder was obtained and dried under vacuum at room temperature (yield 75%).

^{1}H NMR (D_2O, 400 MHz, Fig. S1a in Supporting Information): δ 1.60 (m, 2H, –CH_2–CH_2–CH_2–), 1.74 and 1.87 (m, 2H, –CH(COOH)–CH_2–), 1.92 (s, 3H, –CH_3), 3.18 (t, 2H, –NH–CH_2–), 4.22 (q, 1H, –NH–CH(COOH)–), 5.44 and 5.70 (s, 2H, =CH_2). ^{13}C NMR (D_2O, 400 MHz, Fig. S1b): δ 17.74 (–CH_3), 24.56 (–CH_2–CH_2–CH_2–), 28.81 (–CH(COOH)–CH_2–), 40.67 (–NH–CH_2–), 54.86 (–NH–CH(COOH)–), 121.17 (=CH_2), 139.04 (=C(CH_3)–), 156.75 (–NH–C(NH)–NH_2), 171.25 (–NH–CO–), 178.61 (–COOH). MS (ESI, Fig. S1c): *m*/*z* 243 ($M+H^+$, theoretical value M = 242), 485 ($2M+H^+$, theoretical value 2M = 484).

2.3. Synthesis of poly(M-Arg) (*II*)

The monomer M-Arg (I) was polymerized *via* the redox-initiated radical polymerization, using APS and TMEDA as the redox initiator pair. M-Arg (2 g, 8.3 mmol) and APS (80 mg, 0.4 mmol) were dissolved in deionized water (40 mL) and nitrogen was passed through the solution for 30 min to remove oxygen. TMEDA (80 μL, 0.5 mmol) was added under stirring. The reaction proceeded at room temperature for 24 h, and then the precipitate in the solution were obtained by filtration and washed with water for three times. The resulted white powder was dried under vacuum at room temperature (yield 88%).

^{1}H NMR (D_2O, 400 MHz, Fig. S2a in Supporting Information): δ 0.75–1.25 (m, 3H, –CH_3), 1.44–2.24 (broad, 6H, –CH_2–CH_2–CH_2–, –CH(COOH)–CH_2–, –(CH_3)C(COR)–CH_2–), 3.22 (m, 2H, –NH–CH_2--), 4.23 (m, 1H, –NH–CH(COOH)–). ^{13}C NMR (D_2O, 400 MHz, Fig. S2b): δ 17.09 (–CH_3), 25.15 (–CH_2–CH_2–CH_2–), 27.83 (–CH(COOH)–CH_2–), 40.68 (–NH–CH_2–), 45.05 (–(CH_3) C (COR)–), 52.31–55.01 (–NH–CH(COOH)–, –(CH_3)C(COR)–CH_2–), 156.74 (–NH–C(NH)–NH_2), 175.48 (–NH–CO–), 178.94 (–COOH).

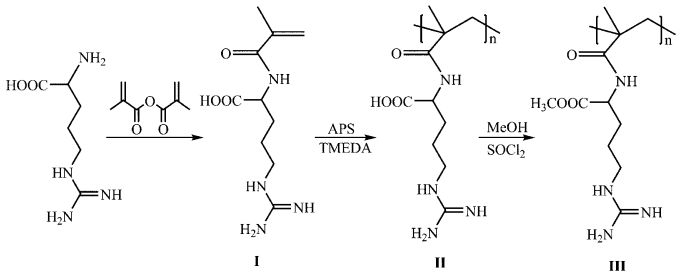
2.4. Synthesis of poly (M-Arg methyl ester hydrochloride) (poly (M-Arg-OMe·HCl), *III*)

The suspension of poly(M-Arg) (1 g, corresponding to 4.1 mmol M-Arg unit) in methanol (20 mL, 0.5 mol) was cooled with an ice/water bath. $SOCl_2$ (0.5 mL, 6.9 mmol) was added dropwise under stirring and the suspension gradually turned into a clear solution. The solution was then refluxed at 70 °C for 24 h. The solvent was evaporated with a rotary evaporator, and the residue was then redissolved in methanol and precipitated in acetone. The precipitation step was repeated twice. White powders were obtained after filtration and dried under vacuum at room temperature (yield 89%).

^{1}H NMR (D_2O, 400 MHz, Fig. 3a): δ 0.75–1.24 (m, 3H, –CH_3), 1.47–2.16 (broad, 6H, –CH_2–CH_2–CH_2–, –CH($COOCH_3$)–CH_2–, –(CH_3)C(COR)–CH_2–), 3.25 (m, 2H, –NH–CH_2–), 3.76 (m, 3H, –$COOCH_3$), 4.28 (m, 1H, –NH–CH($COOCH_3$)–). ^{13}C NMR (D_2O, 400 MHz, Fig. 3b): δ 16.97 (–CH_3), 25.25 (–CH_2–CH_2–CH_2–), 27.75 (–CH(COOH)–CH_2–), 40.77 (–NH–CH_2–), 45.23 (–(CH_3)C(COR)–), 52.97 (–$COOCH_3$), 53.29–54.46 (–NH–CH(COOH)–, –(CH_3)C(COR)–CH_2–), 156.82 (–NH–C(NH)–NH_2), 174.17 (–NH–CO–), 179.28 (–$COOCH_3$).

2.5. Solubility determination of organic compounds in the presence of arginine and poly(M-Arg-OMe)

The solubility of coumarin, pyrene and Dox in PBS with additives at different concentrations (0–100 mmol/L; for polymers, the concentration refers to the concentration of repeating unit) were measured as follows. Stock solutions of additives at different concentrations were prepared in PBS (10 mmol/L phosphate, 137 mmol/L NaCl and 2 mmol/L KCl) and were adjusted to pH 7.4 using concentrated NaOH or HCl solutions. Excess amounts of coumarin or pyrene (~10 mg/mL) powder were added into the additive solutions. For the group of Dox, Dox·HCl suspension was prepared at 20 mg/mL in PBS and pH was adjusted to 7.4. Then the suspension was added into additive stock solutions and each of the final solutions contained 10 mg/mL Dox·HCl. The samples of



Scheme 1. Synthesis route of the arginine-derived polymer.