J. Biochem. 2011;149(4):389–394 doi:10.1093/jb/mvr004

JB THE JOURNAL OF BIOCHEMISTRY

Arginine increases the solubility of alkyl gallates through interaction with the aromatic ring

Received September 29, 2010; accepted November 9, 2010; published online January 28, 2011

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We have recently proposed the application of solubilizing effects of arginine to poorly soluble aromatic compounds for drug discovery research. In this study, we compared the solubilizing effects of arginine with those of other amino acids, salts and a surfactant using alkyl gallates as model drug substances of low aqueous solubility. The solubilizing effects of arginine on the alkyl gallates were distinct compared with those of other amino acids and salts; the effects were even greater than those achieved using a strongly chaotropic guanidinium ion. Transfer free energy of the alkyl gallates from water to arginine solution depended weakly on their dissolution free energy in water, which is in contrast to sodium dodecyl sulphate that showed strong dependence. The present results suggest that arginine solubilizes alkyl gallates through interaction with the aromatic moiety and sodium dodecyl sulphate does so by interacting with alkyl groups.

Keywords: arginine/gallate/solubility/surfactants/transfer free energy.

Abbreviations: Arg, arginine hydrochloride; Gdn, guanidine hydrochloride; Gly, glycine; Lys, lysine hydrochloride; NaCl, sodium chloride; SDS, sodium dodecyl sulphate.

Arg has been shown to be effective in suppressing aggregation of proteins against various stresses and to have no apparent deleterious effects on proteins (*1–3*). In the biotechnology field, Arg is widely used for various purposes, such as protein refolding, formulation and chromatography (*3–12*). We have previously observed that Arg can increase the solubility of several small organic compounds, suggesting its potential application for solubilization of drug substances (*11–13*). The solubilizing effect of Arg was accounted for by the interaction between guanidinium group of Arg and aromatic moieties of the substances. However, the interaction between Arg and alkyl chain moieties has not been clarified. There may be some possibility that Arg interacts with alkyl chain moieties because Arg possibly shows a surfactant-like property as suggested by molecular dynamics (MD) simulation (*14*). Although our previous studies have shown the interaction between Arg and alkyl gallates with short alkyl chain, i.e. methyl, ethyl, propyl and butyl gallates (*13*), there is little detailed information regarding the interaction of Arg with the alkyl chain moieties. Thus, in the present study, we investigated the solubilizing effect of Arg on the alkyl gallates with long alkyl chain including octyl gallate to clarify the interaction of Arg with alkyl chain moieties. In addition, we compared the solubilizing effect of Arg with that of a surfactant to distinguish those solubilizing effects. The observed solubilizing effect of Arg should be applied to enhance the bioavailability of the alkyl gallates, such as antioxidative (*15*, *16*), anti-virus (*17*, *18*) and antifungal activity (*19*, *20*).

Although surfactants are generally used to improve the dissolution performance of poorly soluble drug products (*21–28*), they can be toxic because of their destabilizing actions on proteins and lipid membranes. Arg as an additive for solubilization of the drug substances can potentially ameliorate the above-mentioned problems.

Materials and Methods

Chemicals

All alkyl gallates and sodium dodecyl sulphate (SDS) were obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Arginine hydrochloride was provided by Ajinomoto Co., Inc. (Tokyo, Japan). Lysine hydrochloride, guanidine hydrochloride, Gly and NaCl were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All compounds used were of the highest commercially available grade.

Solubility measurement

The solubility of all alkyl gallates in the presence of solvent additives and 50 mM surfactant at pH 7.0 was measured as follows. Aqueous solutions of the additives were prepared by mixing water and the additives. The weight concentration was converted to the molar concentration using the densities of the prepared solutions. Appropriate amounts of alkyl gallate powders were transferred into test tubes to which 0.5 ml of water or the additive solution was added. The suspension was heated at 40°C for 1 h with frequent vortexing for complete dissolution of alkyl gallate powders. The solution was then incubated at 25°C for 3 days with frequent vortexing. Subsequently, the suspension was centrifuged at 25°C and 16,000*g* for 20 min to obtain a supernatant saturated with the alkyl gallates. After appropriate dilution of the supernatant with water, the absorbance of the supernatant was determined spectrophotometrically at 271 nm using an ultraviolet–visible (UV-VIS) spectrophotometer (ND-1000; NanoDrop Technologies Inc., Wilmington, DE, USA). The absorbance value was converted to the concentration on the basis of the standard curve determined for each alkyl gallate. Solubility was determined in triplicate from which the averages and standard errors were obtained. As expected, the accuracy of absorbance measurements decreased with decreasing solubility. Nevertheless, the standard deviation was <10% of the average value in most cases.

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Calculation of transfer free energy and dissolution free energy

The transfer free energy ΔG_{tr} of the alkyl gallates from water to the additive solutions was calculated according to the following equations:

$$\Delta G_{tr} = \mu_a^0 - \mu_w^0 = -RT\ln(x_a/x_w), \quad (1)$$

$$\begin{cases} \mu_w = \mu_w^0 + RT\ln x_w \\ \mu_a = \mu_a^0 + RT\ln x_a \end{cases}, \quad (2)$$

$$\begin{cases} x_w = n_{g,w}/(n_{g,w} + n_{H_2O,w}) \\ x_a = n_{g,a}/(n_{g,a} + n_{H_2O,a} + 2n_{a,a}) \end{cases} \quad (3)$$

In the above-presented equations, μ_a and μ_w are the chemical potentials of the alkyl gallate in the presence and absence of the solvent additive, respectively, and μ_a^0 and μ_w^0 are the corresponding standard chemical potentials. The transfer free energy of the alkyl gallate from water to the additive solution can be calculated from the solubility of the alkyl gallate in the respective solutions x_a *and* x_w, and is expressed as the mole fraction solubility of the alkyl gallate in the presence and absence of the additive. The mole fraction concentration is calculated using $n_{i,a}$ and $n_{i,w}$, which correspond to the molarity of the component i at saturation in the presence and absence of the additive. Subscript g, H_2O and a are used to express the molarities of the gallate, water and the additive at saturation of the gallate, respectively. For example, μ_a indicates the chemical potential of an alkyl gallate in an aqueous solution containing an additive, and $n_{g,a}$ is the molarity of the alkyl gallate in the same solution. The activity coefficient was considered to be close to unity because of poor solubility of the alkyl gallate. R and T correspond to the gas constant and absolute temperature, respectively.

The dissolution free energy ΔG^{H_2O} of the alkyl gallates was calculated according to the following equation:

$$\Delta G^{H_2O} = -RT\ln x_w \quad (4)$$

Thus, ΔG^{H_2O} corresponds to the free energy difference between liquid and precipitate phases in the absence of the solvent additive.

Results

Solubility of the alkyl gallates in amino acid and salt solutions

Methyl, ethyl, propyl and butyl gallates were used as model compounds to examine the effects of solvent additives. Figure 1 shows the effects of Arg, Lys, Gdn, Gly and NaCl on the solubility of methyl gallate. The solubility of methyl gallate linearly increased with Arg concentration up to 1 M, which is the highest Arg concentration examined, reaching ~26 mg/ml in 1 M Arg versus ~9.5 mg/ml in water (see also Table I). Lys also appeared to increase the solubility of methyl gallate, but only at 0.2–0.4 M. The solubility of methyl gallate in 1 M Lys was only ~11 mg/ml, which was not much different from the solubility observed in water. As observed in Fig. 1, a marginal increase was observed in the solubility of methyl gallate in Lys solution. Thus, a distinct difference was observed in the effects of Arg and Lys on the solubility of methyl gallate. The large increase in the solubility of methyl gallate in Arg, but not in Lys, suggests the importance of the guanidinium side chain. However, the guanidinium group alone was insufficient to explain the observed effects of Arg because Gdn itself was less effective than Arg in solubilizing the alkyl gallates. Figure 1 also shows that the effects of Gly, with an essentially unchanged solubility of methyl gallate, i.e. the backbone structure of the amino acid had no impact on the solubility of methyl gallate. This in turn implies that a part of the Arg side chain other than the guanidinium group contributed to the observed strong solubilizing effects of Arg. Since Arg is a cation, the ionic property of Arg may play a role in the observed effect, although unlikely, because Lys is also a cation. As expected, NaCl significantly suppressed the solubility of methyl gallate, perhaps consistent with its weak salting-out effects on proteins.

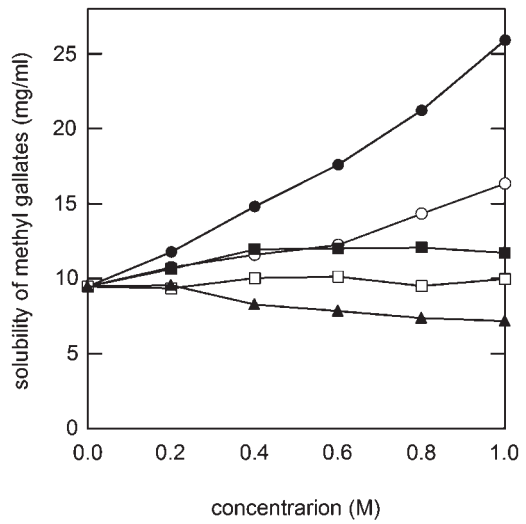

Fig. 1 Solubility of methyl gallates in the absence and presence of additives as a function of additive concentration. Closed circles, Arg; open circles, Gdn; closed squares, Lys; open squares, Gly; closed triangles, NaCl.

Table I lists the solubility of the alkyl gallates in the presence of 1 M additives. The observed differences between different additives (1 M) were significant, far above the standard deviations for all the results. Based on these data, the solubility ratio of the four alkyl gallates in the presence of 1 M additives to that in the absence of 1 M additives was calculated as a function of carbon number of the alkyl chain (Fig. 2A). Surprisingly, the solubility ratios of methyl, ethyl, propyl and butyl gallates in the presence of 1 M Arg were similar [all at ~2.6–2.8 (see grey bars)], i.e. 1 M Arg increased their solubility with a similar magnitude. This is also true for other 1 M additives, i.e. with the ratio ranging ~1.4–1.6 for Gdn, ~1.1–1.2 for Lys, ~1 for Gly and below 0.8 for NaCl. Thus, these 1 M additives showed the same solubility ratios for the gallates, independent of the alkyl chain length. Such independence suggests that these additives interact primarily

Table I. Solubility of the alkyl gallates in the absence and presence of 1 M solvent additives.

	Solubility (mg/ml)			
Additives	**Methyl gallate**	**Ethyl gallate**	**Propyl gallate**	**Butyl gallate**
No additive	9.470 ± 0.119	11.519 ± 0.112	2.939 ± 0.090	1.590 ± 0.094
1 M Arg	25.896 ± 0.302	29.093 ± 0.281	7.723 ± 0.188	4.198 ± 0.100
1 M Gdn	16.339 ± 0.162	18.698 ± 0.258	5.075 ± 0.152	2.618 ± 0.099
1 M Lys	11.708 ± 0.115	13.454 ± 0.724	3.648 ± 0.096	2.066 ± 0.111
1 M Gly	9.969 ± 0.253	12.035 ± 0.222	3.071 ± 0.910	1.751 ± 0.096
1 M NaCl	7.177 ± 0.113	8.201 ± 0.127	1.895 ± 0.094	0.823 ± 0.095

with a gallate moiety and not with the alkyl chain moiety of the alkyl gallates, either favourably to increase the solubility (Arg and Gdn), neutrally with the gallates (no change in solubility) (Lys and Gly), or unfavourably to decrease the solubility (NaCl).

The solubility of solutes can be determined by solute–solute and solute–solvent interactions. Here, assuming that solute–solute interactions did not change in any of the solutions, the observed change in the solubility of the alkyl gallates by the addition of solvent additives was considered to reflect solute–solvent interactions. The thermodynamic interaction of the alkyl gallates with additive solutions can be estimated from the change in solubility. Figure 2B shows the transfer free energy of the alkyl gallates from water to 1 M additive solutions. The transfer free energy was negative for Arg, Gdn and Lys, close to zero for Gly and positive for NaCl, with the magnitude more or less independent of the alkyl chain length. Thus, solvent interactions with these four alkyl gallates were favourable for the first three additives, neutral for Gly and unfavourable for NaCl. The change in transfer free energy increased in the order of Arg < Gdn < Lys < Gly; thus, the interaction of Arg with each alkyl gallate was thermodynamically more favourable than that of the others. A similarity in the magnitude of favourable interactions between Arg (as well as Gdn) and the alkyl gallates independent of the alkyl chain length suggests the primary interaction to be with the gallate moiety. Conversely, 1 M NaCl showed chain length dependence with an increasing unfavourable interaction for a longer alkyl chain, indicating that the salting-out effect was enhanced with a longer alkyl chain length.

The above-described results suggest the potential interaction of Arg (as well as Gdn and Lys) with the gallate moiety as the mechanism underlying the increased solubility of the alkyl gallates. The specific effect of Arg on the gallate moiety and its inability to interact with the alkyl chain may limit the effectiveness of this additive as a solubilizing agent. The effectiveness of Arg is expected to be different from that of surfactants because the effectiveness of Arg is a result of its direct interaction with the solutes, which is likely to be different as inferred from the micelle structure of surfactants. Therefore, the effects of 50 mM SDS on the solubility of the alkyl gallates were compared with those of Arg (Table II), where the concentration of SDS was substantially higher than CMC. The solubility of methyl and ethyl gallates increased in 50 mM SDS, but with lesser magnitude than that in 1 M Arg. The solubility of propyl and butyl gallates in 50 mM SDS was significantly greater than that in 1 M Arg. Table II includes the data for octyl gallate, which had an extremely low solubility in water because of the long alkyl chain and strong hydrophobicity. While 1 M Arg could effectively solubilize octyl gallate, 50 mM SDS was much more effective in solubilization of octyl gallate than 1 M Arg. Because of low solubility, substantial errors were present in the solubility data for octyl gallate. Solubility linearly increased with SDS concentration for all alkyl gallates examined (Supplementary Fig. S1). The increase in the slope of solubility was steeper for butyl gallate than for propyl gallate, resulting in the reversal of the solubility order at 50 mM SDS, i.e. solubility in water was greater for propyl gallate and solubility in 50 mM SDS was greater for butyl gallate. This indicates that water

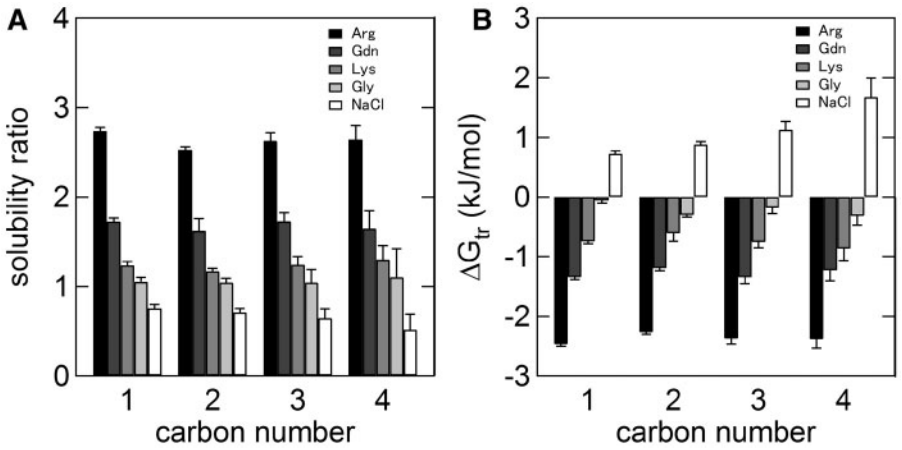

Fig. 2 (A) The solubility ratio of the alkyl gallates in the presence of 1 M additives to that in the absence of 1 M additives as a function of carbon number in the alkyl chain. (B) Transfer free energy of the alkyl gallates from water to 1 M additive solutions.

Table II. Solubility of the alkyl gallates in the absence and presence of 1 M Arg and 50 mM SDS.

	Solubility (mg/ml)				
Additives	**Methyl gallate**	**Ethyl gallate**	**Propyl gallate**	**Butyl gallate**	**Octhyl gallate**
No additive	9.470 ± 0.119	11.519 ± 0.112	2.939 ± 0.090	1.590 ± 0.094	0.018 ± 0.004
1 M Arg	25.896 ± 0.302	29.093 ± 0.281	7.723 ± 0.188	4.198 ± 0.101	0.080 ± 0.008
50 mM SDS	13.608 ± 0.492	16.938 ± 0.295	8.398 ± 0.203	9.252 ± 0.115	4.878 ± 0.093

was a better solvent for propyl gallate and aqueous solution containing 50 mM SDS was a better solvent for butyl gallate.

The dependence of solubilizing effects of Arg and SDS on the alkyl chain length can be better expressed by the solubility ratio. Figure 3A and B show these data as a function of carbon number. As shown in Fig. 3A, the solubility ratio in 1 M Arg to that in water was relatively constant, whereas the ratio in 50 mM SDS to that in water became increasingly higher for longer alkyl chain gallates. The solubility ratio of octyl gallate (~260) in 50 mM SDS was ~60-fold higher than that in 1 M Arg (~4). Such difference between 50 mM SDS and 1 M Arg was also expressed by the transfer free energy of the alkyl gallates from water to the additive solutions in Fig. 3B. While the transfer free energy was relatively constant for 1 M Arg regardless of the alkyl chain length, it gradually became more negative for 50 mM SDS with increasing chain length.

The aqueous solubility of the alkyl gallates decreased with increasing alkyl chain length, except for that of ethyl gallate. Such a decreased solubility for longer alkyl chain gallates indicates either unfavourable interaction of the alkyl chain moiety with water in the liquid phase, favorable interaction between alkyl moieties in the solid phase or both. In either case, the change in solubility is ascribed to the contribution of the alkyl chain moiety. The solubility of the alkyl gallates can be converted into the dissolution free energy, i.e. the free energy between liquid and solid phases. Such dissolution free energy (ΔG^{H_2O}) of these five alkyl gallates is plotted in Fig. 4. As the alkyl chain became longer, the dissolution free energy became more positive, suggesting the greater contribution of the alkyl chain to the transfer free energy of the alkyl gallates from solid to liquid phases. When the transfer free energy was plotted against the dissolution free energy, a marginal dependence was observed for the 1 M Arg system. On assuming that Arg did not interact with the alkyl gallates in the solid state, the marginal dependence on the dissolution free energy suggests that the solubilizing effect of Arg on the alkyl gallates could be due to its interaction with the gallate moiety of the alkyl gallates. On the contrary, a sharp dependence of the transfer free energy on the dissolution free energy was observed for the 50 mM SDS system. In this case, on assuming that SDS also did not interact with the alkyl gallates in the solid state, the solubilizing effect of SDS on the alkyl gallates could be due to its interaction with the alkyl moieties of the gallates.

Discussion

Arg has been known as a solubilizer for poorly soluble aromatic compounds, including aromatic hydrocarbons and heteroaromatic compounds (*11*, *12*). The specific interactions of Arg with aromatic rings are supported by MD simulation (*13*). Although the MD simulation has suggested that Arg stabilizes alkyl gallates in solution by interacting with the gallate moiety, the interaction between Arg and their alkyl chain moiety has not been fully understood. In the present study, the thermodynamic effects of Arg on solubilization of the alkyl gallates, including octyl gallate that has a long alkyl chain (carbon number, 8), were

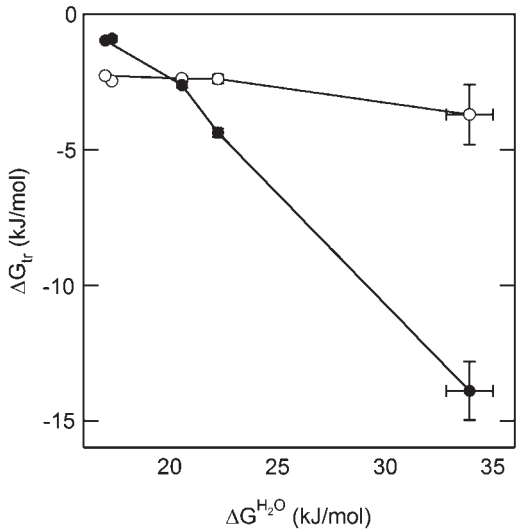

Fig. 4 Transfer free energy of the alkyl gallates from water to 1 M Arg or 50 mM SDS solution versus the dissolution free energy of the alkyl gallates in water. Closed circles, 1 M arginine; open circles, 50 mM SDS.

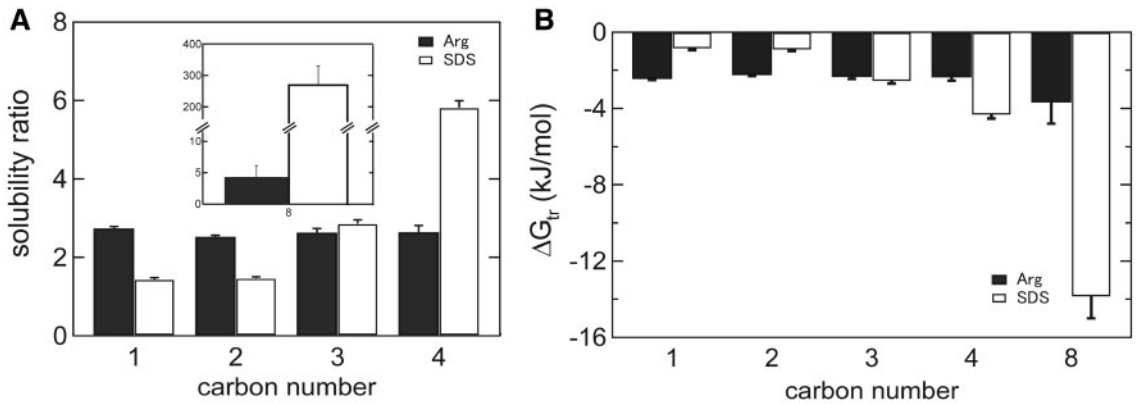

Fig. 3 (A) The solubility ratio of the alkyl gallates in the presence of 1 M Arg and 50 mM SDS to that in the absence of 1 M Arg and 50 mM SDS as a function of carbon number in the alkyl chain. (B) Transfer free energy of the alkyl gallates from water to 1 M Arg and 50 mM SDS.

compared with those of other amino acids (Gly and Lys), salts (NaCl and Gdn) and SDS.

Comparison of solubility and thermodynamic interaction parameters showed that Arg interacts most favourably with alkyl gallates, regardless of their chain length. Although the exact mechanism may require more extensive analysis of the interactions, the following discussion can be justified. The stronger interaction of Arg than Lys observed in this study clearly indicates the importance of the guanidinium group (Figs 1 and 2A). However, the interaction of Arg was even stronger than that of Gdn, suggesting that the guanidinium group alone is insufficient and the three methylene groups may have played a role in the observed solubilizing effects of Arg. The observed solubilizing effects of Arg on the alkyl gallates were independent of the chain length and dissolution free energy, suggesting that Arg interacts with the gallate moiety. The interaction of Arg with the gallate moiety is consistent with the known π-cation interaction (*13*, *29*, *30*), hydrophobic interaction (*14*) or hydrogen bond between the hydroxy groups of the gallate and guanidium group of Arg. The stronger solubilizing effects of Arg than Gdn observed in this study suggest that the π-cation interaction was stronger for Arg, perhaps due to the three methylene groups in Arg that mediate hydrophobic interactions with the aromatic ring structure. The aromatic ring structure has both electrostatic and hydrophobic properties (*31*). As the solid phase of alkyl gallates is most likely stabilized by aromatic ring stacking via π–π interactions (*31*, *32*), the potential π-cation and/or π–π interaction of Arg should disrupt the π–π interactions in the solid phase of alkyl gallates and hence enhance the solubility. This in turn indicates that Arg may be less effective against non-aromatic groups such as alkyl chains, as observed in this study. In drug discovery, surfactants are often used for facilitating the *in vitro* and *in vivo* dissolution of drug substances. Based on their long alkyl chains and ability to form micelles, the solubilizing effects of surfactants are expected to be different from those of Arg. The solubilizing effects of SDS were larger for longer alkyl chain gallates and showed strong dependence on the dissolution free energy. This clearly indicates that the primary interaction of SDS is with the alkyl chains. In fact, the observed weaker effects on methyl and ethyl gallates may indicate that SDS is ineffective in solubilizing aromatic groups. Thus, Arg and SDS increase the solubility of alkyl gallates through entirely different mechanisms and are expected to show a synergistic effect on solubilization of compounds with both aromatic and aliphatic groups.

In conclusion, the solubilizing effect of Arg in aqueous solution is thermodynamically distinct from that of surfactants. In contrast to surfactants, Arg stabilizes aromatic moieties of poorly soluble alkyl gallates independent of the dissolution free energy in water, i.e. hydrophobicity. Arg, which has no chaotropic properties, preferentially interacts with proteins without any adverse effects on them (*33*, *34*). Therefore, this prominent property of Arg would be advantageous for solubilizing drug substances with poor aqueous solubility because it solubilizes not only small molecules but also peptides, proteins and nucleic acids in a manner different from that of salts and surfactants, and is not detrimental to these solute molecules. Finally, based on the difference in the thermodynamic stabilizing effects of Arg and surfactants, synergistically enhanced solubilization systems for drugs using both additives should be developed in future studies.

Supplementary Data

Supplementary Data are available at *JB* Online.

Acknowledgements

We thank for Dr. D. Ejima for valuable discussion.

Conflict of interest
None declared.

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