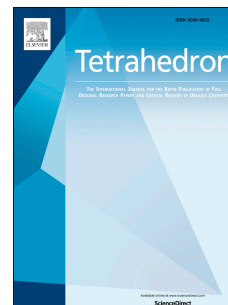


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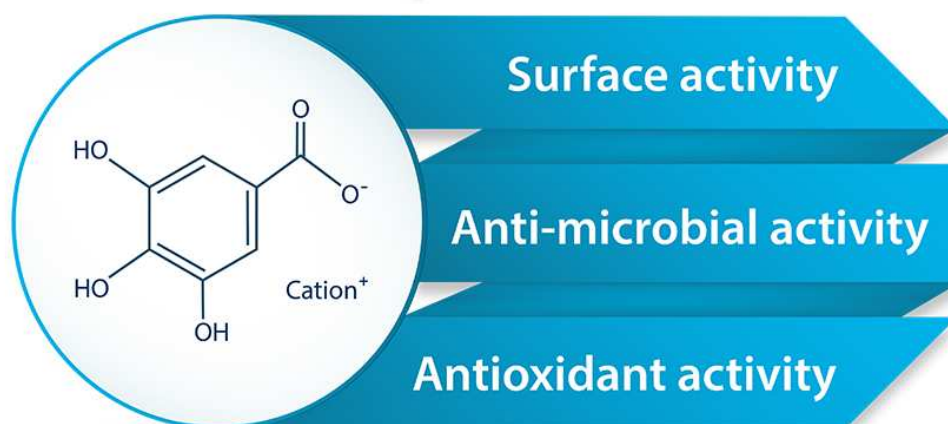
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Gallate Ionic Liquids



ACCEPTED MANUSCRIPT

Synthesis and properties of gallate ionic liquids

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Abstract

An efficient method for the synthesis of novel antioxidants in the form of ionic liquids (ILs) was described in the framework of this study. The ILs were obtained by the reaction of quaternary ammonium hydroxides with gallic acid as well as the protonation of amphoteric betaine. The following physicochemical properties of the obtained ILs were characterized: solubility in water as well as in polar and non-polar organic solvents, octanol-water partition coefficient, thermal stability, and surface activity. The investigation of bactericidal activity indicated that the synthesized gallates exhibited high efficacy against bacteria, especially against *Bacillus subtilis*. The DPPH radical scavenging assay confirmed the antioxidant properties of gallate ILs.

Keywords: Ionic liquids; Gallic acid; Antioxidant; Radical scavenging activity.

1. Introduction

Antioxidants are substances which are capable of preventing oxidation as a result of reducing the concentration of free radicals or chelating metal ions. Some well-known antioxidants include L-ascorbic acid (vitamin C), α -tocopherol (vitamin E), carotenoids or β -carotene.^{1,2} Among natural antioxidants occurring in plants in the form of polyphenols, gallic acid (GA) exhibits one of the strongest antiradical properties due to efficient protection against different reactive species.³ GA has also exhibited other forms of biological activity, such as anticancer properties, due to the inhibition of the growth of lung cancer or prostate cancer cells with stem-like properties.⁴ This natural phenolic acid can be used as a reductant for the preparation of highly reduced graphene oxide at room temperature,⁵ or can generate hydrogen peroxide *in situ* from air in slightly basic media.⁶

During recent years, ionic liquids (ILs) have been described as solvents with high chemical or thermal stability and low vapour pressure.⁷ ILs have found wide application in the synthesis of various forms of antioxidants. Primarily, they can be used as environmentally friendly catalysts for the preparation of GA esters,⁸ or act as the reaction solvent in the galloylation of catechins.⁹ ILs are applied as sustainable dual solvent-catalysts for the preparation of an α -tocopherol derivative.¹⁰ Moreover, they have been used in the preparation of novel compounds with antioxidant activity *e.g.* the synthesis of naphthoquinone - urazole hybrids.¹¹ In addition, ILs have been used for the production of polypyrimidine-amide antioxidants by polycondensation in a mixture of IL and triphenyl phosphite.¹² Current research has demonstrated that imidazolium ILs could be potential candidates for antioxidants capable to neutralize the hydrogen peroxide or radicals.¹³

The rapid progress of studies in this field contributed to a steady advance from first generation ILs (with unique, designable physical properties), through the second generation (with targeted chemical properties, combined with selected physical properties), to the third generation (with targeted biological properties, combined with physical and chemical properties).¹⁴ The third generation of ILs have been discussed as active pharmaceutical ingredients.^{7c,15} Herbicidal ionic liquids were introduced in 2011.¹⁶ In recent years, widely applied formulations of antioxidants were esters, such as propyl or lauryl gallates.¹⁷ Moreover, it is possible to prepare water soluble antioxidants in the form of cholinium-based quaternary salts.¹⁸ The aim of this work was improve activity and properties of gallic acid by turning it into multifunctional ILs. These compounds may have a wider range of tunable properties than traditional forms of antioxidants. Except high water solubility, ILs can also exhibit antibacterial properties and improved surface activity.

2. Result and discussion

2.1. Synthesis of ILs precursors

Quaternary ammonium salts and an amphoteric surfactant (Fig. 1) were applied as starting materials in order to obtain ILs with the gallate anion. Each bromide salt was obtained by the quaternization (Menshutkin reaction) of tertiary amines and long chain alkyl bromides (Scheme S1, ESI). The time of the reaction was optimized to achieve full conversion. Optimal time was determined with *in situ* IR spectroscopy (ReactIR 15, Mettler Toledo) and processed by iC IR software. This method let us monitor the direct alkylation of the amine and define the mechanism of the reaction.¹⁹ IR spectra of the reaction mixture at the beginning and end of the synthesis are shown in Fig. S1-S4, ESI. In the case of [C₁₀DMEA][Br], the

disappearance of band intensity at 1035 cm^{-1} was mainly observed. This band can be assigned to the C-O out-of-phase stretching vibrations of 2-dimethylethanolamine.²⁰ During the quaternization of 1-methylmorpholine, stretching vibrations at 1145 and 1122 cm^{-1} can be observed which are attributed to C-N stretching vibrations.²¹ Slight differences between the IR spectra were observed in the case of the reaction involving 2-[2-(dimethylamino)ethoxy]ethanol. Initially, a reduction of the intensity at 1055 cm^{-1} occurred.

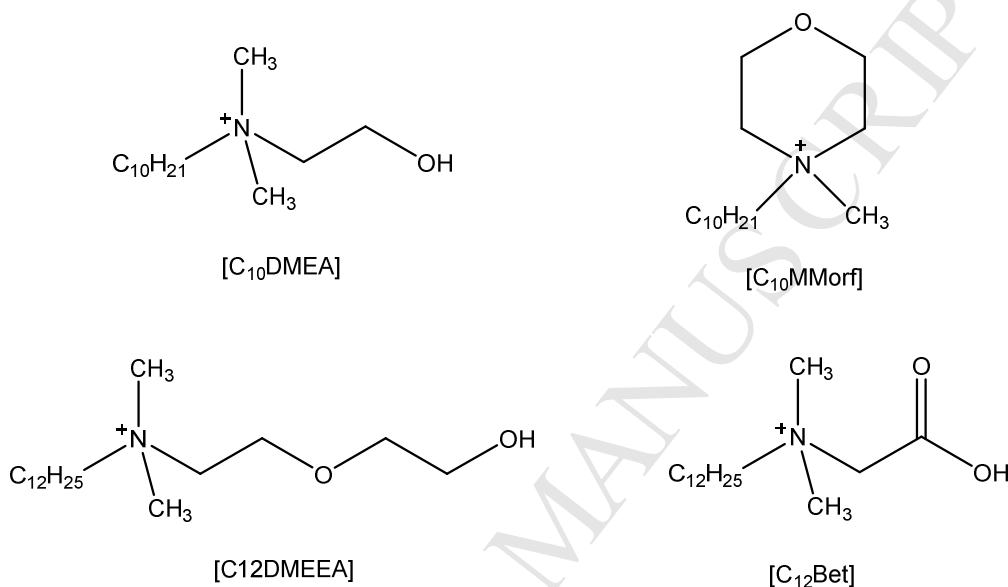


Fig. 1. Chemical structures of the cations.

Table 1. Prepared precursors of ILs.

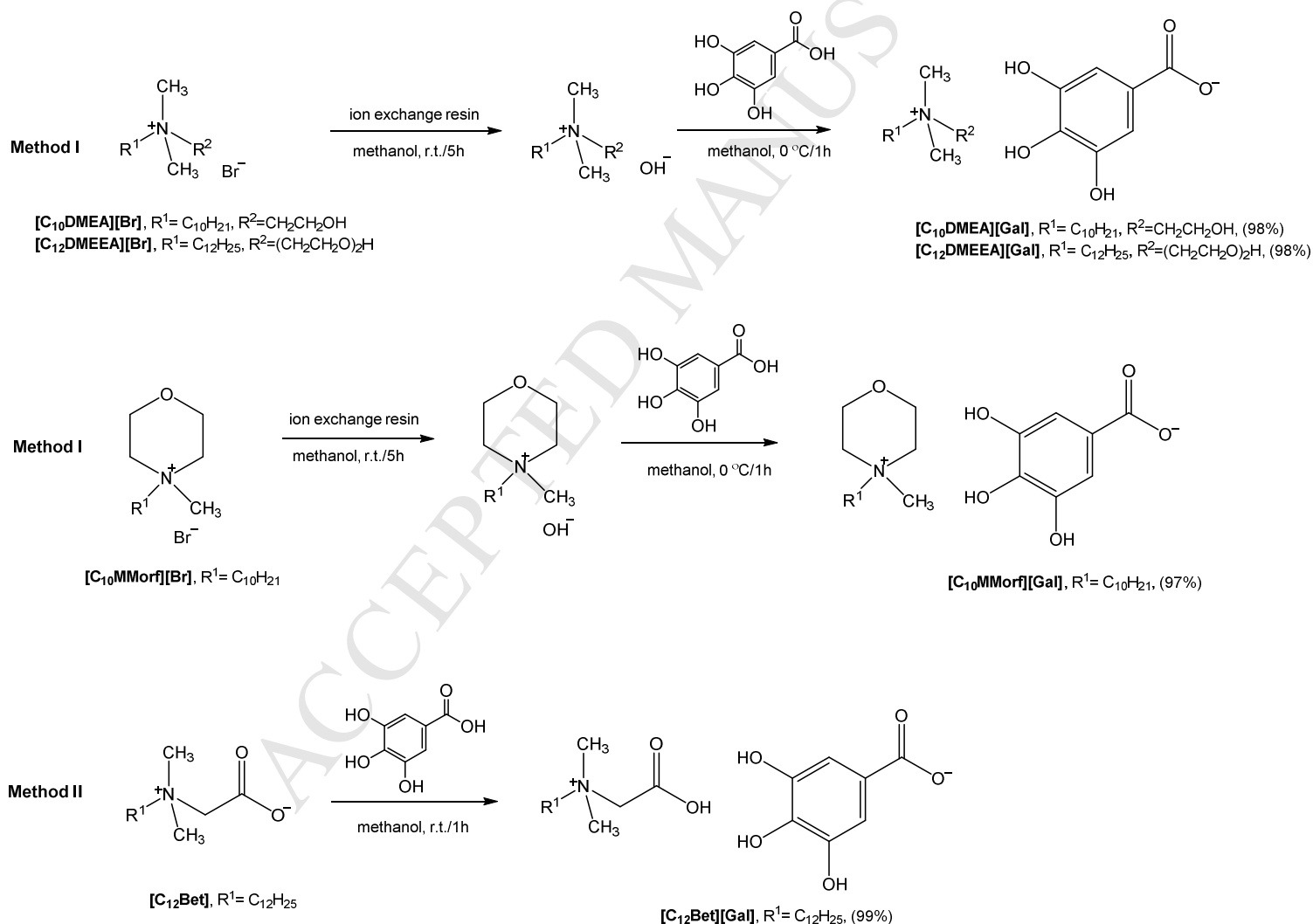
Compounds	R ¹	R ²	Time (h)	Yield(%)	T _m (°C)
[C ₁₀ DMEA][Br]	C ₁₀ H ₂₁	CH ₂ CH ₂ OH	2.75	94	156
[C ₁₀ MMorf][Br]	C ₁₀ H ₂₁	-	23.00	95	188
[C ₁₂ DMEEA][Br]	C ₁₂ H ₂₅	(CH ₂ CH ₂ O) ₂ H	2.50	98	56
[C ₁₂ Bet]	C ₁₂ H ₂₅	-	2.00	96	-

The reaction also results in the appearance of specific bands which can be assigned to the complexes with the quaternary ammonium ion.²² The new bands appeared in the region ranging from 1100 to 700 cm^{-1} ($1089, 970, 921\text{ cm}^{-1}$ for [C₁₀DMEA][Br]; $1044, 917, 899\text{ cm}^{-1}$ for [C₁₀MMorf]; and $1070, 977, 921\text{ cm}^{-1}$ for [C₁₂DMEEA][Br]). The quaternization reaction between a fatty amine and the potassium salt of chloroacetic acid was applied for the preparation of alkyl betaines. The characteristic absorption peaks of C=O stretching vibrations of the carbonyl group appeared at 1648 cm^{-1} . The longest reaction time necessary to obtain

the maximum concentration of the product was observed in the case of $[C_{10}MMorf][Br]$ and was 23 h (Table 1). The other precursors of ILs could be synthesized more rapidly (in the range of 2-2.75 h). No major side products were observed. After the purification of products from the starting reactants, the compounds were obtained in yields ranging from 94 to 98%. The resulting bromides were white or yellow solids with a melting point in the range of 56-188 °C and the amphoteric surfactant had a greasy consistency.

2.2. Synthesis of ILs

Antioxidant ILs were prepared using the two methods presented in Scheme 1. The first method, based on a neutralization reaction, consists of two stages and can be used to synthesize various types of ILs.²³



Scheme 1. Synthesis of gallate ILs.

Table 2. Prepared ILs and their physicochemical properties.

ILs	Method	Yield (%)	State at 25°C	T _g ^a (°C)	T _{onset5} ^b (°C)	T _{onset50} ^c (°C)
[C ₁₀ DMEA][Gal]	I	98	liquid	6.7	174	241
[C ₁₀ MMorf][Gal]	I	97	wax	35.8	193	254
[C ₁₂ DMEEA][Gal]	I	98	liquid	-3.6	185	260
[C ₁₂ Bet][Gal]	II	99	wax	15.3	194	275

^aT_g – glass transition temperature; ^bT_{onset5} – decomposition temperature of 5% sample; ^cT_{onset50} – decomposition temperature of 50% sample.

The synthesis started by preparation of a solution of quaternary ammonium hydroxide in methanol using an anion exchange resin to replace the bromide ion. Next, a neutralization reaction with GA was conducted at low temperatures. In addition, a hydroxide solution was progressively introduced to the acid solution due to the low stability of GA at high pH.²⁴ The IL with [C₁₂Bet] cation was obtained using the second method, which involved a one-step protonation of the carboxylate group of betaine²⁵ in methanol with GA. An overview of the prepared ILs is shown in Table 2. In both methods the synthesized ILs do not require further purification after evaporation of the solvent. In addition, the products were dried under reduced pressure (5 mbar) for 24 h at ambient temperature and stored at a low temperature in the dark. The described methods gave the ILs with a yield exceeding 97%. Water content was determined by Karl-Fischer titration and amounted to 500-800 ppm. Two of the obtained ILs containing hydroxyl groups were liquids at room temperature. Other salts were waxes. The structure of the synthesized compounds was confirmed by ¹H and ¹³C NMR spectroscopic analysis. The obtained spectra are presented in Fig. S1-S4, ESI. The synthesized ILs showed only one signal derived from the anion in the form of a singlet in the range of 6.84-6.93 ppm, which is generated by the protons of the gallic acid aromatic ring.²⁶ In the case of the cations, the protons of the long alkyl chain are located at 0.86 ppm for the methyl group and approximately 1.24 and 1.63 ppm for the methylene groups.²⁷

2.3. Thermal properties

Short-term thermal stabilities of the salts were determined by temperature-ramped TGA experiments.²⁸ As shown in Table 2, all the prepared ILs exhibited high thermal stability and manifested T_{onset50} in the range of 241-274 °C. Nonetheless, obtained compounds were less stable than GA.¹⁸ According to the literature, ILs containing short ether groups are less thermally stable compared to alkyl-substituted analogues.²⁹ However, the least stable salt among the antioxidant ILs was [C₁₀DMEA][Gal], without an ether linkage, which also

exhibited the lowest value of T_{onset5} (174 °C). The obtained results indicate that the presence of long alkyl chains and their elongation does not affect the stability of ILs. The prepared antioxidant ILs with long alkyl chains mainly underwent a three-step decomposition (Fig. S20. ESI). [C₁₂Bet][Gal] was an exception, with a clear two-step thermal degradation process. No prepared ILs demonstrated melting points and their crystallization temperatures were in the range of -100 to 120 °C. Based on the results of DSC analyses, it could be concluded that gallate ILs have no tendency to crystallize upon cooling and mainly remain in the glass state. Additionally, they can exhibit high glass transition temperature *e.g.* $T_g = 35.8$ °C in the case of a compound with a morpholinium cation. The lowest values ($T_g = -3.6$ °C and 6.7 °C) were observed for ILs [C₁₂DMEEA][Gal] and [C₁₀DMEA][Gal], which comprised the ethoxyl or the hydroxyl substituent in the structure of the cation, respectively.

2.4. Octanol–water partition coefficient

The octanol–water partition coefficients (K_{ow}) were determined in order to describe the hydrophobicity of the gallate ILs. In addition, this parameter allows definition of the environmental risk as associated with bioaccumulation or toxicity, because it reflects the partition of the compounds in biotic systems. The K_{ow} values calculated for gallate ILs are shown in Table 3.

Table 3. Solubility in water and octanol-water partition coefficients of gallate ILs and GA (2 mmol L⁻¹) at 25 °C .

Compound	Solubility \pm sd (g L ⁻¹)	Log K_{ow}
[C ₁₀ DMEA][Gal]	49.16 \pm 1.79	-0.35 \pm 0.02
[C ₁₀ MMorf][Gal]	33.92 \pm 2.17	-0.42 \pm 0.03
[C ₁₂ DMEEA][Gal]	totally miscible	0.07 \pm 0.01
[C ₁₂ Bet][Gal]	20.77 \pm 0.71	0.31 \pm 0.01
GA	11.00 \pm 0.06	0.32 \pm 0.01

Based on the obtained data, it was established that ILs containing the [C₁₀MMorf] and [C₁₀DMEA] cations were the least hydrophobic compounds. Elongation of the alkyl chain in the cation increased the K_{ow} , due to their higher solubility in *n*-octanol. Similar relationships were found for imidazolium ILs.³⁰ Only [C₁₂Bet][Gal] exhibited a similar hydrophobicity to gallic acid. The advantages of synthesized ILs can be observed in comparison to other forms of this antioxidant acid. The most commonly used esters of gallic acid with a long alkyl chain (*e.g.* dodecyl gallate) exhibit significant hydrophobicity (log $K_{\text{ow}} = 5.3$), which can

theoretically facilitate their interaction with the lipid membrane.³¹ Based on the measured K_{ow} values, it can be concluded that obtained ILs have a very promising properties. Basically, compounds with low hydrophobicity and K_{ow} values may exhibit a less risk of bioaccumulation.³² However, the K_{ow} of different ILs was not constant and depended on the concentration of the compound in the aqueous phase due to the different dissociation of the ILs in the water and the octanol phases.³³ The K_{ow} were measured in the concentration range of 0.25-2 mmol L⁻¹ in order to evaluate this relationship in case of gallate ILs (Fig. S14, ESI). A slight increase in the partition coefficient with increasing concentrations of obtained ILs was observed, except for [C₁₀MMorf][Gal]. For this IL the greatest range of log K_{ow} was measured between -0.93 and -0.42.

2.5. Solubility

All the prepared ILs exhibited higher solubility in water than GA (11.00 ± 0.06 g L⁻¹) which is shown in Table 3. However, the properties of gallate ILs strongly depended on the structure of the cation. The highest solubility in water (beyond 1000 g L⁻¹) at 25 °C was observed for [C₁₂DMEEA][Gal]. The presence of alkoxy chains in the cation and the hydroxyl group can significantly improve the hydrophilicity and water miscibility of salts.²⁹ In addition, the increase of hydrophobicity due to the longer alkyl chain does not significantly affect the solubility in the presence of strongly hydrophilic groups. The lowest water solubility was determined for [C₁₂Bet][Gal] and amounted to 20.77 ± 0.71 g L⁻¹. Thus, the selection of an appropriate cation can successfully change the solubility of ILs with the gallate anion to a different degree, until complete dissolution is achieved. The solubility of the synthesized ILs in other solvents is presented in Table 4. Due to their polar character, all the obtained ILs were also highly soluble in polar protic and aprotic solvents such as methanol and DMSO. However, not all gallate ILs exhibited solubility in acetonitrile. Likewise, the prepared ILs were characterized by low solubility in the case of other, less polar solvents. ILs containing an alkyl group with 12 carbon atoms exhibited solubility in isopropanol, but only [C₁₂Bet][Gal] was easy dissolved in acetone and showed limited solubility in ethyl acetate. Like most of the ILs, the antioxidant salts are not soluble in alkanes³⁴ (e.g. hexane) and other non-polar solvents due to the significant difference in polarity.

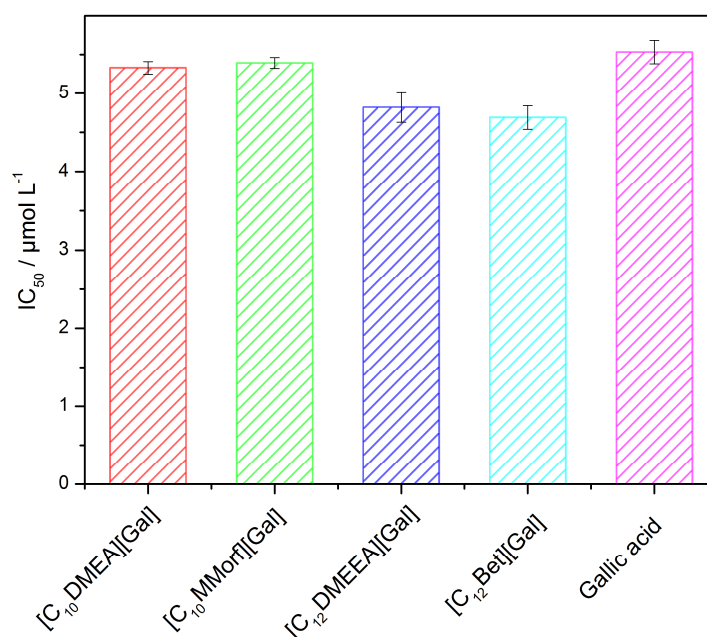
Table 4. Solubility of the prepared ILs at 25 °C^a.

Solvent	Cation			
	[C ₁₀ DMEA]	[C ₁₀ MMorf]	[C ₁₂ DMEEA]	[C ₁₂ Bet]
Methanol	Green	Green	Green	Green
DMSO	Green	Green	Green	Green
Acetonitrile	Red	Red	Red	Red
Acetone	Red	Red	Red	Green
2-Propanol	Red	Red	Yellow	Green
Ethylacetate	Red	Red	Red	Yellow
Chloroform	Red	Red	Red	Red
Toluene	Red	Red	Red	Red
Hexane	Red	Red	Red	Red

^a “green”, complete solubility; “yellow”, limited solubility; “red”, insoluble.

2.6. Antioxidant properties

Antioxidant activity of gallate ILs was measured using the DPPH assay. This method involves the reduction of a stable free radical located on the nitrogen atom of the DPPH molecule by the tested antioxidants and is widely used to evaluate the scavenging properties of a single compound or plant extracts containing various antioxidant substances³⁵ due to its simplicity and high repeatability.

**Fig. 2.** Measured IC₅₀ values of tested ILs.

The scavenging efficacy of ILs against DPPH radicals in methanol as a solvent is shown in Fig. 2. Our study indicates that all gallate ILs are very good antioxidants and exhibit better activity than commonly used compounds, such as Trolox.³⁶ GA was used as a positive control and the results were expressed as the IC₅₀ parameter. Generally, GA derivatives (such as esters) exhibit lower antiradical activity in comparison to the free acid.³⁷ The presence of a linear chain and the steric effect or the intramolecular and intermolecular hydrogen bonding of such chains could affect the activity of antioxidants.³⁸ The obtained results indicate that all the synthesized ILs exhibited slightly higher or statistically insignificant differences in radical scavenging capacity compared to GA (IC₅₀ = 5.53 ± 0.15). Additionally, the negative impact of a long alkyl chain in the cation on the antioxidant properties was not observed in case of the gallate ILs. [C₁₂Bet][Gal] and [C₁₂DMEEA][Gal] were the most effective in the inhibition of DPPH radicals in a methanol solution, with IC₅₀ values equal to 4.69 ± 0.15 and 4.82 ± 0.19, respectively. In general, betaine derivatives may exhibit a different activity *e.g.* glycine betaine does not have antioxidant activity.³⁹

2.7. Anti-microbial activity

Phenolic acids, such as gallic acid, exhibit antibacterial activity against both Gram-positive (*S. aureus* and *L. monocytogenes*) and Gram-negative bacteria (*E. coli*, MIC = 1.5 mmol L⁻¹ and *P. aeruginosa*, MIC = 5.9 mmol L⁻¹).⁴⁰ The determined minimal inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values are shown in Table 5. The results indicate that all the synthesized ILs exhibit antimicrobial properties and that their activity is selective. Generally, the synthesized gallate ILs are moderate bactericides. All salts exhibit weaker activity in comparison to *e.g.* benzalkonium chloride or didecylmethylammonium chloride.⁴¹ The lowest antimicrobial activity was observed for [C₁₀MMorf][Gal] with MBC values of 9.5 mmol L⁻¹ against *M. catarrhalis* and *E. faecium*, and 19.0 mmol L⁻¹ against *S. marescens*. The most effective ILs were [C₁₂Bet][Gal] and [C₁₂DMEEA][Gal], followed by [C₁₀DMEA][Gal] and [C₁₀MMorf][Gal]. [C₁₂Bet][Gal] exhibited anti-microbial activity against all tested bacterial strains at a concentration of 2.2 mmol L⁻¹ and lower, except for *P. aeruginosa* (activity at 8.8 mmol L⁻¹ and higher). Generally, the antimicrobial activity of ILs increased with the extension of the alkyl chain and the optimal number of carbon atoms was usually between 10 and 16.⁴² It was also observed that the differences between the MIC and MBC values obtained for the studied ILs were marginal.

Table 5. MIC and MBC values^a for gallate ILs.

Strains		[C ₁₀ DMEA]	[C ₁₀ MMorf]	[C ₁₂ DMEEA]	[C ₁₂ Bet]
<i>M. luteus</i>	MIC	4.9	9.5	2.1	2.2
	MBC	4.9	9.5	2.1	2.2
<i>S. epidermidis</i>	MIC	2.5	4.7	2.1	1.1
	MBC	2.5	9.5	2.1	1.1
<i>S. aureus</i>	MIC	2.5	2.4	2.1	2.2
	MBC	4.9	2.4	2.1	2.2
<i>M. catarrhalis</i>	MIC	4.9	9.5	2.1	1.1
	MBC	4.9	9.5	2.1	1.1
<i>E. faecium</i>	MIC	2.5	9.5	2.1	1.1
	MBC	2.5	9.5	2.1	1.1
<i>E. coli</i>	MIC	2.5	9.5	1.0	1.1
	MBC	4.9	9.5	1.0	1.1
<i>P. aeruginosa</i>	MIC	4.9	9.5	2.1	8.8
	MBC	9.8	9.5	4.1	8.8
<i>S. marescens</i>	MIC	9.8	19.0	4.1	1.1
	MBC	9.8	19.0	4.1	1.1
<i>P. vulgaris</i>	MIC	4.9	4.7	2.1	1.1
	MBC	9.8	9.5	2.1	1.1
<i>B. subtilis</i>	MIC	1.2	2.4	1.0	1.1
	MBC	1.2	2.4	1.0	1.1

^a in mmol L⁻¹.

2.8. Surface activity

Critical micelle concentration (CMC), surface tension at CMC (γ_{CMC}), maximum surface excess (Γ_{max}), minimum area per molecule (A_{min}), adsorption efficiency (pC₂₀) and contact angle (CA) were characterized and are shown in Table 6. The precursors of the obtained ILs demonstrated good surface activity. In the case of [C₁₀Morf][Br] and [C₁₀DMEA][Br] the critical micelle concentrations were at 61 mmol L⁻¹ and 63 mmol L⁻¹, respectively.⁴³ In contrast, pure GA did not reduce the surface tension of water.

Table 6. Surface properties of synthesized ILs.

ILs	CMC (mmol L ⁻¹)	γ_{cmc} (mN m ⁻¹)	$10^6 \Gamma_{\text{max}}$ (mol m ⁻²)	A_{min} (nm ²)	pC ₂₀	CA (°)
[C ₁₀ DMEA][Gal]	27.54	35.12	2.55	6.51	2.16	75.9
[C ₁₀ MMorf][Gal]	21.87	35.63	2.49	6.65	2.25	65.2
[C ₁₂ DMEEA][Gal]	8.71	30.34	2.39	6.96	2.88	72.4
[C ₁₂ Bet][Gal]	0.71	34.61	2.32	7.15	3.82	53.8

However, the aqueous solutions of the obtained antioxidant ILs efficiently reduced the surface tension of water. Significantly lower values of CMC are characteristic for ILs containing the dodecyl alkyl chain in the cation. The lowest value of CMC was observed for [C₁₂Bet][Gal] (0.71 mmol L⁻¹) and for [C₁₂DMEEA][Gal] (8.71 mmol L⁻¹). Thanks to low CMC values, these salts can be described as good surfactants with surface activity similar to conventional compounds such as cetyltrimethylammonium bromide (1.0 mmol L⁻¹)⁴⁴ or sodium dodecyl sulfate (8.4 mmol L⁻¹).⁴⁵ Antioxidant ILs have good wettability properties. Contact angle (CA) values of gallate ILs were determined based on drop shape analysis on the examined surface (paraffin) and are also presented in Table 6. The value of CA of water as a pure solvent on paraffin is approximately 111°. In turn, the lowest value of contact angle on the same tested surface was observed for [C₁₂Bet][Gal] – 53.8°. Fig. S21. in Supplementary data shows the surface tension as a function of the logarithm of concentration. As can be seen, the surface tension values of the aqueous solutions showed a progressive decrease with increasing concentration and remained constant above the CMC.

3. Conclusions

The conducted studies introduce a new direction in the synthesis of antioxidants by preparation of ILs, which may exhibit strong radical scavenging activity and also act as efficient bactericidal and surface active agents. Different ILs derived from naturally occurring gallic acid can be easily prepared with high efficiency using solvents with low toxicity (methanol, acetone). The selection of an appropriate cation allows to design the properties of the gallate ILs, such as solubility in water, octanol-water partition coefficient or surface activity.

Introduction of an antioxidant anion into the structure of ILs allows to obtain salts, which may be an alternative to commonly applied compounds, e.g. gallic acid esters commonly applied in the cosmetics industry. In contrast to such compounds, the gallate ILs exhibit several additional advantages (low CMC, beneficial octanol-water partition coefficient, low MIC/MBC values against Gram-positive and Gram-negative bacteria).

4. Experimental

4.1. Materials

The following reagents used throughout the study were purchased from Sigma-Aldrich and used without further purification: 1-Bromodecane (98%, CAS 112-29-8), 1-bromododecane (97%, CAS 143-15-7), dimethyldodecylamine (97%, CAS 112-18-5), 2-

dimethylaminoethanol (99,5%, CAS 108-01-0), 2-[2-(dimethylamino)ethoxy]ethanol (98%, CAS 1704-62-7), 4-methylmorpholine ($\geq 98\%$, CAS 109-02-4), chloroacetic acid ($\geq 99\%$, CAS 79-11-8), gallic acid (97.5-102.5%, CAS 149-91-7) and 2,2-diphenyl-1-picrylhydrazyl (DPPH, 95%, CAS 1898-66-4). Other chemicals and all solvents were obtained from Avantor Performance Materials Poland S.A. and used as received from the supplier.

4.2. General

^1H and ^{13}C NMR spectroscopic analyses were carried out on a Varian Mercury 300 spectrometer operating at 300 and 75 MHz. Elemental analyses were performed at the Adam Mickiewicz University, Poznan (Poland). The water content measurements were conducted using Aquastar volumetric Karl Fischer titration with composite 5 solution as the titrant and anhydrous methanol as the solvent.

4.3. Thermal analysis

Thermogravimetric analysis was performed using a Mettler Toledo Stare TGA/DSC1 unit. ILs (between 2 and 10 mg) were placed in aluminum pans and heated from 30 to 450 °C at a heating rate of 10 °C min⁻¹ under the flow of nitrogen.

Thermal transition temperatures of the prepared salts were determined using a Mettler Toledo Stare DSC1 apparatus under nitrogen. ILs (between 5 and 15 mg) were placed in aluminum pans and heated from 25 to 120 °C at a heating rate of 10 °C min⁻¹, cooled with an intracooler at a cooling rate of 10 °C min⁻¹ to -100 °C and then heated again to 120 °C.

4.4. Antioxidant properties

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay was carried out according to the method described by Brand-Williams et al.⁴⁶ Methanol solutions of ILs at different known concentrations (0.1 mL) was added to the DPPH solution (3.9 mL, 0.06 mmol L⁻¹). The mixture was shaken vigorously and left in the dark. After 30 min of incubation at room temperature, the absorbance was measured at 515 nm with a Rayleigh UV-1800 spectrophotometer. Gallic acid was used as the reference standard. All determinations were performed in triplicate. DPPH antioxidant activity was calculated on the basis of the following equation:

$$\% \text{ radical scavenging activity} = \left(\frac{A-B}{A} \right) \cdot 100\%$$

where A is the absorbance of the control and B is the absorbance of the samples.

The concentrations of ILs which reduced 50% of the free-radical concentration (IC_{50} values, Table S1, ESI) were processed from the sigmoidal dose response curves (Fig. S15-S19, ESI) using the OriginPro 8.5 program.⁴⁷

4.5. Solubility

The water solubility was determined according to a modified method described by Marrucho et al.⁴⁸ Saturated solutions of ILs were prepared in 10 mL glass vials by addition of an excess amount of salts to DI water (1 mL). The vials were mixed at a temperature of 25 ± 0.2 °C using a Heidolph MR Hei-End stirrer equipped with a Heat-On anodized block. After 48 h of stirring, equilibrium was reached and the samples were centrifuged in order to enhance the complete phase separation. The concentrations of ILs in the saturated solution were quantified *via* UV/Vis spectrophotometry. All measurements were performed in triplicate. The calibration curves of ILs were prepared in DI water and the maximum absorbance values of salts at different known concentrations were collected at the characteristic wavelength of 265 nm for [C₁₂Bet][Gal] and gallic acid or 259 nm for the other ILs. All obtained calibration curves are presented in the ESI (Table S2, ESI).

The solubility of the ILs (0.1 g) in other solvents was measured using the method described in Vogel's Textbook of Practical Organic Chemistry.⁴⁹ 'Complete solubility' applies to ILs, which were dissolved in 1 mL of the solvent, 'limited solubility' means that ILs were dissolved in 3 mL of the solvent, 'insoluble' applies to ILs, that did not dissolve in 3 mL of the solvent. All ILs were thermostated at 25 °C in a water bath MEMMERT WNB 7.

4.6. Octanol–water partition coefficients

Octanol-water partition coefficients (K_{ow}) of gallic acid and gallate ILs were estimated by the shake-flask method according to OECD guidelines.⁵⁰ Measurements of K_{ow} values were conducted using mutually saturated solvents (water and *n*-octanol) and in a 15 mL glass vial containing a magnetic stir bar. Firstly, 5 mL of ILs or free acid solution in saturated water (concentrations in the range of 0.25 to 2 mmol L⁻¹) were added to 5 mL of saturated *n*-octanol. All vials were shaken at a constant temperature of 25 °C. After 24 h, all the samples were centrifuged and the water phase was collected by a syringe. The concentrations of ILs in the water solution were determined spectrophotometrically using a UV/Vis spectrophotometer. Three repetitions of each measurement were performed. The calibration curves are presented in Table S3, ESI.

4.7. Anti-microbial activity test procedure

Anti-microbial activity was determined by the broth microdilution method, according to the approved standard for aerobic bacteria (CLSI document M07-A9). Minimal Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) values were determined. All antimicrobial agents were tested in a series of twofold dilutions from 0.49 to 500 mg mL⁻¹. Cultures of standard tested strains (24 hrs) were suspended in Mueller-Hinton Broth (MHB) to a concentration of 10⁵–10⁶ CFU mL⁻¹.

The following microorganisms were used during the tests: *Micrococcus luteus* NCTC 7743, *Staphylococcus aureus* NCTC 4163, *Staphylococcus epidermidis* ATCC 49134, *Moraxella catarrhalis* ATCC 25238, *Enterococcus faecium* ATCC 49474, *Pseudomonas aeruginosa* NCTC 6749, *Escherichia coli* ATCC 25922, *Serratia marcescens* ATCC 8100, *Proteus vulgaris* NCTC 4635, and *Bacillus subtilis* ATCC 6633. Reference strains were supplied by the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures.

4.8. Surface activity

Surface tension measurements were carried out using a DSA 100 analyzer (Krüss, Germany, accuracy ±0.01 mN m⁻¹), at 25 °C. The surface tension was determined using the pendant drop method. Basically, the principle of this method is to form an axisymmetric drop at the tip of a needle of a syringe. The image of the drop (3 mL) is taken from a CCD camera and digitized. The surface tension (γ in mN m⁻¹) is calculated by analyzing the profile of the drop according to the Laplace equation. Temperature was controlled using a Fisherbrand FBH604 thermostatic bath (Fisher, Germany, accuracy 0.1 ± °C). The values of the critical micelle concentration (CMC) and the surface tension at the CMC (γ_{CMC}) were determined from the intersection of the two straight lines drawn in low and high concentration regions in surface tension curves (γ vs log C curves) using a linear regression analysis method. The image of the drop on the examined surface (paraffin) is the basis for the determination of the contact angle. After determination of the actual drop shape and the contact line, the drop shape is adapted to fit a mathematical model used to calculate the contact angle. The most exact method to calculate this value is Young–Laplace fitting (sessile drop fitting). Complete drop contour is evaluated. After successful fitting of the Young–Laplace equation, the contact angle is determined as the slope of the contour line at the 3-phase contact point (solid–liquid and liquid–air).

4.9. Synthesis of ILs precursors

An acetonitrile mixture (15 ml) containing the long alkyl bromoalkane (15 mmol) or the potassium salt of chloroacetic acid (11.25 mmol) was placed in a semi-automated system EasyMax 102 (Mettler Toledo) equipped with a 50 mL glass reactor, magnetic stirring bar and ReactIR probe. After 5 min of stirring at 80 °C, the appropriate tertiary amine (15 mmol) or dimethyldodecylamine (11.25 mmol) was quickly added. The reaction was carried out at 80 °C and the optimal time of the reaction was determined by ReactIR iC15 (Mettler Toledo) equipped with a MCT detector and a 9.5 mm AgX probe with a diamond tip. Data were sampled from 2500 to 650 cm^{-1} with 8 cm^{-1} resolution and processed by iCIR 4.3 software. Upon completion, the mixture was cooled to 20 °C and the solvent was removed by rotary evaporator under vacuum. Next, the obtained precursors were purified by washing repeatedly with acetone and dried under reduced pressure (5 mbar) at 60 °C for 24 h.

4.10. Synthesis of ILs

Preparation of ILs was carried out in the semi-automated reactor system EasyMax 102 (Mettler Toledo).

Method I: the appropriate quaternary ammonium bromide (0.01 mol) was dissolved with 50 mL of methanol in a 100 mL reaction glass equipped with and mechanical stirrer. Next, 40 mL of anionic resin Dowex Monosphere 550A in the form of methanolic suspension were added and the mixture was stirred for 5 h at 25 °C. After the anion exchange reaction, the resin was filtered off and rinsed repeatedly with methanol. Afterwards, the obtained solution of quaternary ammonium hydroxides was slowly introduced into 50 mL of a methanolic solution of GA (0.01 mol). The neutralization reaction was conducted for 1 h at 0 °C. At the end, the solvent was evaporated by rotary evaporator under vacuum and the product was dried under reduced pressure (5 mbar) at 25 °C for 24 h.

Method II: the amphoteric surfactant (0.01 mol) and 20 mL of methanol were poured into a 50 mL glass reactor containing a magnetic stirring bar. Next, equimolar amount of GA dissolved in 20 mL of methanol was added and the reaction was conducted for 1 h at a temperature of 25 °C. Afterwards, methanol was evaporated by a rotary evaporator under vacuum and the product was dried under vacuum for 24 h at a temperature of 25 °C.

[C₁₀DMEA][Gal] - decyl(2-hydroxyethyl)dimethylammonium gallate:

¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) = 0.83-0.87 (m, 3H, (CH₂)₇CH₃), 1.18-1.31 (m, 14H, CH₂(CH₂)₇CH₃), 1.63 (br.s, 2H, N⁺CH₂CH₂(CH₂)₇), 3.04 (s, 6H, N⁺(CH₃)₂), 3.26-3.31 (m,

2H, HOCH₂CH₂N⁺), 3.35-3.38 (m, 2H, N⁺CH₂CH₂(CH₂)₇), 3.81 (br.s, 2H, HOCH₂CH₂N⁺), 6.85 (s, 2H, Ar); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ (ppm) = 14.0, 21.8, 22.1, 28.5, 28.7, 28.8, 28.9, 31.3, 50.7, 54.9, 64.2, 64.7, 109.0, 127.0, 136.8, 145.9, 171.4; elemental analysis calcd (%) for C₂₁H₃₇NO₆ (M = 399.53 g mol⁻¹): C = 63.13, H = 9.34, N = 3.51, found: C = 63.29, H = 9.21, N = 3.37; IR (neat) 3600-3100 (br), 2927, 2857, 1681, 1546, 1467, 1348, 1220, 1180, 1091, 1041, 965, 883, 796, 733, 679 cm⁻¹.

[C₁₀MMorf][Gal] - 4-decyl-4-methylmorpholinium gallate:

¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) = 0.83-0.88 (m, 3H, (CH₂)₇CH₃), 1.18-1.31 (m, 14H, CH₂(CH₂)₇CH₃), 1.63 (br.s., 2H, N⁺CH₂CH₂(CH₂)₇), 3.10 (s, 3H, N⁺CH₃), 3.37-3.42 (m, 6H, N⁺CH₂CH₂(CH₂)₇, (N⁺CH₂CH₂O)₂), 3.82-3.93 (m, 4H, (N⁺CH₂CH₂O)₂), 6.84 (s, 2H, Ar); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ (ppm) = 14.0, 22.1, 25.8, 28.5, 28.7, 28.8, 28.9 (2x), 29.0, 29.1, 31.3, 45.8, 58.9, 59.8, 64.0, 109.1, 127.3, 136.9, 146.1, 171.8; elemental analysis calcd (%) for C₂₂H₃₇NO₆ (M = 411.54 g mol⁻¹): C = 64.21, H = 9.06, N = 3.40, found: C = 64.53, H = 9.22, N = 3.21; IR (neat) 3600-3100 (br), 2931, 2857, 1685, 1550, 1525, 1469, 1346, 1217, 1180, 1120, 1092, 1041, 968, 891, 856, 794, 727 cm⁻¹.

[C₁₂DMEEA][Gal] - dodecyl[2-(2-hydroxyethoxy)ethyl]dimethylammonium gallate:

¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) = 0.83-0.88 (m, 3H, (CH₂)₉CH₃), 1.18-1.31 (m, 18H, CH₂(CH₂)₉CH₃), 1.62 (br.s., 2H, N⁺CH₂CH₂(CH₂)₉), 3.03 (s, 6H, N⁺(CH₃)₂), 3.24-3.29 (m, 2H, OCH₂CH₂N⁺), 3.44-3.53 (m, 6H, N⁺CH₂CH₂(CH₂)₉, CH₂OCH₂), 3.79 (s, 2H, HOCH₂CH₂O), 6.85 (s, 2H, Ar); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ (ppm) = 14.0, 22.1, 25.8, 28.5, 28.8, 28.9, 29.0, 29.1, 31.3, 50.7, 60.0, 62.3, 63.9, 64.3, 72.2, 109.1, 126.5, 137.1, 146.0, 171.4; elemental analysis calcd (%) for C₂₃H₄₁NO₇ (M = 443.58 g mol⁻¹): C = 62.21, H = 9.32, N = 3.16, found: C = 62.02, H = 9.17, N = 3.25, IR (neat) 3600-3100 (br), 2927, 2857, 1697, 1538, 1467, 1350, 1218, 1182, 1124, 1041, 974, 881, 794, 729, 659 cm⁻¹.

[C₁₂Bet][Gal] - dodecyltrimethylglycine gallate:

¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) = 0.83-0.88 (m, 3H, (CH₂)₉CH₃), 1.17-1.30 (m, 18H, CH₂(CH₂)₉CH₃), 1.62 (br.s., 2H, N⁺CH₂CH₂(CH₂)₉), 3.14 (s, 6H, N⁺(CH₃)₃), 3.45-3.51 (m, 2H, N⁺CH₂CH₂(CH₂)₉), 3.69 (s, 2H, HOOCCH₂N⁺), 6.93 (s, 2H, Ar); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ (ppm) = 14.0, 22.2, 26.0, 28.7, 28.8, 28.9, 29.1 (2x), 29.2, 31.4, 50.1, 63.0, 63.9, 109.0, 121.4, 138.0, 145.8, 165.6, 168.1; elemental analysis calcd (%) for C₂₃H₃₉NO₇ (M = 441.57 g mol⁻¹): C = 62.56, H = 8.90, N = 3.17, found: C = 62.73, H = 8.79, N = 3.25, IR

(neat) 3600-3100 (br), 2927, 2855, 1689, 1614, 1594, 1554, 1454, 1394, 1332, 1270, 1242, 1188, 1047, 1024, 900, 879, 773, 727, 692 cm^{-1} .

4.11. Statistical analysis

Comparisons of antioxidant measurements were carried out in STATISTICA 12 (StatSoft) using one-way analysis of variance (ANOVA) with Tukey's test for post hoc analysis ($p < 0.05$).

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