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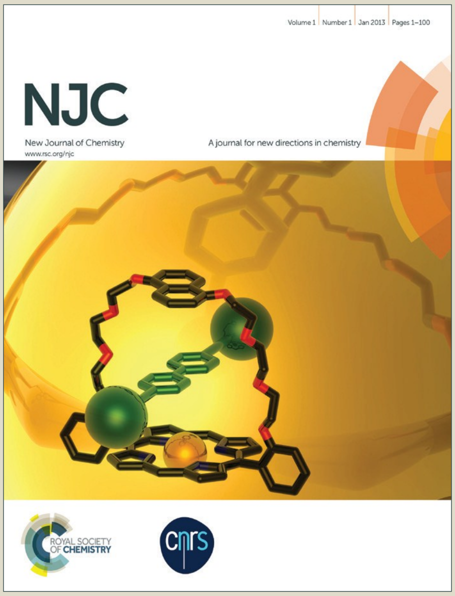

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Herbicidal ionic liquids based on esterquats

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Novel herbicidal ionic liquids (HILs) containing different anions and cations derived from ammonium esterquats were prepared by employing a simple, inexpensive pathway. The basic physicochemical properties of the synthesized salts (such as density, viscosity, refractive index, solubility and thermal stability) were determined. Additionally, their herbicidal efficacy was evaluated under greenhouse and field conditions with subsequent assessment of biodegradability and toxicity (acute oral toxicity towards rats and rainbow trout, growth inhibition test of green algae and acute immobilization test using water flea). The results of greenhouse and field experiments revealed that the herbicidal activity of HILs comprising long alkyl chains has exceeded that of commercial plant protection products. The HIL containing the di(tallowoyloxyethyl)dimethylammonium cation exhibited notable biodegradability (63% after 28 days) and various toxicity classifications depending on the tested organism: category V towards rats with $LC_{50} > 2000$ mg, category II towards fish with LC_{50}/96 h at 10.62 mg/L, category I towards algae and daphnids with E_rC_{50}/72 h at 1.73 mg/L and EC_{50} at 0.28 mg/L, accordingly. These findings provide evidence that synthesis of HILs with a specifically designed structure may be successfully employed for obtaining novel, efficient and environmentally friendly plant protection agents.

Introduction

The use of herbicides has become a necessity for modern agriculture due to the fact that weeds compete strongly with crop plants and significantly reduce the size and quality of yield.[1] The yield losses due to the occurrence of weeds were always much higher than those caused by diseases and pests, therefore the proper protection against weeds is the most cost-effective treatment in plant production.[2]

Currently, chemical herbicides play a dominant role in weed management strategies because their application is the most effective and cheapest method to control weeds throughout the growing season.[3] Moreover, the use of herbicides may reduce or even eliminate soil cultivation, which is very important, especially in areas with water deficits and risk of soil erosion. Without the use of herbicides it would not be possible to implement the no-tillage technology on a wider scale. Chemical weed control offers many advantages but also has several disadvantages.

The herbicides are introduced directly into the environment at relatively high doses. Volatilization and drift of agricultural run-off allows the commercial herbicidal formulations to spread in the environment and cause unintended contaminations. Depending on the environmental conditions, the active substances may not undergo complete biodegradation and instead transform into toxic metabolites, which accumulate and cause negative effects. The commercial formulations of herbicides also contain various additives, which improve their biological activity. In many cases these formulations are more toxic than the active ingredients alone.[4]

Herbicidal ionic liquids (HILs) may be a potential solution to this problem. These novel chemical compounds are defined as organic salts containing herbicidal anions with a melting point below 100 °C. The first publication regarding HILs in 2011[5] showed that it was possible to obtain a new type of herbicides, which exhibit increased biological activity and multifunctional properties. This provided the opportunity to produce novel, effective formulations based on currently manufactured herbicides, such as halogenated derivatives of phenoxyacetic acid (2,4-D, MCPA and MCPP)[5-8] or benzoic acid (Dicamba),[9] fomesafen[10], glyphosate[11] and sulfonylurea (metsulfuron methyl).[12] It is also possible to synthesize HILs, which display two different biological functions. As a result, the HILs may simultaneously act as herbicide and a growth regulator or fungicide, protecting the crops against undesired organisms and allowing to increase their productivity.[13-16]

HILs may be employed as a safer alternative to commonly available crop protection agents. The first advantage of HILs compared to commercial herbicidal formulations is associated with their limited volatility.[9] This eliminates the problem of contamination *via* air emissions. Moreover, the selection of appropriate counter-ions allows to obtain HILs with preferred physiochemical properties and improved efficiency.[8] For example, the common water-soluble herbicide formulations require the addition of a surface-active adjuvant.[17] In contrast, HILs may be synthesized from cations, which were designed to provide surface-active properties. This eliminates the necessity of using additional adjuvants and often increases their biological activity compared to commercial crop protection agents, allowing to achieve similar effects at lower doses.[7,8] Additionally, the chemical structure of the cation may be modified in order to directly regulate the environmental impact, toxicity and biodegradability.[5,15]

Furthermore, several novel reports also show that HILs may be used in order to improve the immunity of plants to pathogenic factors, e.g. by inducing plant systemic acquired resistance towards viral diseases[18,19] or fungi.[20] Recently, protic ILs have been described as solvents for the solubilisation and stabilization of viruses.[21]

The aim of this study was to develop representatives of HILs, which would be cheap, easy to obtain, safe to synthesize, efficient in action (especially in terms of lowering the herbicide dosage) and non-hazardous for the environment. In order to achieve these goals, esterquats were chosen as the source of cations. Esterquats, also known as "cleavable surfactants",[22] are primarily used as the main component of fabric softeners and emulsifiers. These compounds meet European recommendations regarding environmental safety and are biodegradable substitutes to traditional quaternary ammonium salts.[23] The precursors of the planned HILs included esterquats [2-(methacryloyloxy)ethyl]trimethylammonium chloride [MATMA][Cl] and [2-(acryloyloxy)ethyl]trimethylammonium chloride [ATMA][Cl], which are derivatives of choline and methacrylic acid or acrylic acid, respectively. ILs containing the choline cation and its derivatives exhibit low toxicity and high biodegradability.[24-26] The selected chlorides are commonly used as cheap coagulants in industrial cleaning processes and are also utilized in the production of ion-exchange resins and antistatic coatings[27] or co-polymer floculants.[28-30] Additionally, quaternary ammonium methacrylate exhibits fungistatic properties against all strains of *Candida albicans*, *Candida krusei*, and *Candida parapsilosis*.[31] Recently, MATMA-based cation and its derivatives have been used for the synthesis of ionic liquids.[32-34]

Results and discussion

Eleven novel salts were synthesized by employing the metathesis reaction (Scheme 1). Their basic physicochemical and thermal properties as well as solubility were determined and after evaluation of their herbicidal efficiency during greenhouse and field studies, the selected compounds were subjected to biodegradability and toxicity tests. These salts, presented in Table 1, were based on three types of esterquats: [2-(acryloyloxy)ethyl]trimethylammonium (**1-4**), [2-(methacryloyloxy)ethyl]trimethylammonium (**5-8**) and di(tallowoyloxyethyl)dimethylammonium (**9-11**) chlorides. During the one-step metathesis reaction, the chlorides were substituted by herbicidal anions, such as (4-chloro-2-methylphenoxy)acetate (MCPA), 2-(4-chloro-2-methylphenoxy)-propionate (MCPP), (2,4-dichlorophenoxy)acetate (2,4-D) or 3,6-dichloro-2-methoxybenzoate (Dicamba). The structures of the anions were shown in Figure 1.

The synthesis was conducted at ambient temperature using methanol as a solvent. As the result of the anion exchange reaction, the by-product (KCl) precipitated from the reaction medium and was separated by filtration. The products were additionally purified by precipitation of KCl from anhydrous acetone or isopropanol. Finally, the products were dried in vacuum at 45 °C for 24 h and stored over P_4O_{10}. The synthesized salts did not undergo phase transfer to the solid state under 100 °C, therefore they may be classified as ILs. The obtained ILs **1-3** and **5-7** were in liquid state, whereas ILs **4** and **8** (with the 2,4-D anion) as well as ILs **9-11** (comprising two tallow alkyl substituents) were in a semisolid state**,** which was similar to greases. The water content of synthesized ILs was determined by Karl-Fischer measurements. It was found to be less than 500 ppm for ILs **1-8** and less than 1000 ppm for ILs **9-11**. All the ILs were obtained with a yield, exceeding 90% in all cases. They were characterized by ^{1}H and ^{13}CNMR (the spectra were presented in section 1 of ESI, figures S1-S22). The purity of ILs with long alkyl chains (**9-11**) was determined *via* the direct two-phase titration technique (EN ISO 2871-2: 2010), which allows for the determination of the surface active substance content. This method proved to be a quick and precise tool for confirming the high purity of ILs (from 96 to 99%). Physicochemical properties of the obtained room temperature ionic liquids (RTILs) **1-3** and **5-7** were determined at 20 °C and presented in Table 1 (additional data regarding the elemental analysis were presented in section 2 of the ESI).

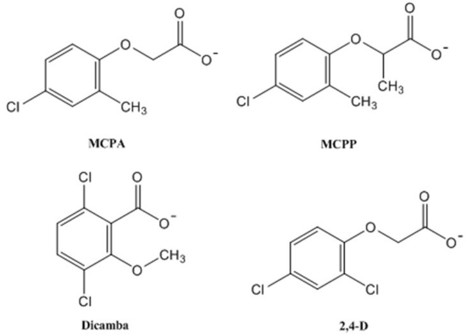
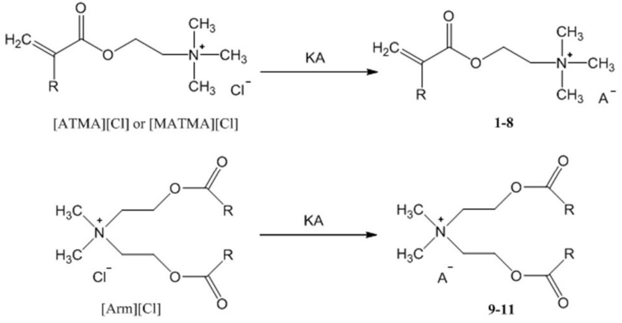


Figure 1. Structure of anions.



Scheme 1. The synthesis of ammonium esterquat HILs.

Table 1. Characterization of the synthesized ILs and their basic physicochemical properties.

IL	R	Anion	Yield [%]	State	Surfactant content [%]	Density[a] (g/mL)	Viscosity[a] (mPa s)	Refractive index[a]
1	H	MCPA	99	Liquid	-	1.2057	51.0	1.5210
2	H	MCPP	96	Liquid	-	1.1663	53.0	1.5126
3	H	Dicamba	97	Liquid	-	1.2527	17.0	1.5230
4	H	2,4-D	91	Grease	-	-	-	-
5	CH_3	MCPA	98	Liquid	-	1.1642	81.0	1.5152
6	CH_3	MCPP	94	Liquid	-	1.1502	139.0	1.5109
7	CH_3	Dicamba	99	Liquid	-	1.2113	19.0	1.5194
8	CH_3	2,4-D	95	Grease	-	-	-	-
9	Tallow[b]	MCPA	97	Grease	99	-	-	-
10	Tallow[b]	MCPP	98	Grease	98	-	-	-
11	Tallow[b]	2,4-D	93	Grease	96	-	-	-

[a]At 20 °C; [b] tallow (alkyl chain distribution $C_{12}H_{25}$ - 1, $C_{14}H_{29}$ - 4,$C_{16}H_{33}$ - 31, $C_{18}H_{37}$ - 64%).

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Table 2. Thermal properties of synthesized ILs (determined by TGA/DSC analysis).

IL	R	Anion	T_g[a] (°C)	T_{cryst}[b] (°C)	T_m[c] (°C)	$T_{onset5\%}$[d] (^{o}C)	T_{onset}[e] (^{o}C)
1	H	MCPA	-16	-	-	200	260
2	H	MCPP	-18	-	-	190	265
3	H	Dicamba	-32	-	-	192	228
4	H	2,4-D	-47	-	-	200	235
5	CH_3	MCPA	-20	-	-	195	250
6	CH_3	MCPP	-22	-	-	200	278
7	CH_3	Dicamba	-15	-	-	187	219
8	CH_3	2,4-D	-13	-	-	198	240
9	Tallow	MCPA	-9	43	42	208	375
10	Tallow	MCPP	-38	36	45	200	300
11	Tallow	2,4-D	-	8	-3	205	290

[a] T_g – glass transition temperature; [b] T_{cryst} – temperature of crystallization; [c] T_m – melting point; [d] $T_{onset5\%}$ – decomposition temperature of 5% sample; [e] T_{onset} – decomposition temperature.

The density of RTILs containing an ester of acrylic acid (**1-3**) was higher compared to the density of RTILs, which were esters of methacrylic acid (**5-7**). The presence of the methyl group near the double bond increased the volume occupied by the molecule, which contributed to a reduction of density. Furthermore, the type of the anion also influenced the value of density for RTILs. RTILs containing the MCPP herbicide (**2**, **6**) exhibited the lowest density, which amounted to 1.1663 and 1.1502 g/mL, respectively. The use of the MCPA anion resulted in a slight increase of density (**1**, **5**), whereas the highest values were achieved for RTILs with the Dicamba anion (**3**, **7**). The data presented in Table 1 allowed to classify the synthesized RTILs as compounds, which possess low viscosity. RTILs **5-7** exhibited viscosity values ranging from 19.0 (for **7**) to 139.0 mPas (for **6**). The absence of methyl group near the unsaturated bond resulted in reduced viscosity (**1-3**). The lowest viscosity value was at 17.0 mPas (for **3**), whereas the highest value was at 53.0 mPas (for **2**). It is also worth noticing that RTILs with the Dicamba anion (**3**, **7**) were characterized by significantly lower viscosity values. It was observed that the value of the refractive index (Table 1) depended on both the type of cation and the type of anion. In all cases, the RTILs containing a cation with the methacrylate group exhibited lower refractive index values compared to RTILs without the methyl substituent. Additionally, RTILs comprising the Dicamba anion (**3**, **7**) exhibited the highest values (1.5230 and 1.5194, respectively).

Thermal gravimetric analysis and differential scanning calorimetry data for the ILs were presented in Table 2. Among the eleven prepared esterquat-based ILs, only three (all containing the di(tallowoyloxyethyl)dimethylammonium cation) possessed a melting point (T_m = 42 °C for **9**; 45 °C for **10** and -3 °C for **11**) and a crystallization event on cooling at 43 °C, 36 °C and 8 °C, respectively. The presence of two high molecular weight alkyl chain substituents in the ammonium cation might be the main cause of this behaviour, which was confirmed the fact that ILs **1-8** (with low weight alkyl chain substituents) did not exhibit melting or crystallization during the analyses. Aside from one exception (**11**), all of the prepared ILs exhibited glass transitions, however, the obtained results were diversified and did not allow to determine the effect of the type of cation or herbicidal anion on this parameter. For example, the lowest glass transition temperature (T_g = -47 °C) was observed for IL **4**, whereas a much higher value was noted for IL **8** (T_g = -13 °C), while both comprised the 2,4-D anion. Furthermore, the highest glass transition (T_g = -9 °C) was observed for IL **9**, while a very low value of glass transition was observed for IL **10** (Tg = -38 °C), which suggests that the presence of long alkyl substituents in the cation may not affect phase transition. Despite the presence of at least one ester or unsaturated bond, all ILs exhibited high thermal stability. The lowest value of decomposition temperatures $T_{onset5\%}$ was observed for both ILs with the Dicamba anion: 187 °C for **7** and 192 °C for **3**, respectively. Moreover, the results demonstrated that ILs containing the di(tallowoyloxyethyl)dimethylammonium cation possessed slightly higher $T_{onset5\%}$ values (from 200 to 208 °C). This tendency is also visible for the obtained values of decomposition temperatures T_{onset}, wherein ILs **9-11** exhibited the highest thermal stability. In accordance with $T_{onset5\%}$ data, the lowest decomposition temperatures (T_{onset}) were observed for both ILs with the Dicamba anion (219 °C for **7** and 228 °C for **3**). On the other hand, the highest value (T_{onset} = 375 °C) was noted for IL **9**, which also exhibited all three phase transitions (glass transition, crystallization and melting).

Table 3. Solubility of the synthesized ILs at 20 °C.

	Solvent									
IL	A	B	C	D	E	F	G	H	I	J
1	+	+	+	+	+	+	+	+	-	-
2	+	+	+	+	+	+	+	+	-	-
3	+	+	+	-	+	+	+	+	+	-
4	-	+	+	-	-	±	-	-	-	-
5	+	+	+	+	+	+	+	+	-	-
6	+	+	+	+	+	+	+	+	-	-
7	+	+	+	+	+	+	+	+	+	-
8	-	+	+	-	-	±	-	-	-	-
9	-	+	+	-	+	+	+	+	+	+
10	-	+	+	-	+	+	+	+	+	+
11	-	+	-	-	-	+	-	+	+	±

A – water, B – methanol, C – DMSO, D – acetonitrile, E – acetone, F – 2-propanol, G – ethyl acetate, H – chloroform, I – toluene, J – hexane; "+"– complete solubility; "±"– limited solubility; "-"– insoluble.

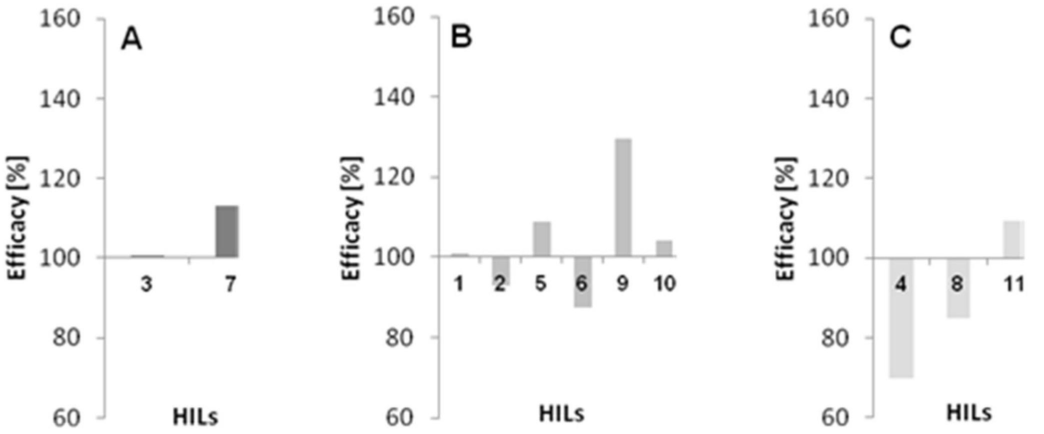

Figure 2. Efficacy of tested ILs **1-11** against white mustard (*Sinapis alba* L.) during greenhouse experiments in comparison to appropriate commercial formulations (commercial formulations = 100%): A - Dicamba; B - MCPA; C - 2,4-D.

The solubility of ILs in popular solvents was shown in Table 3. The experiment proved that the ILs are stable in contact with air and moisture. In general, acrylates and methacrylates demonstrated similar results during solubility studies. This suggests that methyl group located near the double bond has a marginal impact on this property. On the other hand, the influence of the anion was notable. The use of the 2,4-D anion (4 and 8) caused insolubility in acetone, acetonitrile, water, ethyl acetate and chloroform, whereas ILs with the Dicamba anion (3 and 7) exhibited increased solubility in toluene. The remaining ILs, which contained long alkyl substituents in the structure of cation (9-11), were insoluble in water due to their high hydrophobicity. Hence, they were highly soluble in solvents with low polarity indices, such as toluene or hexane. All the obtained ILs were highly soluble in short-chain alcohols and DMSO (except 11).

The herbicidal activity of the synthesized ILs was tested under greenhouse conditions in order to evaluate their effectiveness in weed control. The activity of ILs 1-11 was tested against white mustard (*Sinapis alba* L.). The results of fresh weight reduction compared with appropriate commercial formulations obtained during greenhouse experiments were presented in Figure 2.The highest efficacy of fresh weight reduction in comparison to the commercial formulation was observed for ILs **9** and **5**, which contained MCPA as the anion. These ILs proved to be superior compared to the commercial formulation (Chwastox Extra 300 SL). IL **1** exhibited herbicidal activity at a similar level to that of the reference product. However, the lack of the long substituent in the structure of the cation in ILs with the 2,4-D herbicide (**4**, **8**) decreased the efficacy of this phenoxy acid in comparison to the reference herbicide (Aminopielik Standard 600 SL). On the basis of results obtained during the performed tests, it was established that the commercial formulations as well as IL **3** containing the Dicamba anion did not exhibit a high herbicidal activity against white mustard. Only IL **7** exhibited a marginal impact on the reduction of the plant fresh weight.

Subsequent field studies conducted on lambsquarters overgrowing spring barley were conducted for ILs **3** and **7** with the Dicamba anion and ILs **9-11** with MCPA, MCPP and 2,4-D anions, respectively (Figure 3). Herein, IL **7** has caused complete eradication of lambsquarters in comparison to the commercial product, while the commercial formulation was less effective.

ILs **9-11,** comprising phenoxy acids, exhibited excellent efficacy against lambsquarters during field studies (Figure 3). The obtained results proved that the biological activity of IL **9** was superior compared to that of the commercial formulation (Chwastox Extra 300 SL). Similar results were obtained for IL **11** with the 2,4-D anion. Likewise, IL **10** (containing the rarely used herbicide MCPP) was characterized by a high herbicidal activity, which was higher compared to both commercial preparations. The obtained results allow to classify all of the synthesized ILs as HILs. The highest herbicidal efficacy was observed for HIL **9**, therefore it was subjected to biodegradability studies along with other MCPA-based HILs (**1** and **5**) in order to compare the influence of different cations.

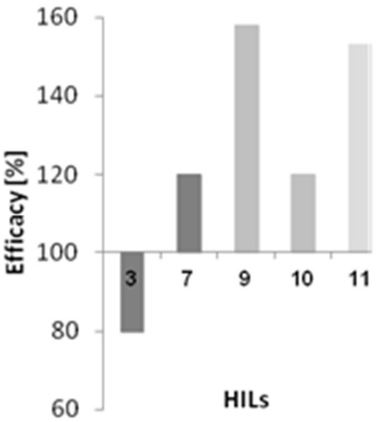

Figure 3. Efficacy of ILs **3**, **7**, **9-11** against common lambsquarters (*Chenopolium album* L.) during field experiments in comparison to appropriate commercial formulations (commercial formulations = 100%).

Table 4. Biodegradation (n=3) of salts and their classification according to OECD 301 F test conditions.

Salt	Biodegradation after 28 days [%]	Time window between 10% and 60% [days]	Classification
[ATMA][Cl][a]	73±4	6	Readily biodegradable
[MATMA][Cl][b]	70±3	7	Readily biodegradable
[Arm][Cl][c]	91±6	4	Readily biodegradable
MCPA free acid	11±4	-	Not readily biodegradable
1	37±3	-	Not readily biodegradable
5	29±5	-	Not readily biodegradable
9	63±5	9	Inherently/readily biodegradable

[a] [2-(acryloyloxy)ethyl]trimethylammonium chloride,
[b] [2-(methacryloyloxy)ethyl]trimethylammonium chloride,
[c] di(tallowoyloxyethyl)dimethylammonium chloride.

The results of biodegradability tests of the studied HILs (**1**, **5**, **9**), their precursor compounds as well as MCPA were presented in Table 4. All of the studied precursor compounds (chlorides) were susceptible to biodegradation, exceeding 60% within a 10 days window frame. This fact allows to classify them as readily biodegradable. [Arm][Cl] exhibited the highest biodegradation efficiency (91±6%) and should be considered as the most promising for commercial use. Exchange of the chloride to MCPA anion resulted in an overall decrease of biodegradability. As a result, both HILs **1** and **5** were classified as not readily biodegradable, reaching a biodegradation efficiency of 37±3 and 29±5% within 28 days, respectively. This effect should be attributed to MCPA, which is well known for being not readily biodegradable according to OECD 301 F tests. Low biodegradability of ILs has been reported in many relevant reviews, however it has also been established that readily or inherently biodegradable representatives may be found.[35,36] Only HIL **9** was biodegraded to the extent allowing to classify this HIL between inherently and readily biodegradable (63±5%), depending on the standard error out of 3 measurements. It should be mentioned that prolonged exposure of the activated sludge to the tested compounds may increase the biodegradation potential, thus final classification might vary. The obtained results suggest that incorporation of the di(tallowoyloxyethyl)dimethylammonium cation into the structure facilitates the biodegradability of HILs. The highest biodegradation efficiency was observed for HIL **9**, therefore it was subjected to further toxicity and ecotoxicity studies.

The comparison of toxicity of the studied HIL **9** and literature data for herbicides in the acidic form was presented in Table 5. The results of acute oral toxicity studies of HIL **9** revealed that the studied compound exhibited marginal toxicity towards rats. Following single administration of the tested HIL at a dose of 300 mg/kg b.w. (body weight) to one animal used in the sighting study, no signs of toxicity were stated. The animal survived the experiment. Following single administration of HIL **9** at a dose of 2000 mg/kg b.w. to the other animals used in the sighting study and the main study, a wavering gait and a slight decrease in locomotor activity were stated on day 0. A wavering gait and a slight decrease in locomotor activity were also noticed on days 1 and 2. The rounded back, a wavering gait, and a slight decrease in locomotor activity were stated on days 3 and 4. No signs of toxicity were observed between day 5 and day 14. The animals survived the experiment, therefore no lethal concentration values could be established. During the 14-day experiment, no notable changes of the body weight have been observed either in the first animal used during the sighting study (dose of 300 mg/kg b.w.) or the remaining animals used during the sighting and main study (dose of 2000 mg/kg b.w.). The results of the gross examinations revealed all of the studied animals did not exhibit any pathological changes. The category for mammalian acute toxicity based on median lethal concentration LC_{50} > 2000 mg per kilogram of body weight is classified as category V.[39] Based on these criteria and the obtained results, it can be established that the acute oral toxicity of HIL **9** towards rats was generally low. Overall, HIL **9** exhibited notably lower toxicity towards rats compared to herbicides in the acidic form.

Table 5. Comparison of toxicity of HIL **9** and herbicides in the acidic form.[37,38]

Type of toxicity test	HIL**9**	MCPA	MCPP	2,4-D	Dicamba
Acute oral toxicity towards rats - LD_{50} [mg/kg]	> 2000	700-1160	930-1210	300-666	757-1707
Acute toxicity towards rainbow trout - 96-h LD_{50} [mg/L]	7-17	50-232	124-240	1-100	100-135
Acute toxicity towards green algae - 72-h E_rC_{50} [mg/L]	1.6-1.9	80	n.d.a.	n.d.a.	n.d.a.
Immobilization of water flea - 48-h EC_{50} [mg/L]	0.2-0.5	>180	>100	>100	>41

n.d.a. – no data available, the tests were carried out with other algae species or salts of herbicides.

Results of the acute toxicity tests towards rainbow trout (*Oncorhynchus mykiss*) were based on the nominal concentrations of the test compound and the results of observations of the fish for mortality. No mortality and no symptoms of intoxication (loss of equilibrium or changes in swimming behavior, respiration, or pigmentation) were observed during the exposure when HIL **9** was administered at concentrations of 0.9 and 1.9 mg/L and in the control. At test concentrations of 4.3 and 9.4 mg/L one fish was dead after 96 h of the exposure. At test concentrations of 20.7, 45.5 and 100 mg/L all fish were dead after 96 h of exposure. The determined endpoint lethal concentration values were at 1.9 mg/L for LC_0, 10.62 mg/L for LC_{50} (95% confidence interval: 6.78 – 16.62) and 20.7 mg/L for LC_{100} after 96 h of exposure, accordingly. The LOEC/96 h value for the yield was at 20.7 mg/L, whereas the NOEC/96 h value for the yield was at 9.4 mg/L. The available results indicate that the toxicity of HIL **9** is within the concentration range of 5-50 mg/L and can be classified as category II towards rainbow trout.[39] Hence, HIL **9** can be classified as slightly to moderately toxic towards rainbow trout. Overall, HIL **9** exhibited higher toxicity towards rainbow trout compared to commercial herbicides in the acidic form.

The results of growth inhibition tests of green algae (*Pseudokirchneriella subcapitata*) revealed different morphological and inhibitory responses depending on the concentration of the tested HIL **9**. At test concentrations of 0.01, 0.03, 0.1 and 0.31 mg/L no morphology differences were reported as compared to the algae cells in the control, whereas when HIL **9** was administered at test concentrations of 1.0, 3.1 and 10 mg/L the algal cells were shaped like a comma. The concentrations causing an inhibition of the growth rate of green algae were established accordingly: E_rC_{10}/72 h value was at 0.56 mg/L (95% confidence limits: 0.47-0.64), E_rC_{20}/72 h value was at 0.82 mg/L (95% confidence limits: 0.72-0.91) and E_rC_{50}/72 h value was at 1.73 mg/L (95% confidence limits: 1.60-1.86). The LOEC/72 h value for the growth rate was at 0.31 mg/L, whereas the NOEC/72 h value for the growth rate was at 0.1 mg/L. The concentrations causing an inhibition of yield of green algae were established accordingly: E_yC_{10}/72 h value was at 0.08 mg/L (95% confidence limits: 0.04-0.13), E_yC_{20}/72 h value was at 0.15 mg/L (95% confidence limits: 0.09-0.21) and E_yC_{50}/72 h value was at 0.48 mg/L (95% confidence limits: 0.37-0.62). The LOEC/72 h value for the yield was at 0.1 mg/L, whereas the NOEC/72 h value for the yield was at 0.03 mg/L. The obtained E_rC_{50} value is within the concentration range of ≤5 mg/L,[39] which indicates that HIL **9** can be classified as category I towards green algae. The toxicity of HIL **9** towards green algae was higher compared to that of MCPA in the acidic form.

Results of acute immobilization tests using water flea (*Daphnia magna*) revealed that no immobilization was observed in the control and during exposure at the test concentrations of HIL **9** of 0.0625 and 0.125 mg/L. After 48 h of the exposure to HIL **9** at a concentration of 0.25 mg/L the immobilization was 15%. At the test concentrations of 0.5, 1.0 and 2.0 mg/L the immobilization was 100%. The determined endpoint effective concentration values were at 0.125 mg/L for EC_0, 0.284 mg/L for EC_{50} and 0.5 mg/L for EC_{100} after 48 h of exposure, accordingly. The LOEC/48 h value was at 0.5 mg/L, whereas the NOEC/48 h value was at 0.25 mg/L. The obtained results indicate that HIL **9** is in the concentration range of ≤5 mg/L,[39] therefore HIL **9** should be classified as category I towards the water flea. The comparison of the EC_{50} value with those of herbicides in the acidic form suggests that the obtained value is lower by three or two orders of magnitude. Higher toxicity towards aquatic organisms may be attributed to the surface-active properties of the cation, which may contribute to an increase of bioavailability of HIL **9** in the aquatic environment.

Conclusions

The conducted studies have presented a simple method for the synthesis of novel herbicidal ionic liquids and confirmed the high application potential of the obtained ionic liquids containing esterquats with short and long alkyl chains in the structure of the cation. All of the eleven synthesized esterquats could be classified as ionic liquids, whereas six of them were room temperature ionic liquids. Despite the presence of at least one ester bond, the obtained compounds were characterized by high chemical stability at a wide temperature range. Moreover, the greenhouse experiments and fields tests showed that some of the novel forms of herbicides exhibited high efficacy against dicotyledonous weeds. Particularly excellent results, which exceeded the currently applied commercial formulations many times, were achieved for the herbicidal ionic liquid based on a di(tallowoyloxyethyl)dimethylammonium cation. This herbicidal ionic liquids was susceptible to biodegradation processes (63% after 28 days) and displayed various toxicity classifications depending on the tested organism: category V towards rats with LC_{50} > 2000 mg, category II towards fish with LC_{50}/96 h at 10.62 mg/L, category I towards algae and daphnids with E_rC_{50}/72 h at 1.73 mg/L and EC_{50} at 0.28 mg/L, accordingly. These traits suggest that such HILs are unlikely to become a hazard or accumulate in the environment. Additionally, their improved herbicidal efficacy may contribute to a lower dosage, which ultimately leads to a decrease of environmental pollution. The presented results open a new path for synthesizing HILs from widely available, inexpensive and environmentally friendly materials in order to obtain an improved and non-hazardous alternative to commercial herbicidal formulations.

Experimental

General

[2-(Acryloyloxy)ethyl]trimethylammonium chloride ([ATMA][Cl], CAS Number 44992-01-0) and [2-(methacryloyloxy)ethyl]-trimethylammonium chloride ([MATMA][Cl], CAS Number 5039-78-1) were obtained from Sigma Aldrich as water solutions (80%). Di(tallowoyloxyethyl)dimethylammonium chloride ([Arm][Cl], purity 80%,) was purchased from Akzo Nobel as Armosoft DEQ. All herbicidal acids were supplied by Organika-Sarzyna S.A. Poland and PESTINOVA Poland. Other chemicals such as sodium hydroxide, potassium hydroxide, inorganic salts and solvents were purchased from Sigma Aldrich and used without further purification. The NMR spectra and the results of CHN elemental analysis can be found in the ESI (section 1).

Preparation of ionic liquids

The appropriate amount (0.05 mol) of [2-(methacryloyloxy)ethyl]-trimethylammonium chloride, [2-(acryloyloxy)ethyl]trimethylammonium chloride or di(tallowoyloxyethyl)dimethylammonium chloride and 35 mL of methanol were mixed in the reaction flask. Afterwards, 15 mL of the methanolic suspension containing the potassium salt of 2,4-D (0.05 mol) or the methanolic solution of MCPA, MCPP or Dicamba potassium salts (0.05 mol) were slowly added. The reaction was conducted under constant stirring at ambient temperature for 1.5 hour. As the result of the anion exchange reaction, the by-product (potassium chloride) precipitated from the reaction solution. The inorganic salt was separated by filtration and methanol was removed by the evaporation under vacuum. The raw product was dried and then dissolved in 50 mL of anhydrous acetone (**1**-**3**, **5**-**7**, **9**, **10**) or anhydrous isopropanol (**4**, **8**, **11**). The obtained precipitate was separated *via* vacuum filtration and the solvent was evaporated. Finally, the product was dried under reduced pressure at 45 °C for 24 h.

Density

Density was measured by employing the mechanical oscillator method, using an Automatic Density Meter DDM2911. Density of the samples (about 2.0 mL) was measured at 20 °C, with respect to temperature controlled *via* Peltier. The apparatus was calibrated using deionized water and reference substances with defined density. After each series of measurements the densimeter was washed with methanol or acetone and dried. The uncertainty of measurements was estimated to be less than 10^{-4} g/mL.

Refractive indices

Refractive indices were determined using an Automatic Refractometer J357 containing electronic temperature control with the accuracy ±0.05 °C.

Dynamic viscosity

Viscosity of all the ILs was determined using a rheometer (Rheotec RC30-CPS) with cone-shaped geometry (C50-2). The viscosity of the samples (about 1.5 mL) was measured at 20 °C.

Thermal analysis

Thermal transition temperatures of the obtained salts were determined by DSC, using a Mettler Toledo Star^e TGA/DSC1 apparatus (Leicester, UK). During analysis of phase transition temperature values samples between 5 and 15 mg were placed in aluminum pans, heated from 25 to 120 °C at a heating rate of 10 °C/min and cooled using an intracooler at a cooling rate of 10 °C/min to -100 °C. During analysis of decomposition temperature values samples 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. Nitrogen was used as a carrier gas.

Solubility

The solubility of the prepared salts was determined according to Vogel's Textbook of Practical Organic Chemistry.[40] Ten popular representative solvents were chosen and ranked in the descending order of Snyder polarity index value (water – 9.0, methanol – 6.6, DMSO – 6.5, acetonitrile – 6.2, acetone – 5.1, ethyl acetate – 4.3, 2-propanol – 4.3, chloroform – 4.1, toluene – 2.3, hexane – 0.0). ‘Complete solubility’ applies to ILs, which were dissolved (0.1 g of IL) in 1 mL of the solvent, while ‘limited solubility’ means that ILs were dissolved in 3 mL of the solvent. The ‘insoluble’ term is used to classify ILs, which did not dissolve in 3 mL of the solvent. All samples were thermostated at 20 °C.

Greenhouse experiments

The herbicidal efficacy of the obtained HILs was tested using white mustard (*Sinapis alba* L.) as the test plant. All salts were dissolved in a mixture of water and ethanol (1:1 v/v). Commercial products Chwastox Extra 300 SL (300 g of sodium and potassium salts of of MCPA in 1 L), Aminopielik Standard 600 SL (600 g of dimethylammonium salts of 2,4-D in 1 L) and Dikamba 480 SL (480 g of dicamba in 1 L) were used as reference compounds.

Plants seeds were sown into pots (0.5 L) and kept in a greenhouse at a temperature of 20 °C, humidity of 60% and photoperiod of 16/8 h day/night. The plants were treated by herbicides at 4-6 leaves growth stage. The treatments were applied using a moving sprayer (APORO, Poznan, Poland) with TeeJet 110/02 flat-fan nozzles (TeeJet Technologies, Wheaton, IL, USA) delivering 200 L of spray solution per 1 ha at 0.2 MPa operating pressure. The distance from the nozzles to the tips of the plant was 40 cm. The experiments were carried out in four replications in a completely randomized setup. After 2 weeks, the plants were cut at the soil level and weighed (at 0.01 g accuracy). The reduction of plant fresh weight was measured and compared to control (plants, which were not sprayed with herbicidal formulations). The synthesized ILs with MCPA, MCPP and 2,4-D anions were applied at a dose of 400 g of active substance per 1 ha. For salts containing Dicamba, the dose was equal to 200 g of active substance per 1 ha.

Field experiments

The field trials were carried out in spring barley in 2012 and 2013 at the Experimental Station in Winna Gora (western Poland - E: 17°26', N: 52°12'). Spring barley was cultivated according to the local agricultural practice. The plot size was 16.5 m^2. The experimental design involved a randomized block with four replications. The test plants were common lambsquarters (*Chenopodium album* L.). The spray solutions were prepared as mentioned above in greenhouse experiments. The treatments were applied at the 4-6 leaves growth stage of weed plants using a small plot spraying equipment with TeeJet DG110/02 flat-fan nozzles (TeeJet Technologies, Wheaton, IL, USA) capable of delivering 200 L/ha of spray solution at 0.3 MPa operating pressure. The standard treatments were the same as in greenhouse experiments. A weed control was evaluated visually 4 weeks after the application of herbicides using a scale of 0 (no effect) to 100% (complete weed destruction).

Ready biodegradability according to OECD 301 F test – manometric respirometry

The test was performed according to OECD guideline for 301 F test. The biological oxygen demand (BOD) was determined every 24 h for 28 days using the OxiTop system (WTWGmbH Weilheim Germany) in a thermostated incubator (IKA Germany) covered with aluminum foil. The activated sludge was collected from a local municipal wastewater treatment plant (Kozieglowy, Poznan, Poland). Prior to use, the activated sludge was aerated for 7 days in mineral medium which was also used for subsequent tests. The mineral medium consisted of KH_2PO_4 - 85 mg/L, K_2HPO_4 – 220 mg/L, $Na_2HPO_4{\cdot}2H_2O$ – 220 mg/L, NH_4CL – 17 mg/L, $CaCl_2{\cdot}2H_2O$ – 37 mg/L, $MgSO_4{\cdot}2H_2O$ – 23 mg/L, $FeCl_3$– 0.25 mg/L. The measured pH was at 7.2. The test was performed in brown glass bottles containing mineral medium, inoculum (cell density at approx. 10^6 cells/mL determined with plastic Paddle Tester for aerobic bacteria, Hach, USA) and tested ILs at a concentration of approx. 10-30 mg/L, which was equal to 100 mg/L of Theoretical Oxygen Demand (ThOD, calculated based on equation 1).

Equation 1.Theoretical Oxygen Demand for a chemical formula given as $C_cH_hN_nO_oP_p$:

$$ThOD = \frac{16\left[2c + \frac{1}{2}(h - 3n) + \frac{5}{2}p - o\right]\frac{mg}{mg}}{molecular\ mass\ of\ the\ test\ substance\ \frac{mmol}{mg}}$$

Allylthiourea (1.16 mg/L) was added to inhibit nitrification. All samples were analyzed in triplicates together with controls (sodium benzoate without inoclum, tested substances without inoculum) and blanks (medium and inoculum without tested substances). Gas tight flasks were equipped with a CO_2 trap (solid NaOH) and incubated in the dark at 20 °C for 28 days. The biodegradation efficiency was calculated based on the oxygen uptake in each bottle (measured automatically by the electronic OxiTop head) and corrected for the oxygen demand of the blank, with the respect to the Theoretical Oxygen Demand and the amount of ILs tested. In case of IL precursors (halides) the ThOD value was calculated for the cation without including the inorganic anions.

Acute oral toxicity test towards rats

The acute oral toxicity study towards rats was carried out using the Wistar female rats (Crl: WI(Han); outbred) obtained from the husbandry of laboratory animals of the Experimental Medicine Centre at the Medical University in Białystok. The experiment commenced with a sighting study, during which HIL **9** was administered to one animal and then to a second animal. The doses of HIL **9** were at 300 mg/kg b.w. and 2000 mg/kg b.w., respectively. On the grounds of the sighting study results, four animals used in the main study were given HIL **9** at a dose of 2000 mg/kg b.w. (the animal from the sighting study which had been given the dose of 2000 mg/kg b.w. was included in the main study). Before the administration, the animals had been fasted for about 19 hours. HIL **9**, in the form of an oil solution in a volume of 0.5 mL/100 g b.w., was administered with a metal stomach tube. After the administration of the tested HIL, the animals were observed for 14 days. During the quarantine, the sighting study, and the main study, the animals were kept in air-conditioned rooms. The study was carried out under the following conditions: temperature at 20-25 °C, humidity at 42-65% and a lighting cycle of 12h light/12 h dark. The animals were kept in plastic cages covered with wire bar lids. The dimensions of the cages were 58 x 37 x 21 cm (length x width x height). In the sighting study, the animals were caged individually. In the main study, there were four animals in one cage. UV-sterilized wood shavings were used as bedding. The animals were given access to the "Murigran" standard granulated laboratory fodder (AGROPOL, Motycz) and drinking tap water. General and detailed clinical observations were conducted daily during the entire experiment. Body weights of the animals were determined on days 0 (directly before the administration of the tested HIL), 7 and 14. After the 14-day observation period, the animals were euthanized and subjected to a necropsy and a detailed gross examination. A detailed description of the testing procedure can be found in the ESI (section 3).

Acute oral toxicity test towards rainbow trout (*Oncorhynchus mykiss*)

The acute toxicity study of HIL **9** towards the rainbow trout, *Oncorhynchus mykiss* Walb. was conducted as a static test according to the OECD Guideline No. 203 (1992). The fish were approximately 2 months old. The test concentrations of 0.9, 1.9, 4.3, 9.4, 20.7, 45.5 and 100 mg/L and a control were used. Test vessels were glass aquaria with a capacity of 10 L. There was one replicate of each test concentration and one replicate of the control. Seven fish were introduced into each aquarium. The fish were observed for mortality and intoxication symptoms after 3, 6, 24, 48, 72, and 96 hours of the exposure. The test was carried out under the following conditions: temperature at 14.1-14.2 ºC; pH of the control at 7.25-7.60; dissolved oxygen concentration at 80.0-100.0%; lighting cycle of 16 h light/8 h dark; no feeding during the exposure and constant aeration. The lethal concentrations (LC_x) as well as lowest observed effect concentration (LOEC) and no observed effect level (NOEC) values were established on the basis of the conducted test. A detailed description of the testing procedure can be found in the ESI (section 4).

Growth inhibition test of green algae (*Pseudokirchneriella subcapitata*)

The growth of the green algae exposed to HIL **9** was investigated during a 72-hour test according to the OECD Guideline No. 201 (2006). The test was performed in glass flasks with a capacity of 250 mL containing 100 mL of each treatment per replicate. The initial density of the algae was 1×10^4 cells/mL. The test concentrations of 0.01, 0.03, 0.1, 0.31, 1.0, 3.1 and 10 mg/L and the control were used. Morphology observations of the algae were performed at exposure termination. The test was carried out under the following conditions: temperature at 22-23.0 ºC; pH of the control at 7.25-8.04; average light intensity at 7176-7320 lx; illumination and shaking was constant; the AAP medium (U.S. EPA) recommended by the OECD Guideline No. 201. The effective concentrations causing a given inhibition of growth (E_rC_x) or yield (E_yC_x) as well as lowest observed effect concentration (LOEC) and no observed effect level (NOEC) values were established on the basis of the conducted test. A detailed description of the testing procedure can be found in the ESI (section 5).

Acute immobilization test using water flea (*Daphnia magna*)

Immobilization of young *Daphnia magna* (< 24 hours old) exposed to HIL **9** was investigated during a 48-hour static test, according to the OECD Guideline No. 202 (2004). Six test concentrations of 0.0625, 0.125, 0.25, 0.5, 1.0, and 2.0 mg/L and a control were used. The test concentrations and the control were divided into four replicates. There were five individuals of *Daphnia magna* in each replicate. The daphnids were observed for immobilization after 24 and 48 hours of the exposure. The test was carried out under the following conditions: temperature at 20.5-20.9 ºC; pH of the control at 7.45-7.54; dissolved oxygen concentration at 8.40-8.72 mg/L; lighting cycle of 16 h light/8 h dark; no feeding during exposure and no aeration. The effective concentrations causing a given inhibition of growth (EC_x) as well as lowest observed effect concentration (LOEC) and no observed effect level (NOEC) values were established on the basis of the conducted test. A detailed description of the testing procedure can be found in the ESI (section 6).

All experiments carried out in the framework of this study were performed in compliance with the relevant laws and institutional guidelines. The toxicity tests have been approved by the Local Ethical Committee for Experiments on Animals in Katowice, Poland.

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Notes and references

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