SAR for Amine Salts of Carboxylic Acids to Hydractinia echinata

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The relationship between the structure and biological activity (toxicity) SAR of the stoichiometric mixtures between anion and cation (or neutral species) proceeded at pH 8.2 from the different amine salts of benzoic, acetic, oxalic, naphthalene carboxylic acids was determined. Their toxicity was determined by using the metamorphosis (transformation) process of the marine invertebrate Hydractinia echinata (Hydrozoa, Cnidaria) from the freely swimming larva to a sessile polyp as a biological test system. The two components of the stoichiometric mixture, the anion and the cation or neutral species react independently, but in a parallel way, the effectiveness of the cation/neutral species being superior. The studied compounds were grouped by their cationic/neutral structure and measured toxicity. All of these series were also characterized by a calculated mean value of the toxicity.

The marine organism, Hydractinia echinata was a good and advantageous alternative for the toxicity testing systems with vertebrate.

Keywords: Hydractinia echinata, Metamorphosis Reducing Concentration (MRC₅₀), amine salts, cumulative toxicity

The environment and the alive organisms are rarely exposed to the toxically effect of a singular substance, but mostly to the mixtures of the many components. In this area, the research is very important and complex [1], being sustainable by the interdisciplinary works [2] and alternative methods [3] because the observed effects are often unexpected. These effects can be additive, antagonistic and synergic. They appear in contact with the human organism in the cases when in the mixture there is at least a component with high lipophilic character, which makes easier absorption/penetration of a hydrophilic derivative [4-8]. The toxicity is lower when the lipophilic character of the molecule is too high, and it can remain in the lipophilic zone of the cell [9], or when the hydrophilic character of the molecule is too high, and then the molecule “prefers” cellular aqueous medium.

Depending on pH, benzoic acid and some benzoic acid derivatives may be a neutral or ionic species. These two species can interact with biological medium, but the speed of action is very different. The speed also depends on the nature of the testing organism, which can be a crustacean Daphnia magna (water flea), fish - Brachydanio rerio (zebra fish) and Pimephales promelas (bony fish) or bacteria - Vibrio fischeri (formerly known as Photobacterium phosphoreum). Within benzoic substituted acids the toxicity to Daphnia magna changes as follows: iodine, bromine>chlorine>amino>fluorine>hydroxy [10-12].

Using Tetrahymena pyriformis (ciliate) as the testing organism the benzoic acid as well as its nonionic halogen derivatives, were more toxic in acid medium than in neutral medium. Also at the physiologic pH=7.4, ortho-substituted halogenated benzoic acids were ten-times more ionized than the meta- and/or para-substituted halobenzoic acids [13].

In the case of alkanol acid salts, the influence of the cation on the toxicity is exclusively remarked. The used test systems were micro alga Selenastrum capricornum, crustacean Daphnia magna (water flea), fish Brachydanio rerio (zebra fish) and Pimephales promelas (bony fish) [14].

The decrease of the toxicity in direct proportion to the number of ionic species was also observed with the other derivatives, like phenols for example, where also the ionic forms contributed to the toxicity of the derivative [15].

The structure of the primary and secondary amines being complementary to the cell membrane, this membrane is permeable for species, protonated and neutral [16]. Because the ionic form of ammonia is not toxic comparatively with neutral form [17], it could be possible that the toxicity of the amines to follow the same trend.

Regarding the toxicity of the alkanolamine tested with Tetrahymena pyriformis [16] and Hydractinia echinata [18], it is the same like that of the corresponding aliphatic amines with till 7 carbon atoms in molecule and it can be affected by the steric hindrance of the hydrocarbon ramification in vicinity of the amino group. 1, 2-Substituted derivatives can make intramolecular hydrogen bonds, these bonds do not influence the toxicity significantly. But, 2-amino-1-propanol disarranges lipidic metabolism, and it is possible then, that the metabolizing products of this alkanolamine to be more toxic than the compounds in which amino group is separated from hydroxy group by one or more methylenic groups [16].

The amine salts of benzoic, acetic, oxalic, naphthalene carboxylic acids with alkanolamines, aliphatic or heterocyclic amines synthesized according to the references [19-23] represent a class of organic compounds characterized by a large structural diversity with supramolecular architectures [23]. It is possible that these compounds or their biodegradable products to appear in environment because they have a practical interest like potential plant growth regulators, fungicides, or preservative solutions for the cut flowers [24-27].

First of all, the purpose of this paper was to determine the relationships between the structure of some amine salts of benzoic substituted acids, acetic and chloroacetic acids, naphthalene carboxylic acids, oxalic acid and their biological activity (SAR), by using the measured influence of the metamorphosis (transformation) process of the marine invertebrate Hydractinia echinata (Hydrozoa, Cnidaria) from the freely swimming larva to a sessile polyp. The two components of the stoichiometric mixture, the anion and the cation or neutral species react independently, but in a parallel way, the effectiveness of the cation/neutral species being superior. The studied compounds were grouped by their cationic/neutral structure and measured toxicity. All of these series were also characterized by a calculated mean value of the toxicity. The marine organism, Hydractinia echinata was a good and advantageous alternative for the toxicity testing systems with vertebrate.
Cnidaria) from the freely swimming larva to a sessile polyp as a biological test system. Secondly, the purpose was to present this marine invertebrate organism Hydractinia echinata as a very good alternative/surrogate biological test system for the toxicity testing with vertebrates, as the other marine organisms like Tetrahymena pyriformis, Pimephales pomelas, Daphnia magna and Vibrio fischeri were.

Experimental part
All the studied compounds listed in the table 1 were synthesized within Institute of Chemistry Timisoara of Romanian Academy and they were purified by recrystallization from ethanol 93%. The amines and the carboxylic acids mentioned in table 2 were purchased from different commercial sources (analytically pure) and were used without other purification. Fresh stock solutions of each compound were prepared in artificial seawater or in artificial seawater with methanol added.

The methods and the experimental conditions were those already used in the previously paper [18]. The toxicity of the tested compound was in terms of the concentration (mol L^{-1}) at which 50% of the larvae did not undergo metamorphosis to the polyp, compared to the control variant. This concentration, was called Metamorphosis Reducing Concentration (MRC_{50}), and measured value of toxicity (M) was presented as the logarithm of the reciprocal value of MRC_{50}, M=(-logMRC_{50}). Depending on

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Compound</th>
<th>M</th>
<th>mC</th>
<th>M-mC</th>
<th>MW</th>
</tr>
</thead>
</table>
| 1   | 2-Hydroxyethylammonium benzoate   | 2.94| -0.27| 183.20
| 2   | 2-Hydroxyethylammonium 4-methylbenzoate | 3.15| -0.06| 197.08
| 3   | 2-Hydroxyethylammonium 2-fluoroaniline | 3.14| -0.07| 201.08
| 4   | 2-Hydroxyethylammonium 4-fluoroaniline | 3.11| -0.10| 201.08
| 5   | 2-Hydroxyethylammonium 4-chloroaniline | 3.12| -0.09| 217.65
| 6   | 2-Hydroxyethylammonium 3-bromoaniline | 3.23| 0.02| 262.10
| 7   | 2-Hydroxyethylammonium 4-bromoaniline | 3.37| 0.16| 262.10
| 8   | 2-Hydroxyethylammonium 2-nitroaniline | 3.33| 0.12| 309.08
| 9   | 2-Hydroxyethylammonium salicylate   | 3.20| -0.01| 199.20
| 10  | 2-Hydroxyethyl-N-N-dimethylammonium salicylate | 3.21| 0.00| 227.26
| 11  | 2-Hydroxyethylammonium 4-hydroxyaniline | 3.04| -0.17| 199.20
| 12  | 2-Hydroxyethyl-N-N-dimethylammonium 4-hydroxybenzoate | 3.14| -0.07| 227.26
| 13  | 2-Hydroxyethyl-N-N-dimethylammonium 4-hydroxybenzoate | 3.13| -0.08| 225.31
| 14  | 2-Hydroxyethylammonium 4-aminoaniline | 3.15| -0.06| 198.22
| 15  | 2-Hydroxyethyl-N-N-dimethylammonium 4-aminoaniline | 3.26| 0.05| 226.26
| 16  | 2-Hydroxyethyl-N-N-dimethylammonium 4-nitroaniline | 3.36| 0.15| 254.33
| 17  | 2-Hydroxyethyl-N-9-propylammonium 4-aminoaniline | 3.08| -0.13| 212.25
| 18  | 2-Hydroxyethyl-N-9-propylammonium 4-aminoaniline | 3.03| -0.18| 212.25
| 19  | 1-Hydroxyethyl-2-ammonium 4-aminoaniline | 3.10| -0.11| 226.26
| 20  | Bis(2-hydroxyethyl)ammonium 4-aminoaniline | 3.27| 0.06| 242.28
| 21  | 2-Hydroxyethyl 3,5-diaminobenzene | 3.19| -0.02| 241.26
| 22  | 2-Hydroxyethyl-N-N-dimethylammonium 4-nitrobenzene | 3.22| 0.01| 256.26
| 23  | 2-Hydroxyethyl-N-N-dimethylammonium 4-nitrobenzene | 3.27| 0.06| 284.31
| 24  | 2-Hydroxyethyl-N-9-propylammonium 4-nitrobenzene | 3.16| -0.05| 242.23
| 25  | 3-Hydroxypropylammonium 4-nitrobenzene | 3.17| -0.04| 242.23
| 26  | 1-Hydroxyethyl-2-ammonium 4-nitrobenzene | 3.22| 0.01| 256.26
| 27  | Bis(2-hydroxyethyl)-ammonium 4-nitrobenzene | 3.24| 0.03| 272.26
| 28  | Tris(2-hydroxyethyl)-ammonium 4-nitrobenzene | 3.37| 0.18| 316.31
| 29  | 2-Hydroxyethylammonium 2-Cl-4-nitrobenzene | 3.22| 0.01| 262.58
| 30  | 2-Nitroethyl-N-N-dimethylammonium 2-Cl-4-nitrobenzene | 3.24| 0.03| 290.67
| 31  | 2-Hydroxyethyl-N-N-dimethylammonium 2-Cl-5-nitrobenzene | 3.10| -0.11| 262.58
| 32  | 2-Hydroxyethylammonium 3,5-dinitrobenzene | 3.23| 0.02| 273.20
| 33  | 2-Hydroxyethyl-N-N-dimethylammonium 3,5-dinitrobenzene | 3.38| 0.17| 301.26
| 34  | 2-Hydroxyethyl-N-N-dimethylammonium 3,5-dinitrobenzene | 3.37| 0.16| 329.21
| 35  | Bis(2-hydroxyethyl)-ammonium 3,5-dinitrobenzene | 3.42| 0.21| 317.26
| 36  | Tris(2-hydroxyethyl)-ammonium 3,5-dinitrobenzene | 3.39| 0.18| 361.31
| 37  | 2-Hydroxyethylammonium 1-naphthylacetate | 3.20| -0.01| 247.29
| 38  | 2-Hydroxyethylammonium 2-naphthylacetate | 3.18| -0.03| 247.29
| 39  | 2-Hydroxyethylammonium 2-naphthylacetate | 3.11| -0.10| 263.28
| 40  | Bis(2-Hydroxyethylammonium) 2-naphthalate | 3.49| 0.28| 338.34
| 41  | N-(2-Hydroxyethyl)aminium 2-naphthalimide | 3.36| 0.15| 241.26
| 42  | Quinolinium salicylate | 3.31| -0.11| 267.27
| 43  | Quinolinium 4-hydroxybenzoate | 3.53| 0.11| 267.27
| 44  | Quinolinium 4-aminobenzoate | 3.31| -0.11| 266.19
| 45  | Quinolinium 3,5-diaminobenzoate | 3.55| 0.13| 281.27
| 46  | Isoamylammonium 4-nitrobenzoate | 3.49| 0.07| 317.26
| 47  | Di-isopropylammonium 4-nitrobenzoate | 3.29| -0.13| 268.31
| 48  | L(+)-l-phenylammonium 4-nitrobenzoate | 3.50| 0.08| 288.29
| 49  | D(-)-l-phenylammonium 4-nitrobenzoate | 3.48| 3.42| 0.06| 288.29
| 50  | Morpholinium 4-nitrobenzoate | 3.14| -0.28| 254.24
| 51  | 2-Hydroxyethylammonium 4-nitrobenzoate | 3.29| -0.13| 391.10
| 52  | Pyridinium-3-methyl 4-nitrobenzoate | 3.50| 0.08| 260.18
| 53  | Pyridinium-4-benzyl 4-nitrobenzoate | 4.07| 0.65| 336.24
| 54  | Pyridinium-3-carboxaldehyde 4-nitrobenzoate | 5.32| 1.90| 274.18
| 55  | Quinolinium 4-nitrobenzoate | 3.36| -0.06| 296.27
| 56  | Quinolinium 3,5-dinitrobenzoate | 3.37| -0.05| 341.27
| 57  | 8-Hydroxyquinolinium monochloroacetate | 3.99| 4.03| -0.04| 239.69
| 58  | 8-Hydroxyquinolinium dichloroacetate | 3.93| -0.10| 274.10
the cationic structure of compounds and their measured toxicity, all the studied compounds could be grouped in series, which were characterized by a calculated mean value $mC = \sum N \cdot \text{log}_N$, where $N$ represents the number of the compounds within a series.

**Results and Discussions**

In the experimental conditions, pH 8.2, and the presence of marine water, above-mentioned compounds made stoichiometric mixtures, which contained anions derived from the acids, and cations or neutral species derived from the amines, depending on their pKa. According to the data from literature and to the software www.syresom/esc/physdemo.htm, the derivatives listed in table 2 were characterized by logPow values between –2.22 and 2.87, and pKa values between 0.51 and 10.71.

An optimal appreciation of the measured values of the toxicity (M) presented in table 1 could be done using the calculated mean value (mC) for a series of compounds. Starting from the fact that the toxicity is owed to the cation in organic acid’s salts [14] and from the fact that neutral molecular species is more effectiveness than ionic one [10,11,13] the sixty seven tested compounds were grouped in three, as it follows:

- derivatives 1-42 which contain in their molecule an alkanolamine or alkanolamine with alkyl-substituted amino nitrogen, and which have a mean value of toxicity $mC \pm 2.2$ logarithm unites (log u.) for the interval [2.94-3.49]

### Table 2

<table>
<thead>
<tr>
<th>No</th>
<th>CAS</th>
<th>Compound</th>
<th>$\log P_{oct}$ m/e</th>
<th>pKa$^a$</th>
<th>%Chi/%Cn</th>
<th>MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141435</td>
<td>Ethanolamine (EA)</td>
<td>2.67</td>
<td>-1.31</td>
<td>9.5</td>
<td>95.12/4.88</td>
</tr>
<tr>
<td>2</td>
<td>111422</td>
<td>Diethanolamine (DEA)</td>
<td>-1.43</td>
<td>8.96</td>
<td>85.19/14.81</td>
<td>105.14</td>
</tr>
<tr>
<td>3</td>
<td>102716</td>
<td>Triethanolamine (TEA)</td>
<td>-1.59</td>
<td>7.76</td>
<td>26.47/73.53</td>
<td>149.19</td>
</tr>
<tr>
<td>4</td>
<td>108010</td>
<td>2-Hydroxyethyl-$N$-dimethylamine</td>
<td>2.84 (-0.94*</td>
<td>9.31</td>
<td>92.80/7.20</td>
<td>89.14</td>
</tr>
<tr>
<td>5</td>
<td>100378</td>
<td>2-Hydroxyethyl-$N$-diethyamine</td>
<td>2.98 (-0.94*</td>
<td>9.87</td>
<td>97.91/2.09</td>
<td>117.19</td>
</tr>
<tr>
<td>6</td>
<td>78966</td>
<td>1-Amino-2-propanol</td>
<td>-0.96</td>
<td>9.94</td>
<td>98.21/1.78</td>
<td>75.11</td>
</tr>
<tr>
<td>7</td>
<td>13054870</td>
<td>2-Amino-1-butanol</td>
<td>-0.46*</td>
<td>9.52</td>
<td>95.43/4.57</td>
<td>89.14</td>
</tr>
<tr>
<td>8</td>
<td>107739</td>
<td>Propylamine</td>
<td>2.72</td>
<td>0.47</td>
<td>10.71</td>
<td>99.69/0.31</td>
</tr>
<tr>
<td>9</td>
<td>75310</td>
<td>Isopropylamine</td>
<td>0.26</td>
<td>10.60</td>
<td>99.60/0.4</td>
<td>59.11</td>
</tr>
<tr>
<td>10</td>
<td>108189</td>
<td>Di-isopropylamine</td>
<td>1.40*</td>
<td>11.10</td>
<td>99.87/0.13</td>
<td>101.19</td>
</tr>
<tr>
<td>11</td>
<td>110918</td>
<td>Morpholine</td>
<td>(-0.60*</td>
<td>8.49</td>
<td>66.10/33.9</td>
<td>87.12</td>
</tr>
<tr>
<td>12</td>
<td>66228</td>
<td>Ureac</td>
<td>3.07 (-0.07*</td>
<td>9.45</td>
<td>94.69/5.31</td>
<td>112.09</td>
</tr>
<tr>
<td>13</td>
<td>81834</td>
<td>1,8-Naphthalimide</td>
<td>3.41</td>
<td></td>
<td></td>
<td>197.29</td>
</tr>
<tr>
<td>14</td>
<td>110864</td>
<td>Pyridine</td>
<td>2.40</td>
<td>0.65</td>
<td>5.20</td>
<td>0.01/99.9</td>
</tr>
<tr>
<td>15</td>
<td>108996</td>
<td>3-Methylpyridine</td>
<td>3.22</td>
<td>1.29</td>
<td>5.63</td>
<td>0.27/99.73</td>
</tr>
<tr>
<td>16</td>
<td>211665</td>
<td>4-Benzylpyridine</td>
<td>4.03</td>
<td>2.62</td>
<td>5.59</td>
<td>0.24/99.76</td>
</tr>
<tr>
<td>17</td>
<td>500221</td>
<td>Pyridine-5-carboxaldehyde</td>
<td>0.57 (-3.08*</td>
<td>4.90</td>
<td>0.04/99.96</td>
<td>107.11</td>
</tr>
<tr>
<td>18</td>
<td>91225</td>
<td>Quinoline</td>
<td>2.95</td>
<td>2.10*</td>
<td>4.90</td>
<td>0.05/99.95</td>
</tr>
<tr>
<td>19</td>
<td>148243</td>
<td>8-Hydroxyquinoline</td>
<td>4.30</td>
<td>2.03*</td>
<td>5.02</td>
<td>0.07/99.95</td>
</tr>
</tbody>
</table>

(a) 8-Hydroxyquinoilium trichloroacetate 4,17 0.14 308.55

(b) 8-Hydroxyquinolinium acetate 3.61 0.02 205.20

8-Hydroxyquinolinium oxalate 3.67 0.08 271.21

8-Hydroxyquinolinium salicylate 3.67 0.08 416.45

8-Hydroxyquinolinium 4-aminobenzoate 3.40 3.59 -0.19 283.27

8-Hydroxyquinolinium 4-nitrobenzoate 3.46 -0.13 282.29

8-Hydroxyquinolinium 3,5-dinitrobenzoate 3.67 0.08 312.27

8-Hydroxyquinolinium 3,5-dinitrobenzoate 3.66 0.07 357.27

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*excluded from mC calculations.
Between the two ion species, anionic (from acid) and cationic (from alkanolamine), more effective was cationic species. This fact was also confirmed by the case of 4-aminobenzoic acid (3.34 log u.), 1-naphthylacetic acid (4.50 log u.), 2-naphthylacetic acid (4.32 log u.) and 2-naphthoxyacetic acid (4.55 log u.), which even if it have individual toxicities greater, their amine salts had the toxicity at the same limits as other derivatives of this group.

The effectiveness of the two species benzoate anion/alkanolamine cation in the mixture depends on their nature, on the strength of hydrogen bonds between carboxyl group and hydroxyl group of alkanolamine, and on the strength of intramolecular hydrogen bonds between amino group and hydroxyl group in 1-2 and 1-3 positions. Thus, the effectiveness of halogeno-substituted benzoates is direct proportional with ascending order of the atomic volume, fluoride < chloride < bromide < iodine, with the lipophilic character, respectively [13].

Within of the alkanolamine cations, primary amino group can be involved in intramolecular hydrogen bonding with the hydroxyl, and also can be oriented by electrostatic attraction with its positive charge towards the phosphatic anion, outside of the double lipidic layer [16]. This kind of bonding can explain the better effectiveness of alkanolamine cation relative to those of benzoate anion. Intramolecular hydrogen bond can be steric affected by the advanced alkylic substitution to the nitrogen, which increases lipophilic character of the molecule, but the toxicity remains constant on interval C₃-C₇ [18].

In bis(2-hydroxyethylammonium) naphthalate (41) the molar ratio anion/cation is 1:2, but the toxicity even a little higher than the calculated mean value, we consider it situated in the limits when the ratio anion/cation is 1:1. Otherwise, the minor influence of ethanolamine was suggested also by the individual toxicity of 2-hydroxyethyl-naphthalimide 3.36 log u., which was approx. identical with that of naphthalimide itself, 3.41 log unites.

### Derivatives 43-57

In this series, the derivatives were different from those of previous series because organic bases were aliphatic amines or aromatic heterocyclic amines. Aliphatic amines being strong bases were protonated species while heterocyclicing amines were neutral species.

Propylamine (2.72 log u.), pyridine (2.40 log u.), 3-methylpyridine (3.22 log u.), quinoline (2.95 log u.), but not 4-benzylpyridine (4.03 log u.) (table 2, a) have individual toxicities lower than calculated mean value mC 3.42 log u. for the stoichiometric mixture, that strengthening the existence of cumulative mechanism.

The great contribution of the neutral species was especially observed in the cases when the lipophilic character increases with the number of the saturated or the aromatic carbon atoms [18], as it was the case of 3-methyl (3.22 log u.) and 4-benzylpyridine (4.03 log u.) [28] related to pyridine (2.40 log u.). Pyridine-3-carboxaldehyde

| log Po/w, pKa: software www.syvres.com/esc/phs/demo.htm [10, 16]. Abbreviations: M - measured individual toxicity; EA-ethanolamine; DEA-dietanolamine; TEA-triethanolamine; logP/cm<sup>*</sup> - logarithm of the measured 1-octanol water partition coefficient m/calculated e<sup>*</sup>; pK<sub>a</sub>-acid dissociation constant; Cn - neutral species concentration; C<sup>i</sup>-ionic species concentration, MW-molecular weight |
|---------------------------------|-----|-----|-----|-----|-----|
| 20                             | 64197 | Acetic acid | 2.87 | -0.17 | 4.76 | 99.978/0.021 | 60.08 |
| 21                             | 79118 | Chloroacetic acid | 0.22 | 2.87 | 99.99/0.00005 | 94.90 |
| 22                             | 79436 | Dichloroacetic acid | 0.92 | 1.26 | 99.999/0.00001 | 128.94 |
| 23                             | 76039 | Trichloroacetic acid | 1.60 | 1.33 | 0.51 | 99.999/0.00001 | 163.39 |
| 24                             | 144627 | Oxalic acid | 3.03 | -2.22* | 1.25 | 99.999/0.00001 | 90.04 |
was also an exception because of the aldehydic group where carboxyl oxygen atom could be an acceptor of the hydrogen bond if there is a suitable receptor [8]. Though di-isopropilamine has a higher lipophilic character it has a smaller toxicity than isopropylamine because of the steric hindrance at the nitrogen atom [16], but in accordance with minimal variation of the toxicity for the amines with up to 6 carbon atoms [18].

Concerning ethynphenylamines there were no differences between the two optical isomers D(+) (50) and L(-) (49), the reactivity of amino group depends on the nature of the substituent not on their steric positions. It is very possible that cis-trans isomerism does not influence the toxicity of some unsaturated amines as there are not differences between geometric isomers of 1,2-dimethylcyclohexane and of decaline [29].

Morpholinium (heterocycle with O and N) (51) and uracilium (heterocycle with two N atoms characterized by lactam-lactim tautomerism) (52) derivatives had lower toxicity values probably due to their strong hydrophilic character (log P OW negative).

Derivatives 58-67

This series had as neutral species 8-hydroxyquinoline, heterocycle with nitrogen atom and a phenolic hydroxyl on it. Therefore, it is possible to make intramolecular hydrogen bonds. The high individual toxicity of 8-hydroxyquinoline (4.30 log u.) was the cause of higher effectiveness of binary mixtures with acetate, oxalate, or hydroxyquinoline (4.30 log u.). Therefore, it is possible to make intramolecular heterocycle with nitrogen atom and a phenolic hydroxyl for the amines with up to 6 carbon atoms [18].

The effectiveness of the anion did not depend on its aliphatic nature with one or two carboxylic groups or aromatic nature with one carboxylic group.

In mono-halogenated derivatives the toxicity varied inverse proportional with the electronegativity of the halogen: fluorine < chlorine < bromine < iodine. In monocarboxyl aliphatic acids with multiple halogen substitution at the same carbon atom, though its individual toxicity is lower, the toxicity of the salts increase because of higher contribution of 8-hydroxyquinoline, but its individual toxicity was diminished.

The toxicity of the cation/neutral species increased with the increase of their lipophilic character and varied as follows: alkanolamines < aliphatic amines < heterocycles with nitrogen < 8-hydroxyquinoline, with the specification that the alkanolamines and specially ethanolamine and 8-hydroxyquinoline make intramolecular hydrogen bonds.

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Conclusions

Hydractinia echinata test system is an available test for the determination of the toxicity of the stoichiometric mixtures, anion : cation /neutral species which result at pH 8.2 from the amine salts of the some organic aliphatic or aromatic acids with alkanolamines, aliphatic and heterocyclic amines.

The measured toxicity (M) is a cumulative result of two parallel and independent reactions of anion and cation/neutral species with biological medium; the reaction rate of the two species is different; neutral species being higher than that of the anion as it results in the tests with 8-hydroxyquinoline.

The cumulative mechanism was confirmed in all the cases where mean calculated value mC was higher than measured values M of the individual components of the mixture, excepting 8-hydroxyquinolinium derivatives (58-67).
29. CHICU, S. A., BERKING, S., Chemosphere, 34, nr. 8, 1997, p. 1851

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