

Is The Toxicity Of Bipyridylium Herbicides Two-Fold?

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Abstract

The bipyridylium herbicides are quaternary ammonium salts. Their mode of action is well understood and brought about by chemical changes that their di-cations undergo in plant cells. Little attention has been paid to the role of the anions, chloride and bromide in the products of the market. It is hypothesized that these anions will form strong acids concomitant with the chemical changes of the di-cations. Toxic effects in animals and humans, especially regarding skin, epithelia and eyes, might be due to occurring hyperacidity in affected cells. Therefore, a commercial product was transformed into a diacetate salt that was tested in comparative trials with respect to herbicidal activity and damage towards human monocytes. While the desired plant harming effect compared very favourably with the marketed product, the damaging result with human monocytes was substantially reduced.

The scientific literature abounds in publications on the activity, mode of action, toxicity and other aspects of the so-called bipyridylium herbicides (also called quats) since their patenting and introduction on the market half a century ago (1). The two main representatives paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) and diquat dibromide (6,7-dihydrodipyrido(1,2-a:2',1'-c) pyrazinediium dibromide) still prove useful as contact herbicides and protect many crops worldwide. This, notwithstanding widespread criticism based on the occurrence of numerous accidents and fatalities incurred by users (2). For extensive reports on toxicity and mode of action the reader's attention is called to papers listed under (3).

In chloroplasts or other affected plant cells these herbicides are initially reduced to radical cations which, in turn, give rise to oxygen containing free radicals. These attack the sensitive unsaturated lipids of the cell membrane by peroxidation, eventually leading to the loss of membrane function. The quat-derived cation-radical can be oxidized again to form a redox cycle in which the di-cations (the quats) adopt the role of a catalyst (4).

Stoichiometry requires that the di-cations must have, as in any salt, the equivalent of anions as counterpart. In the case of paraquat two chloride ions, with diquat two bromide ions establish the balance. On investigating the manufacturing processes it turns out that the respective reagents used in the synthesis dictate the nature of these anions. With paraquat which is formed by double alkylation of 4,4'-dipyridyl with

methyl chloride, it is the two chloride ions that compensate the charges of the di-cation, with diquat on the other hand, alkylation of 2,2'-dipyridyl is brought about by reaction with 1,2-dibromoethane. Here the positive charges of the di-cation are made up by two bromide ions.

In none of the numerous toxicological investigations were the possible roles or effects of the anions taken into consideration. The observed symptoms could be explained by the mode of action governed by the activity of the di-cation. Furthermore, in the case of paraquat this omission seems obvious and comprehensible, since chloride ions are ubiquitous in living cells. With diquat, however, the weight of the bromide ions represents more than half the weight of the herbicidal active substance. It is, therefore, somewhat surprising that no attention was paid to the possible toxic effects of these ions, inasmuch as these do not normally occur in appreciable amounts in living matter. The belief must prevail that the role of these ions can be disregarded.

There are observations which indicate that halides of the quats show chromatographic parameters that differ from the ones of corresponding acetates (5). Quaternary salts can be regarded as being derived from quaternary hydroxides which are comparable in basic strength to alkali hydroxides. In the quats' cases these bases are too unstable to be known, because the inversely charged ions react with one another leading to decomposition. Consequently it is well-known that quats are unstable in an alkaline medium (6). If the quats di-cations undergo a chemical reaction in which their

electrical charge is reduced, stoichiometry requires that the counterions, halides in our cases, will have to balance the change in charges. In an aqueous system, such as the cytoplasm, this will be achieved by combining with a proton and concomitant formation of a hydrogen halide.

Acidification of the medium is the consequence. As long as the buffering capacity of the affected cell compartment can cope with the acid thus formed all is well. If not, the cytoplasm and structures in touch will incur damage that may lead to denaturation of proteins and loss of function.

That aqueous solutions of the quats can corrode aluminium alloy containers was recognized early on. The shiny metal surface reacts with the di-cation by reducing it to the radical-cation or even further to an uncharged weak base that cannot neutralize the hydrogen chloride or bromide formed.

Therefore, the solution turns acidic, leading to further and enhanced corrosion. Additives, such as thiophosphates, were invented that shield the metal surface and prevent corrosion (7).

In addition, the severe toxic attacks perpetrated by the quats on epithelia, eyes and lungs resemble the ones that are observed on exposure of skin to the mustard gases, phosgene or its dimer. Respiratory failure may result just as in many cases of paraquat poisoning. The author is not aware of a direct comparison of toxic effects of the two groups of substances in question. Phosgene is a suitable agent for a qualitative comparison here, because in its action which involves its hydrolysis or acylation of a substrate (e.g. proteins in the pulmonary alveoli) hydrochloric acid and eventually the innocuous carbon dioxide are the sole products formed. Similarly and confirmatively, pulmonary toxic effects with alveolar damage can be brought about by mere aspiration of sprayed dilute hydrogen chloride solution (8).

The common denominator these toxic agents share is hydrogen halide. With the quats it is formed on reduction of the di-cation; with the chemical warfare agents mentioned it develops upon hydrolysis, in an alkylation or acylation reaction that these agents can undergo. The warfare agents lack a bipyridylum di-cation, nonetheless they exert a powerful toxic action.

It has been well established that the cationic moiety of the quats is responsible for the herbicidal activity. As hinted, little attention has been paid to the nature of the anions. In order to measure their possible effect, other quats salts, especially those of a weak acid had to be prepared and

tested. The proven mode of action now predicts the formation of a weak acid, unlike with the products in use and the warfare agents. A diquat solution was chosen for the experiments. Acetate ions suggested themselves for the exchange, being derived from both a weak and physiological acid (9). The resulting diquat diacetate solution was used for comparative herbicidal tests with *Heuchera*. This ornamental plant is indigenous to California and was suggested by a botanist; first, because it was not in a hibernating state and available in quantity, and secondly its leaves are suitable for application of the test-solutions by pipets, thus permitting indoor experiments. Not surprisingly, the expectation was fulfilled. Judged by the rate and amount of wilting and crust formation the diacetate solution proved at least as active as the commercial dibromide product (10).

Will the new formulation with acetate ions as anionic counterpart be less toxic? Experiments with animals were out of reach for the author but will eventually be needed for final evaluation. Comparative tests with human monocytes were commissioned (11). While in a Trypan Blue test the two solutions proved equally active, pointing to equal damage of the cell walls, the two solutions differed significantly in the so-called WST-1 test (12), when the 1 mM solution of the diacetate behaved more closely to the control than to the solution of the dibromide. At a tenfold higher concentration, however, the diacetate solution was damaging, too. These results were corroborated by experiments at higher temperature and reduced exposure time. Phase contrast microphotographs taken 72 hours after initiation of cell cultivation showed that the cells looked less damaged than the ones that were treated with the commercial product's solution. Quantitative results, however, cannot be obtained from this test-setup.

It can be expected that, at least in contaminations of vital surfaces (e.g. mucous membranes or eyes), bipyridylum herbicidal solutions containing anions of weak acids will prove less toxic than the commercially available products.

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