Efficient In Vitro Paraquat Removal via Irreversible Immobilization into Zeolite Particles

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Abstract. A new efficient mineral adsorbent, zeolite ZSM-5, has been evaluated for its ability to durably immobilize the herbicide paraquat in conditions simulating acute poisoning by oral ingestion of this toxic compound. The sorption properties have been studied in water, normal saline solution, as well as in artificial and simulated human gastric juices. Uptake kinetics and capacities have been determined and compared to the ion exchange resin Amberlite IR-120. Significant advantages of ZSM-5 over the resin have been demonstrated, especially with respect to long-term retention capability of the toxic herbicide. This solid is a promising primary treatment of acute paraquat poisoning.

Paraquat poisoning is still an actual problem of human toxicology and, unfortunately, no true pharmacological antagonist for this poison exists at the present time, even though a large variety of treatments have been advocated over the past 30 years (Bismuth et al. 1995).

Paraquat is a contact herbicide that is primarily used in agriculture for weed control (Calderbank 1968). It acts by interfering with intracellular electron transfer systems, thereby inhibiting reduction of NADP during photosynthesis. This non-selective, quick-acting agent is commercially available in the form of concentrated aqueous solutions (40–200 g/L). When properly used, it does not display any residual properties in soils because of strong adsorption by clays (Calderbank and Slade 1976). In the case of accidental or intentional oral ingestion, however, it causes a great deal of suffering and a slow death is often the final outcome (Bismuth et al. 1990). Death may occur within several hours to few days, caused by multiple organ failure. Deaths associated with accidental paraquat poisoning have been reported in the literature to range between 33% and 55% (Bismuth et al. 1982). Ingestion of paraquat in its undiluted form may result in a burning sensation in the mouth and esophagus. This is followed by a sore throat, difficulty in swallowing, abdominal pain, nausea, vomiting, and diarrhea. All of these occur in the first 24 hours (Onyeama 1984).

As there is no specific antidote for paraquat poisoning up to now (Bateman 1987; Bismuth et al. 1990), it is necessary to act rapidly to interrupt the pathway for paraquat toxicity. Goal of therapeutic management is thus primarily directed at removing the poison from the gastrointestinal tract and increasing its excretion from blood (Vale et al. 1987). Gastric lavage is performed as immediately as possible and is followed by the administration of a solid adsorbent, such as diatomaceous clays, activated charcoal, and ion exchange resins (Vale et al. 1979; Bismuth et al. 1987; Proudfoot 1987). Gastric emptying may also be performed, using the adsorbent in the lavage solution. These adsorbents are indeed effective in removing paraquat from infected gastric solutions (Staff et al. 1973; Machijima et al. 1994; Meredith and Vale 1995), but they have serious drawbacks. Upon filling with paraquat, clay minerals can significantly leach the herbicide into the gastric juices (Staff et al. 1980), especially at a low pH (Nakamura et al. 1992). Activated charcoal requires highly concentrated saline solutions to be really efficient (Nakamura et al. 1989; Kitakouji et al. 1989; Tanada et al. 1992). Finally, ion exchange resins are reported as the best adsorbents, according to in vitro experiments, although they are not widely used for practical decontamination purpose. Their action is based on competitive electrostatic binding, so their use at a low pH and/or in the presence of high cation concentrations results in rather high amounts of residual paraquat in solution (≈ 2–5 × 10⁻⁵ M) (Tanada et al. 1988; Kitakouji et al. 1989). To enhance the elimination of paraquat from the body, it appears useful to find more efficient adsorbents, leading to durable immobilization of this herbicide in conditions as harsh as those encountered in the gastrointestinal tract (Horowitz 1967).

In the present work, a novel zeolite-based adsorbent (ZSM-5) for paraquat has been investigated, exploiting the unusually strong interaction between the cationic herbicide and the rigid, three-dimensional structure of the aluminosilicate. Zeolite ZSM-5 has been chosen for two main reasons: its stability in acidic mediums (compatible with the low pH of gastric juice) and the fact that it displays pore sizes very close to the paraquat diameter (durable encapsulation may be ex-
pected). A commercially available polymeric ion exchange resin was also used for comparison purposes.

**Materials and Methods**

Zeolite ZSM-5 is a highly siliceous, synthetic zeolite (crystalline aluminosilicate made of spatially arranged tetrahedra SiO$_4$ and AlO$_4$) of the MFI group (Kokotailo et al. 1978). The chemical formula of the sample used in this study is Na$_2$Al$_2$Si$_2$O$_8$·16H$_2$O. It displays a theoretical ion exchange capacity of 0.64 meq/g. The ion exchange resin used was the Amberlite IR-120 (gel type, Sigma-Aldrich), which is made of a styrene-divinylbenzene matrix containing covalently-attached sulfonate groups (4.4 meq/g as dry powder; 1.9 meq/g when hydrated). It was conditioned in pure water for 48 h before use. Paraquat (methyl viologen dichloride hydrate, N,N'-dimethyl-4,4'-bipyridinium dichloride, 98%) was purchased from Sigma-Aldrich and used without further purification. All other reagents (HCl, NaCl, NaOH, KCl, CaCl$_2$) were analytical grade. All solutions were prepared with high-purity water (18 MΩ cm) obtained from a Millipore Milli-Q water purification system. A solution containing 0.1 M HCl was considered as artificial gastric juice, while simulated human gastric juice was prepared according to a published procedure (Staif et al. 1980), with pepsin A (EC 3.4.23.1, from Sigma) used as the protein component (0.1% by weight).

The uptake capacity of the adsorbents for paraquat (noted PQ$^{2+}$ hereafter) was determined *in vitro* at various solid-to-solution ratios and several PQ$^{2+}$ concentrations, after 24 h of contact in artificial and simulated gastric juices. Experiments have been performed typically in Nalgene centrifuge tubes. The extent of PQ$^{2+}$ removal was determined quantitatively by measurement of the herbicide concentration remaining in the supernatant obtained after thorough centrifugation after equilibration. Detection was made by UV spectrophotometry (spectrophotometer CARY 5G, double beam, Varian) after reduction of PQ$^{2+}$ into its blue radical-cation (by 0.1 M sodium dithionite at pH 13), by measuring the absorbance at 600 nm (Calderbank 1968). Direct UV detection of PQ$^{2+}$ at 258 nm was prevented because of the strong absorbance of pepsin at this wavelength. Appropriate reagent blanks were used to compensate for background interferences.

Kinetics of PQ$^{2+}$ removal have been measured *in situ* in three different media: pure water, a normal saline solution (0.1 M NaCl), and 0.1 M HCl (artificial gastric juice without pepsin, to enable *in situ* monitoring of PQ$^{2+}$ by direct UV spectrophotometry at 258 nm). Typically, selected amounts of adsorbent were introduced into 30-mL solutions containing PQ$^{2+}$ at well-defined initial concentrations (from 0.04 to 0.12 mM) and shaken for selected periods of time. At regular intervals, the reaction was stopped by centrifugation and solution-phase PQ$^{2+}$ was monitored by UV spectrophotometry. The extent of uptake was calculated by the difference from the corresponding initial concentration.

Gastric availability of PQ$^{2+}$-filled adsorbents was studied by incubation of PQ$^{2+}$-loaded ZSM-5 (0.27 mmol/g) or Amberlite IR-120 (1.38 mmol/g) with simulated human gastric juice for 24 h. Solutions were then centrifuged and the supernatant was analyzed after reduction (dithionite) in order to measure the amount of PQ$^{2+}$ released in the gastric juice. Control experiments have been performed in 0.1 M NaCl, 0.1 M HCl, and artificial gastric juice without pepsin.

X-Ray Photoelectron Spectroscopy (XPS) was applied to demonstrate the nature of the mechanism involved in the uptake of PQ$^{2+}$ by zeolite ZSM-5. XPS spectra were obtained using an electron energy analyzer (VSW, MCD 5000) and an unmonochromatized MgKα source (1253.6 eV). The energy scale was calibrated using the aliphatic adventitious hydrocarbon C(1s) peak, located at a binding energy of 284.6 eV. Narrowly scanned spectra were used to evaluate the relative composition of samples for Si, Al, O, Na, N, and Cl.

**Results and Discussion**

Zeolites are natural or synthetic crystalline aluminosilicates that behave as cation exchangers (Breck 1974). They are characterized by a rigid structure, made of cages and channels of molecular dimension, which gives rise to molecular sieving properties (size and shape selectivity). Their ion exchange property arises from the substitution of one SiO$_4$ tetrahedra by AlO$_4$ at the center of the zeolite lattice, so their ion exchange capacities are directly proportional to their Al content. Al-rich zeolites with large pores (e.g., types L, Y, or X) are known to readily accumulate PQ$^{2+}$ species by ion exchange with Na$^+$ ions initially present in the structure, at capacities of about 1 mmol/g (Hennessy et al. 1999; Walcarius et al. 1999a; Ranjit and Kevan 2002). These solids, however, are not stable in acidic mediums (Al centers can be hydrolyzed in the presence of protons, especially in zeolites displaying low Si/Al ratios), which why they are used as antacid agents (Greb et al. 1984). They are therefore not suited to recover PQ$^{2+}$ in a low pH medium, such as gastric juice.

On the other hand, ZSM-5 is a zeolite displaying a high Si/Al ratio (23 for our sample), which makes it much more stable in acidic mediums (down to pH 1), similar to other highly siliceous zeolites (Breck 1974). This zeolite is liable to accommodate PQ$^{2+}$ species within its microporous structure with restricted mobility, as compared to that observed in large-pore zeolites, because ZSM-5 possesses channels with dimensions close to that of PQ$^{2+}$ (Walcarius et al. 1999b). By treating 100-mg ZSM-5 with a 100-mL solution containing an excess of paraquat (5 mM), a capacity of 0.27 mmol/g was observed, corresponding to 84% of the ion exchange sites being filled, on the basis of one PQ$^{2+}$ cation for 2 AlO$_4^-$ centers in the zeolite. This is less than the values obtained with zeolites Y or L (Hennessy et al. 1999; Walcarius et al. 1999a), but this apparent drawback is largely compensated by the strong interaction existing between the mineral structure and the herbicide and by the ability to use ZSM-5 in acidic media without any efficiency loss, as demonstrated below. For the sake of comparison, the capacity of the ion exchange resin Amberlite IR-120 was also determined in the same conditions and was found to be 1.38 mmol/g, that is, about five times higher than ZMS-5.

The chemical mechanism responsible for the accumulation of PQ$^{2+}$ species in ZSM-5 has been proven to be ion exchange by comparing XPS spectra obtained before and after treatment of the zeolite with paraquat. XPS measurements of the starting solid have revealed the presence of 1.3 wt/wt % of sodium (agreeing well with the theoretical value of 1.5%, as calculated from the zeolite composition) and, as expected, the absence of nitrogen. The same measurements performed after treatment with paraquat showed the disappearance of the sodium signal concomitantly with the existence of nitrogen at a loading of 1.4 wt/wt % (arising from the PQ$^{2+}$ that had been introduced in the zeolite structure). Other elements (Si, Al, O) remained unchanged. At the same time, no chloride was observed, indicating that PQ$^{2+}$ species entered the ZSM-5 without their counterion. This proves that electrostatic binding is the driving force of the process, which can be ascribed unambiguously to ion exchange, and not to van-der-Waals interactions, as in the case