

Enhancing Urate Stone Dissolution: Physicochemical Insights into Biocompatible Organic Bases

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Abstract

The dissolution rates and rate constants of native urate stones in saline solutions simulating the urine from a healthy individual were studied, as functions of the concentrations of organic bases and urinary ammonia. The findings demonstrate that dissolution efficiency depends on both the properties of the amine component and the properties of the products formed through the interaction between the amines and urine components. Employing organic bases with distinct mechanisms of interaction with uric acid enables urate stones dissolution while preserving kidney and urinary tract function.

INTRODUCTION

It is estimated that one in ten people will develop a kidney stone of one type or another at some point in their lifetime [1]. In the late 1970s, approximately 3.8% of the population had kidney stones, whereas this figure has now increased to 8.8%. The risk of urolithiasis is approximately 19% in men and 9% in women. Typically, the first episode of kidney stone disease occurs after the age of 30. However, many cases occur earlier, even in children under five years of age [2].

Uric acid stones present one of the four principal types of kidney stones, which are solid masses of crystallized minerals formed in the kidneys or urinary tract. Uric acid stones account for 10% of all kidney stones and are the second most common type of urinary stones after calcium oxalate and calcium phosphate stones. The primary risk factor for uric acid crystallization and stone formation is low urine pH (below 5.5), rather than increased urinary excretion of uric acid. Major causes of low urine pH include tubular disorders (such as gout), chronic diarrhea, or severe dehydration. Uric acid production is associated with diets high in purines, particularly those found in animal proteins such as beef, poultry, pork, eggs, and fish. The highest purine levels are concentrated in organ meats such as liver, and in fish. Excessive consumption of animal protein can result in increased uric acid accumulation in urine. Uric acid may precipitate and form a stone either independently or in combination with calcium. However, dietary factor alone do not account for uric acid stone formation. The risk of uric acid stone formation is higher in individuals with obesity or diabetes. Patients who have received chemotherapy are also prone to developing uric acid stones.

Urate nephrolithiasis can be prevented, and urate stones are among the few urinary tract stones that can be successfully dissolved. Accordingly, interest is increasing in combined methods of kidney stone removal with minimal tissue trauma, particularly removal of the “stone street,” including maximally sparing lithotripsy, percutaneous lithotomy, and “surface litholysis” of fragmented stones [3, 4].

The problem of effective litholysis of stones directly within the human kidney, including surface litholysis, is the least studied of the approaches listed above. Therefore, investigation of the mechanism of surface litholysis appears highly relevant to improving the management of urolithiasis and reducing its recurrence.

EXPERIMENTAL PART

To clarify the mechanism by which the cationic component and nitrogen-containing bases – imidazole (Im), triethanolamine (TEA), or piperazine (PP) – affect the dissolution of uric acid stones and, consequently, the effectiveness of litholytic compositions, the present work investigated the dissolution kinetics of urate stones (their dissolution rates and rate constants) in saline solutions simulating urine from a healthy individual, as functions of the concentrations of organic bases and urinary ammonia.

The experiment used 111 structurally homogeneous native urate stones with alternating protein layers, each ground to a spherical shape and weighing approximately 100 mg. The stones were analysed for the absence or presence of uric acid, phosphoric acid, or oxalic acid salts using infrared (IR) spectroscopy in KBr. Experimental samples, suspended on a torsion balance by a filament, were placed in the center of a thermostated 100 mL round-bottom flask containing a stationary litholytic solution ($t = 37^{\circ}\text{C}$). Dissolution was conducted continuously at $37 \pm 0.2^{\circ}\text{C}$ and pH 8. The course of the process was monitored gravimetrically.

The concentrations of ammonium and inorganic cations in the solutions simulating human urine were varied from 0.1 to 3.5 times their statistical normal values, obtained by averaging their concentrations in the urine from healthy people [8, 9]. Amine concentrations in the solutions ranged from 0.01 to 1.5 M. At pH 8, more than 85% of total ammonia is present as NH_4^+ ; therefore, under the experimental conditions, the ammonium-cation concentration was taken as equal to the ammonia concentration in the urine from a healthy individual. Chloride ion (potassium chloride), which has no specific effect on the dissolution process, was used as the anion. The required amount of citric acid was added to the model solution as a complexing agent for Ca^{2+} and Mg^{2+} . The prepared solution was titrated to pH 8 with hydrochloric acid. The pseudo-first-order stone dissolution rate constants k (s^{-1}) were calculated from the loss of stone mass at each time point t . The initial dissolution rate constants k_0 were determined by extrapolating the time-dependent dissolution rate constants to zero time.

To investigate the characteristics of litholysis in the presence of amines, dissolution of urate stones was studied in the amine-potassium chloride-complexing agent system in order to exclude the combined effect of ammonium ions. Figure 1 shows the kinetic curves for the dissolution of urate stone fragments (the change in their mass as a percentage of the initial sample mass) in solutions containing PP (1), TEA (2), and Im (3).

RESULTS AND DISCUSSION

During litholysis, the interaction of uric acid in urate stones with ammonium cations (NH_4^+) considerably increases the initial dissolution rate of urate stones but, paradoxically, substantially decreases their equilibrium solubility [5]. By contrast, the addition to the solutions of bases that are “soft” according to Pearson-Drago [6] considerably increases the equilibrium solubility of urate stones and thus substantially stabilizes the overall process of their litholysis. It has also been shown that, in systems with cation

concentrations substantially below their normal levels in the urine of healthy people, weak bases – imidazole (Im) or triethanolamine (TEA) – should be used to increase the solubility of urate stones, whereas, at ammonium and inorganic cation concentrations above normal levels, the stronger base piperazine (PP) provides a stable and fairly high urate dissolution rate [7].

It was established that in solutions containing PP (curve 1), the stone mass decreased rapidly during the initial stage of litholysis (< 1.5 h). At such a high dissolution rate, an average-sized urate stone would be dissolved within several hours. However, after two hours of litholysis, stone dissolution slowed significantly. During this period, the masses of the native samples decreased by an average of approximately 45%; according to IR spectroscopy, the surface of the urate stone sample became coated with a thin, dense layer of the piperazinium salt of uric acid, and the stone mass began to increase slowly due to crystallization of piperazinium urate on the sample surface.

In solutions containing TEA (curve 2 in Fig. 1), the stone dissolved substantially more slowly at the initial stage. However, unlike in PP solutions, a decrease in the stone dissolution rate in TEA solutions was observed only after three hours of litholysis. Thereafter, stone dissolution in this solution continued at a rate that changed little; as a result, the stone mass decreased by 55–60% during the five-hour experiment.

In terms of the average decrease in stone mass and the average dissolution rate over five hours of litholysis, the system containing Im occupies an intermediate position between the PP and TEA systems.

Differences in the dissolution rates of urate stones in litholytic solutions containing PP, TEA, and Im (Fig. 1) also determine differences in the stone dissolution rate constants. Figure 2 shows the dependence of the stone dissolution rate constants on the amine concentration [Am]. For PP solutions (curve 1), the same figure shows the pseudo-first-order dissolution rates of the stones, which remained constant during the first 1.5 h of dissolution, irrespective of [PP], at $1.3 \times 10^{-4} \text{ s}^{-1}$.

For solutions containing TEA and Im (curves 2 and 3 in Fig. 2), the initial dissolution rate constants (k_0) exhibit similar behavior; the dissolution rate and the time-dependent k values for these systems decrease as the process proceeds.

Analysis of the dependences in Fig. 2 showed that, at the initial stage of dissolution, a high rate is characteristic of solutions containing the strong base PP. The dissolution rate constants are practically independent of the PP concentration within the concentration range studied, whereas in systems containing the weaker bases TEA and Im, the kinetic characteristics at the initial stage of the process depend strongly on the concentrations of these amines in the solutions. This can be explained by the fact that the solubility of uric acid in urate stones is determined primarily by the concentration of the protonated form of the amines in solution.

The data obtained show that, in the model amine-potassium chloride-complexing agent system, even low concentrations of piperazine ensure a high urate stone dissolution rate during the first 1–1.5 h of

dissolution. Subsequently ($t > 2$ h), the stone becomes coated with sparingly soluble piperazinium urate, halting further stone dissolution. By contrast, solutions containing TEA and Im provide a lower but consistent stone dissolution rate over time.

It was also important to study the contribution of ammonium ions, which form a layer of sparingly soluble ammonium urate on the surface of the stones. The next stage was to investigate the effect of amines on the rate and kinetics of urate stone dissolution in urine-simulating solutions. To evaluate the effect of the ammonium cation, we measured the rates and calculated k and k_0 for urate stone dissolution in systems containing PP, TEA, and Im at different ammonium-cation concentrations.

Figure 3 presents the k_0 values for urate stone dissolution in solutions containing PP (curve 1), TEA (curve 2), and Im (curve 3) at different ammonium-cation concentrations $[\text{NH}_4^+]$. It can be seen that TEA solutions are characterized by low k_0 values, which decrease monotonically as the NH_4^+ concentration increases. The k_0 values for stone dissolution in PP solutions are practically constant.

At the same time, in Im-containing systems, the dependence of k_0 on $[\text{NH}_4^+]$ is non-monotonic, with a maximum at the cation concentration $[\text{NH}_4^+]$ corresponding to that in urine [8, 9]. It can be seen that at this NH_4^+ concentration, the stone dissolution rate constants in the presence of Im are approximately two orders of magnitude greater than those in PP and TEA solutions: 5.5×10^{-6} for PP, 7.1×10^{-6} for TEA, and 6.3×10^{-4} for Im. It is also appropriate here to compare the given urate stone dissolution rate constants for PP, TEA, and Im solutions containing a physiological ammonia concentration (4.6×10^{-2} M) with the stone dissolution rate constants in solutions containing only the three amines listed above.

The comparison shows that adding ammonium cations to the PP solution reduces the rate constant, and hence the stone dissolution rate, by over two orders of magnitude. For TEA solutions, k_0 decreases by approximately a factor of 15. By contrast, adding ammonium cations to Im solutions increases the initial urate stone dissolution rate constant by approximately a factor of 15. In the latter case, the initial stone dissolution rate becomes even higher than in piperazine-containing systems that do not contain NH_4^+ , Mg^{2+} , or Ca^{2+} cations.

A possible qualitative explanation is as follows. By binding uric acid anions in solution, the strong base PP accelerates the release of uric acid molecules from the stone into the solution at the initial stage of the process. However, the sparingly soluble piperazinium urate salt formed near the stone surface precipitates on the surface of the stone and hinders further dissolution. The addition to the solution of ammonium ions, which form an even “harder” and less soluble salt with uric acid, additionally slows the litholysis process.

CONCLUSIONS

The results obtained indicate that dissolution efficiency depends not only on the properties of the amine component but also on the properties of the products formed through the interaction between the amines with urine components or with the components of urine models. Combined litholytic

compositions containing strong and weak bases that differ in their mechanisms of interaction with uric acid may provide an optimal urate stone dissolution rate while preserving kidney and urinary tract function.

Declarations

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[†] This paper is dedicated to the memory of our co-author, Volodymyr Bilobrov, who devoted a significant part of his life to the chemistry of urolithiasis.

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Figures

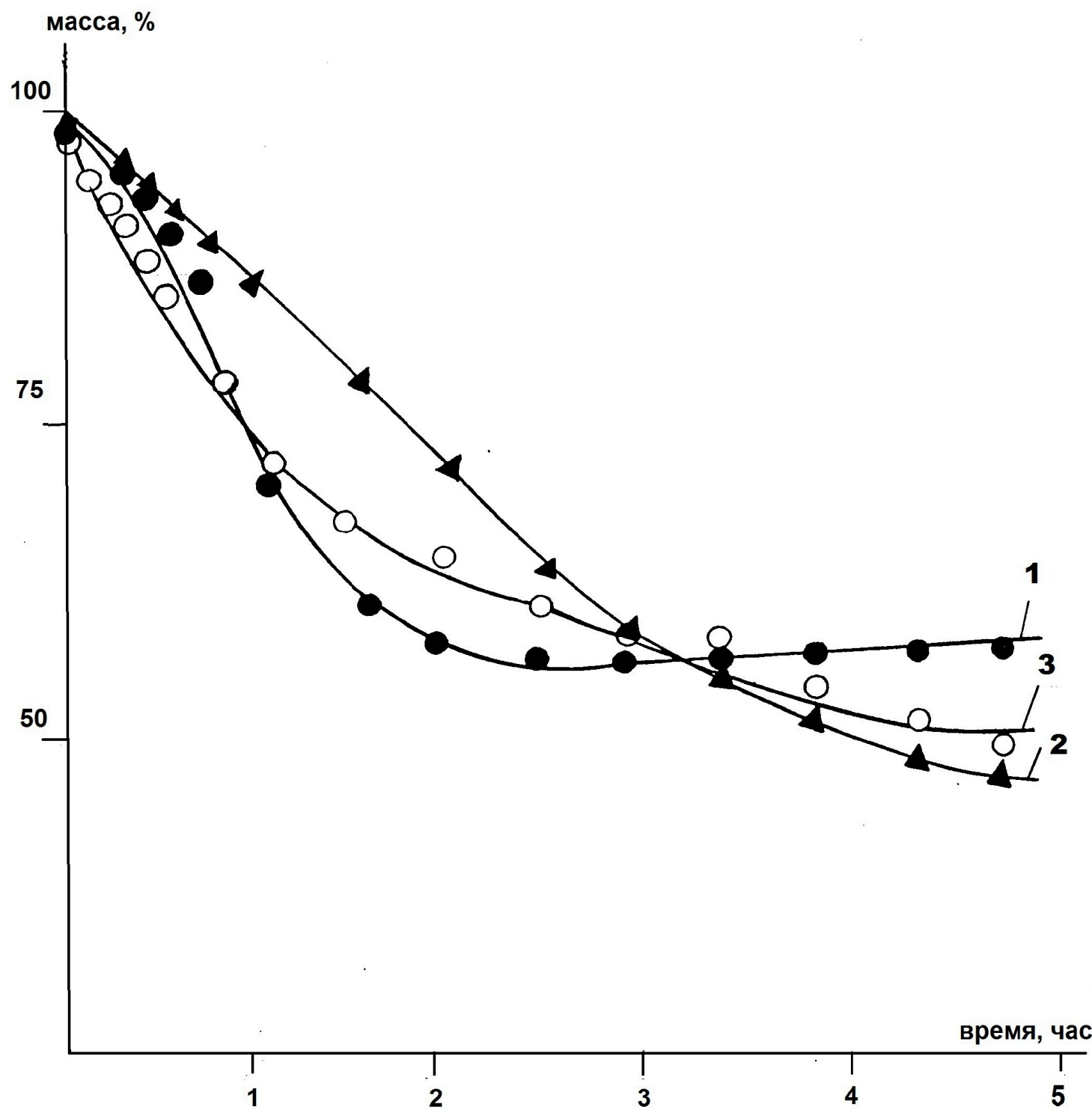


Figure 1

Relative change in the mass (%) of uric acid stones during litholysis.

1 – piperazine (PP); 2 - triethanolamine (TEA); 3 - imidazole (Im)

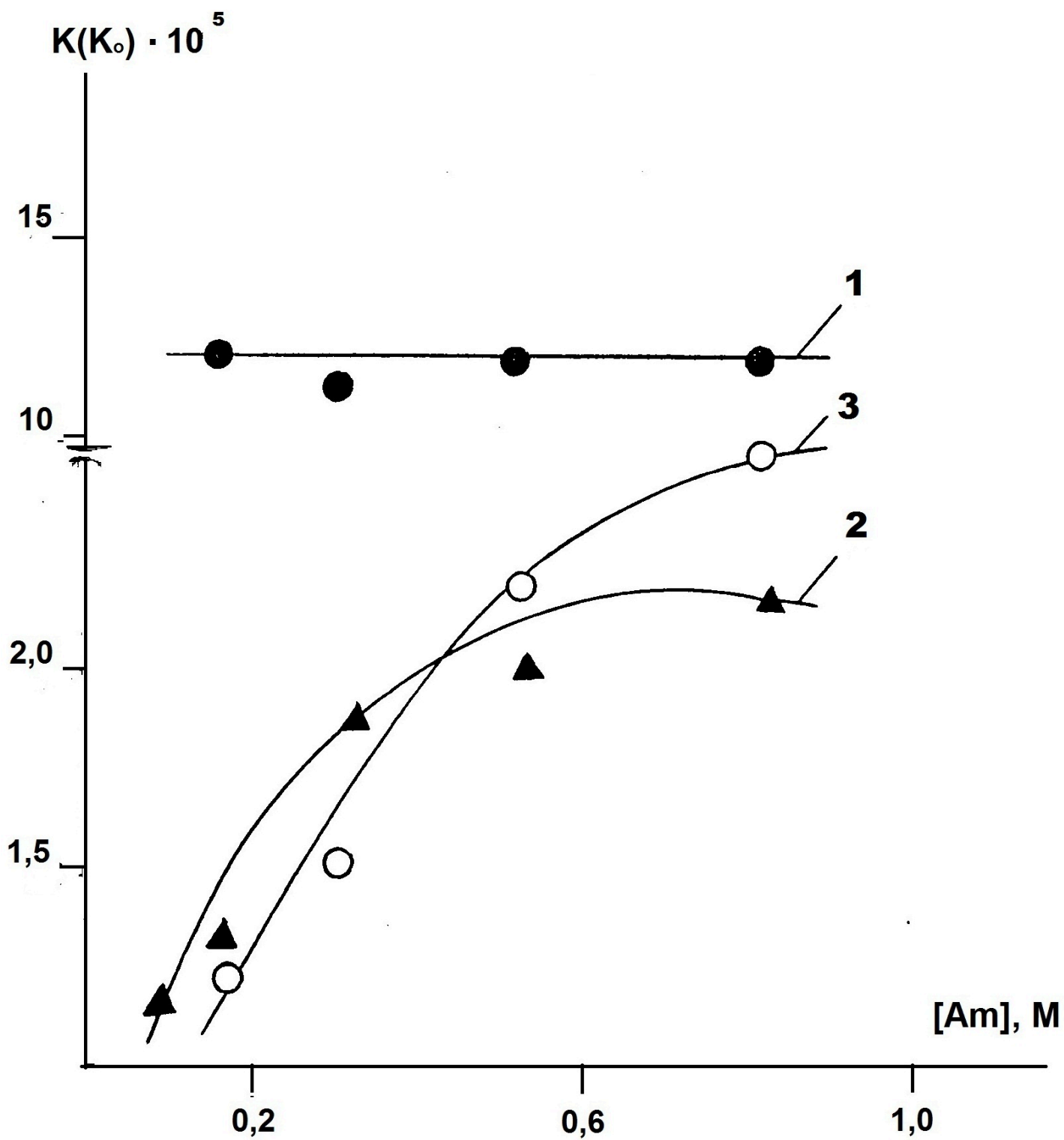


Figure 2

Dependence of the uric acid stone dissolution rate constants on amine concentration.

1 – piperazine (PP); 2 - triethanolamine (TEA); 3 - imidazole (Im)

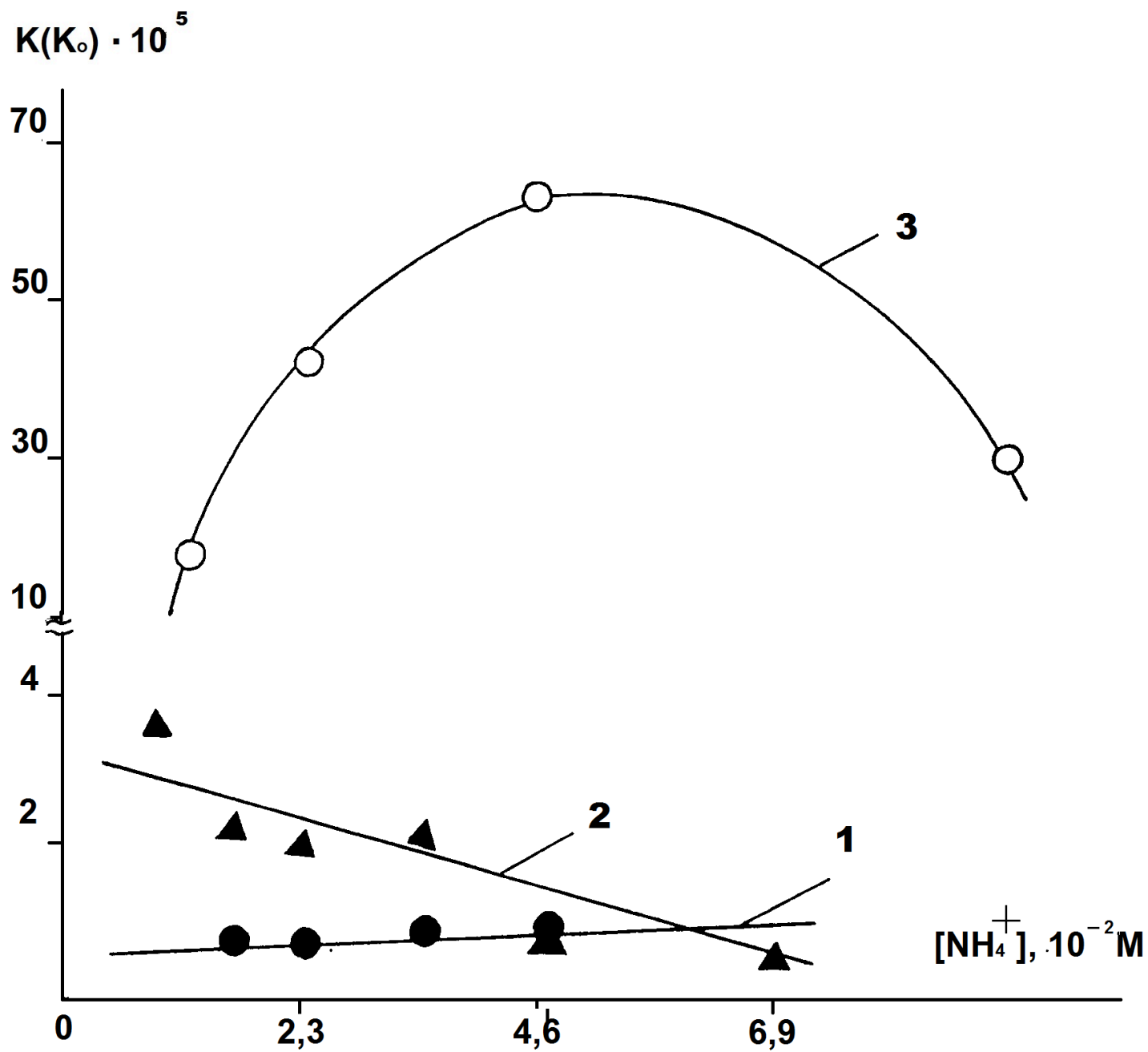


Figure 3

Dependence of the uric acid stone dissolution rate constants on ammonium-ion concentration.

1 – piperazine (PP); 2 - triethanolamine (TEA); 3 - imidazole (Im)