Urol Res (1994) 22:119–126

ORIGINAL PAPER

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EQUIL93: a tool for experimental and clinical urolithiasis

Received: 22 June 1993 / Accepted: 4 November 1993

Abstract An extensively updated version of the EQUIL software is described. The former version, designated EQUIL2, is widely used to study urolithiasis and related areas of biomineralization. In this report, we discuss recent enhancements which give EQUIL93 an expanded scope of application. This program has been frequently used in studies of the physicochemical processes underlying stone salt crystallization, especially crystal growth and nucleation, but it has also been employed as an aid for in vivo research and as an evaluator of therapeutic measures. We illustrate several new applications, including some outside the urologic realm, and we discuss how the enhanced software can be helpful in stone risk assessments.

Key words Urolithiasis · EQUIL93 · Stone risk assessment · Evaluation of therapy results

Understanding the pathophysiological mechanisms leading to urolithiasis represents a major challenge for both biologists and chemists [24]. The biologist is challenged to understand how cellular processes and structures affect the deposition of crystalline substances through the involvement of metabolite transport, membrane interactions, changes in pH, and the release of proteins and other low-molecular-weight metabolites into urine. The chemist needs to address the solution chemistry of a multisolute system which varies widely in concentration from nearly ideal behavior in the most dilute glomerular filtrate, through regular solution behavior as tubular processes introduce additional solutes and remove water, and then beyond Debye-Hückel behavior as urine itself leaves the kidney. Moreover, the interface between solvent and crystalline materials involves the consideration of the kinetics and thermodynamics of mass transfer processes, including electrostatic phenomena, adsorption, and the detailed mechanics of crystal growth at the lattice itself [6]. Both chemical and biological characterization of urolithiasis require development of appropriate quantitative models. Because the composition and behavior of urine must be crucial factors in lithogenesis, a comprehensive numerical treatment is an essential component of such modeling efforts [22]. Fortunately, urine and various experimental model urine-like solutions are amenable to treatment with established physical theory, and concurrent advances in these theories and our understanding of lithogenesis permit development of increasingly sophisticated computer models.

In this report, we consider the EQUIL93 computer software that calculates the distribution of various anions and cations among their many states of ionization (i.e., protonation and metal complexation) in aqueous solutions; this distribution is often referred to as the solution "speciation". Over the past 20 years, various versions of EQUIL have found broad utility in the field of urolithiasis in applications ranging from clinical evaluation of stone patients to evaluating in vitro assays of lithogenic materials. In addition, EQUIL93 finds increasing value for experimental design in urolithiasis and in other biological researches where knowledge of free ion concentration or ion complex formation is important. The current EQUIL93 software supersedes formerly reported versions [12, 28] and extends the compass of the physico-chemical events by inclusion of calcium oxalate monohydrate's interfacial chemistry. We have also engaged in a critical re-evaluation of published thermodynamic constants; where necessary, earlier values are now supplemented with additional experimental findings and analyses. This effort has also allowed us to extend the number of solutes considered by EQUIL93.

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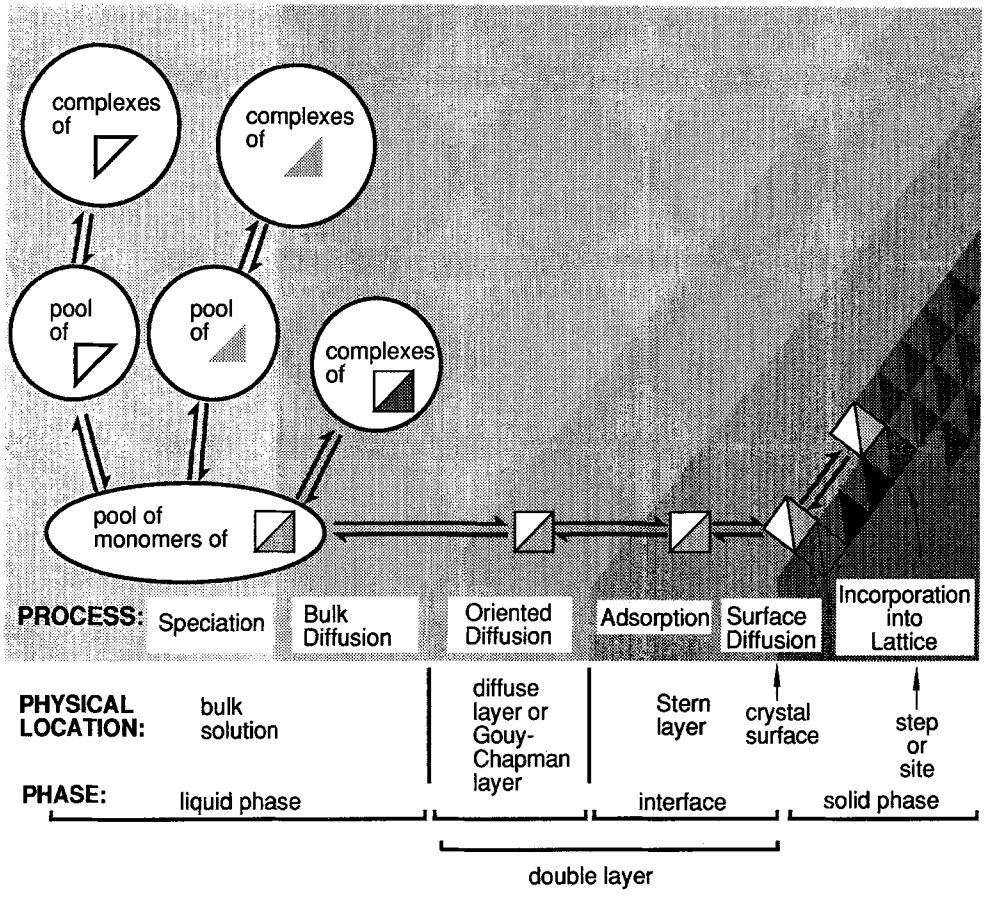

Fig. 1 Diagram showing various processes contributing to crystal growth in aqueous solution

COM physical chemistry considered by EQUIL93

Measurements of crystal growth are often summarized by a single kinetic parameter, the growth rate constant. While such a number can be quite useful in characterizing crystal growth for purposes of comparisons among similar growth systems, it is important to note that crystals grow by means of multiple steps that connect dissolved crystal components to a solid lattice. Figure 1 presents a postulated scheme for crystal growth and indicates that the growth rate represents a convolution of several other kinetic constants. Understanding more than the gross features of crystal growth requires a detailed characterization of each step in this process. The network of complexes at the left of Fig. 1 represents ionic speciation in the solution phase (described above) of a potentially insoluble salt, and the relative supersaturation (RS) of this salt in solution relative to the solid is the primary thermodynamic driving force for crystallization. Calculation of RS requires knowledge of metal-ligand stability constants and acid/base equilibrium constants that describe the interaction of all relevant chemical solutes. Because the interaction and interconversion of solutes is extremely rapid compared to other processes in solution, speciation may be considered as a set of equilibria. Likewise, the adsorption process, whereby solutes become chemically attached to the surface, may be approached as an equilibrium. Diffusion processes depicted in Fig. 1, however, cannot be so simplified and require more complicated mathematical treatments to be described adequately. The EQUIL93 software performs the speciation and adsorption calculations necessary to predict the relative supersaturation and amounts of solutes adsorbed to the crystal surface. Therefore, it allows one to understand the central driving forces for nucleation, crystal growth, and growth inhibition in relatively complex solutions.

The central problem solved by EQUIL93 is graphically depicted in Fig. 2 as the functional linkage of the equilibria which might not be easily discerned from tables of constants or computer output. Shaded circles represent total concentrations of calcium, citrate, and oxalate in hypothetical solutions; typically, only total concentrations are measured in the laboratory. The goal is to discover how much of these total concentrations are present as free ions or as complexes. In the latter case, a complex could be a potential component of a specific crystal lattice, and knowledge of its concentration would allow calculation of RS; or, a complex could bind an ion necessary for building a specific lattice and thereby diminish crystal growth. The network of open circles and interconnecting arrows overlying the shaded circles indicate the many complexes that form from these ions in aqueous solution. (Circle area is proportional to molar concentration). EQUIL93 utilizes a database defining relationships among complexes to calculate their exact concentrations. Specifically, Fig. 2

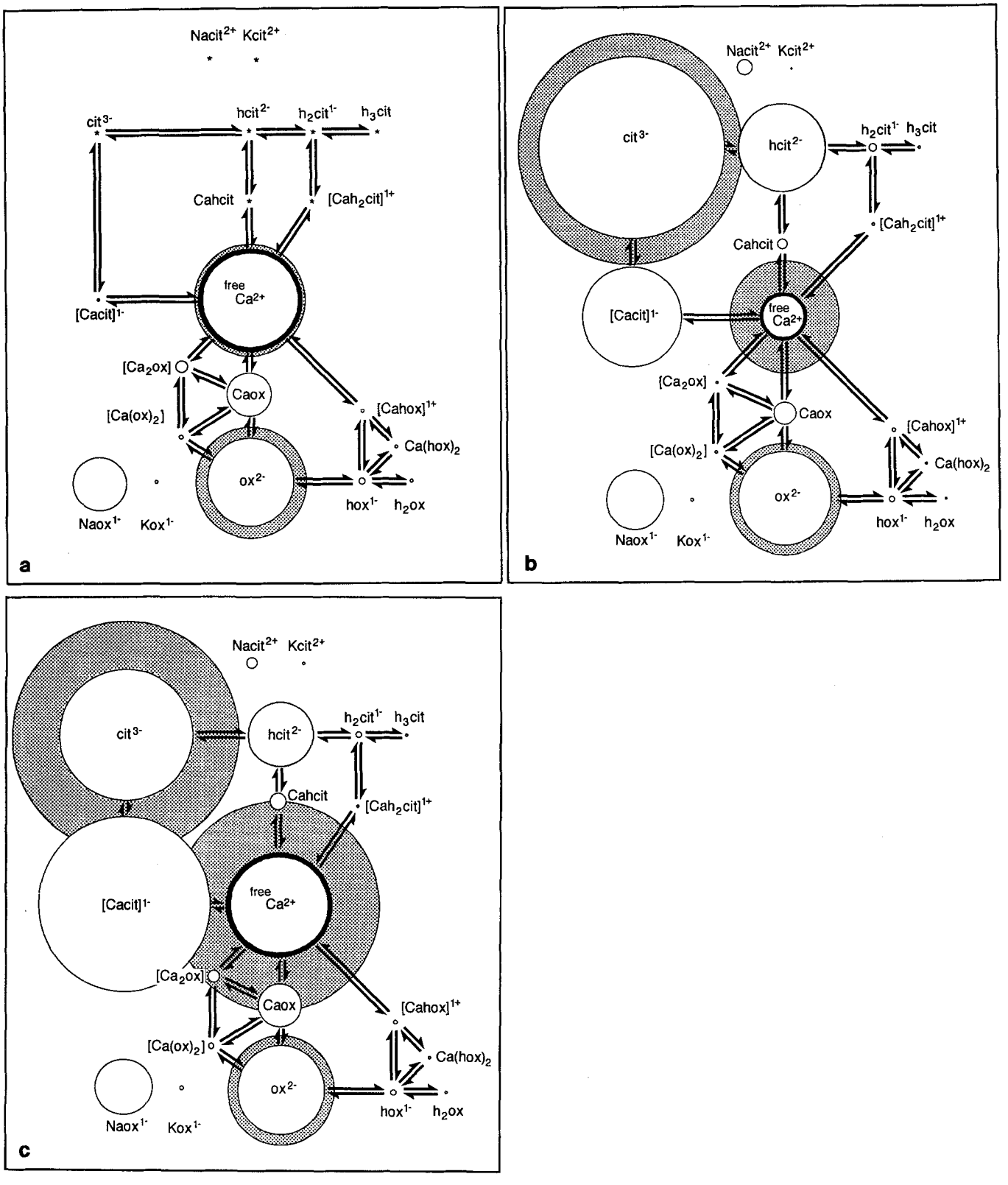

Fig. 2a–c Diagrams showing the impact of citrate on the equilibrium calcium ion and oxalate ion. The areas of the *circles* are proportional to the concentration of the species they represent. **a** Buffered saline solution supersaturated with respect to calcium oxalate monohydrate. **b** The same solution after the addition of 3.5 mmol/l potassium citrate. Note the decreases in free calcium, relative supersaturation, and calcium-to-oxalate ratio. **c** The solution in **b** after adjustment of total calcium according to EQUIL93 calculations. This solution is now directly comparable to the control in **a** except for the presence of citrate and its complexes

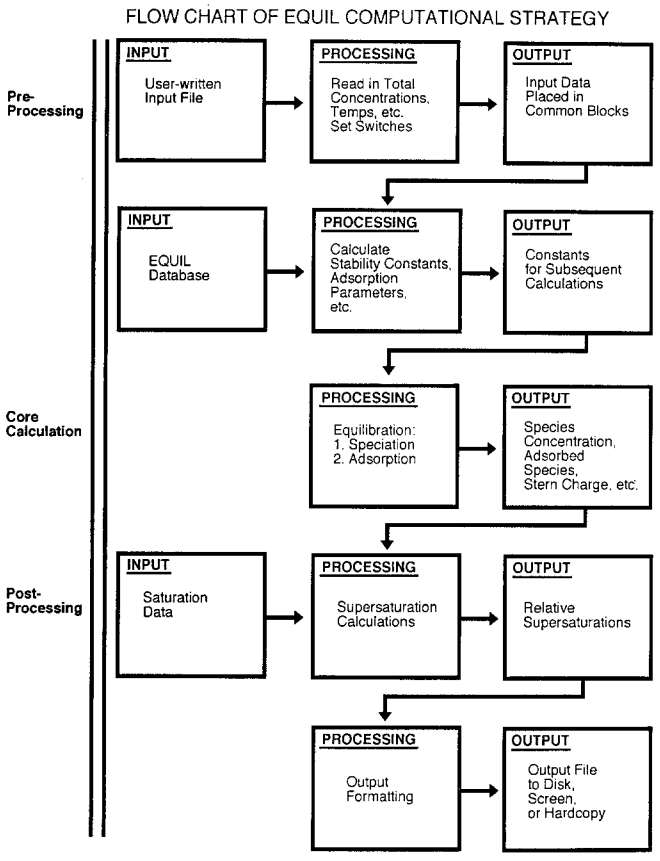

Fig. 3 Simplified flow chart of the EQUIL93 software

charts the distribution of calcium ions and oxalate ions among various forms in three buffered saline solutions, both with and without citrate ions present. Such solutions might be used in a crystal growth study to determine the inhibitory capacity of citrate. An obvious approach might be to take identical solutions and add citrate to one of them; this experiment is illustrated in Figs. 2a and 2b. In Fig. 2a, most calcium exists as free ions nevertheless, sufficient calcium oxalate complex is present to supersaturate the solution with respect to calcium oxalate monohydrate (COM) solid phase. Figure 2b shows what happens when citrate is added to this system; much calcium becomes calcium citrate complex, and calcium oxalate complex (and therefore RS) decreases substantially. Crystals immersed in the solution of Fig. 2b would grow more slowly, but for several reasons: (1) RS has decreased significantly, (2) surface active agents, such as citrate ion and calcium citrate complex, can interfere mechanically with crystal growth, and (3) the calcium-to-oxalate ratio has been altered. Reduction of RS by citrate has been reported as growth inhibition, but true inhibition is a surface event in which growth sites on a crystal are blocked and mass accretion is delayed if not halted. True inhibitory effects of citrate would be clarified if growth conditions (i.e., RS and Ca^{2+}/ox^{2-}) in these solutions were directly comparable. Thus, Fig. 2c represents an experimental solution which matches the control; EQUIL93 adjusted RS automatically, and the user brought Ca^{2+}/ox^{2-} to 1:1 as in the control. Overall, elevated total calcium compensated for added citrate. Citrate and its calcium complexes are surface-active on COM, and they truly inhibit growth by associating with specific crystal faces thus slowing mass accretion at these sites. Adsorption calculations performed by EQUIL93 assist in estimating this effect; about 20 of EQUIL93's 23 major ions and 104 complexes are considered in adsorption calculations.

Computational enhancements of the EQUIL93 software

In our effort to expand the scope and increase the utility of EQUIL93, we increased the number of ions which may be entered as input from 15 to 23, and the total number of complexes among these solutes now exceeds 100. Moreover, we now use EQUIL93 to evaluate most of these equilibria and some relative supersaturations in a temperature-dependent manner. The physical chemical constants underlying relative supersaturation calculations have also been thoroughly reevaluated, and additional solid phases have been incorporated. In addition, four new specialized simulation computations have extended the functionality of the program: first, the user may simulate precipitation of COM; second, the user can "charge balance" the solution by computer adjustment of pH; third, the program can calculate recipes from which to produce solutions with desired relative supersaturations with respect to COM. Lastly, we have included a database that will allow the user to specify inclusion of a typical human urine as a component of input data.

Brief overview of the EQUIL93 computational strategy

A flow chart showing the EQUIL93 program in broad procedural steps is given in Fig. 3. The diagram shows that the program has a nested iterative structure and operates on a large database. Surface depletion of solutes is part of speciation calculations for accurate accounting of solution composition. Convergence is attained in the core calculation when mass conservation is better than 1 part in 10000 for all major ions. The core calculation may be used several times as a subroutine to the precipitation or charge balancing schemes discussed below. Table 1, a sampling of EQUIL93's output information, gives partial results for the human urine 1 (HU1).

Expanded base of major ions

EQUIL93 speciation calculations encompass 23 major ions, as opposed to 15 in EQUIL2. Expressed in terms of states of protonation and/or complexation, EQUIL93 now incorporates over 100 equilibria. Both versions include pH, sodium, potassium, calcium, magnesium, ammonium, oxalate, sulfate, citrate, urate, chloride, pyro-

Table 1 Selected values taken from EQUIL93 output for human urine 1 (see text)

Input (concentrations given as mmol/l)					
pH	6.5	Sodium	182	Potassium	64
Calcium	5.7	Magnesium	3.9	Ammonium	41
Phosphate	32	Sulfate	61	Oxalate	0.303
Citrate	3.2	Urate	2.9	Chloride	189
Output					
Relative supersaturations					
Whewellite	7.6	Apatite	2×10^{9}	Brushite	2.8
Struvite	0.8	Uric acid	2.5	Bobierrite	0.01
Concentrations of protonated forms and metal ion complexes					
Ionic calcium	1.9 mmol/l				
Oxalate (ox = $C_2O_4^{2-}$; species shown in Fig. 1 selected)					
ox^{2-}	124 µmol/l	Hox^-	0.3 µmol/l	H_2ox	2×10^{-12} mol/l
Caox	47 µmol/l	Ca_2ox^{2+}	6 µmol/l	$Caox_2^{2-}$	0.1 µmol/l
Citrate (cit = $C_6H_5O_7^{3-}$; species shown in Fig. 1 selected)					
cit^{3-}	697 µmol/l				
$Hcit^{2-}$	124 µmol/l	H_2cit^-	0.7 µmol/l	H_3cit	0.4 nmol/l
$Cacit^-$	1.5 mmol/l	CaHcit	11 µmol/l	CaH_2cit^+	5 nmol/l
Other values					
Ionic strength	0.343				
Surface charge	4.0×10^{-7} C cm^{-2}				
Stern charge	-1.4×10^{-6} C cm^{-2}				

phosphate, TRIS buffer, and carbonate; new in the current version are acetate, fumarate, glutamate, HEPES buffer, lactate, malate, and PIPES buffer. EQUIL2 included species known to be of great importance for urine, and many new species have been added in response to the needs of workers in urolithiasis and others.

New solid phases

The previous version of EQUIL93 gave relative supersaturation information for nine solid phases: calcium hydroxide, magnesium hydroxide, whitlockite, bobierrite, apatite, brushite, struvite, uric acid, and whewellite. To these have been added $Mg_3(PO_4)_2\cdot22H_2O$ and $MgKPO_4\cdot6H_2O$. The relative supersaturation calculation for COM has been rendered temperature-dependent based on the work of Garside et al. [14].

Surface chemistry

We incorporated into EQUIL93 a computational picture of the COM surface as it relates to simplified urine-like solutions. Many interesting effects in crystal growth and solubility phenomena result from solutes acting at crystal surfaces. For urolithiasis researchers, the most important of these may well be inhibition of crystal growth. Solutes may act to block growth sites and thus reduce the rate of crystal growth. To the solution chemist, the surface acts as an additional complexing agent which removes species from the bulk solution and thus distorts solution speciation. Lastly, to the surface chemist, solutes alter the electrical environment of the crystal surface and the layers between it and the solution. Any of these three effects can influence crystal growth rates and resultant morphology of crystals. Additionally, surface chemical calculations form the basis of studies of agglomeration.

EQUIL93 informs the experimenter about COM surface chemistry in three ways. First, the software calculates the quantities of species present on the surface on a per unit area basis. Second, if a specific surface area is supplied as input data, the program calculates the molar depletion of individual species. Third, the quantities and types of adsorbed species are used to calculate parameters that characterize the electrical environment at or near the surface, i.e., the surface charge, the Stern charge, and the Gouy charge. The Stern charge is often taken to be equivalent to the zeta potential, which is experimentally accessible through electrophoretic mobility measurements. Curreri et al. [11] and Finlayson et al. [13] have already described the theoretical basis of these calculations in terms of the Nernst-Gouy-Stern-Grahame model. Further examination of the theory may be found elsewhere [15, 27], and surface science texts contain more introductory treatments (e.g., [16]). Because adsorption is specific to individual crystal faces, the calculations offered by EQUIL93 are necessarily macroscopic averages.

Critical review of thermodynamic constants

In reviewing the literature on stability constants, we sought to meet two goals: to review critically the constants already used in EQUIL2, and to develop a critical collection of constants spanning temperatures of 10–60°C.

We relied heavily on the critical collection of Martell and Smith and on the London Society/IUPAC compiliations [4, 9, 10, 17, 19, 20, 21, 25, 26]. Three criteria were applied in selecting values for use in developing suitable approximations of the dependence of complex stability on temperature. First, the range of values for a particular complex had to include the critical value from Martell and Smith. Second, where possible, we sought a single literature source for values spanning the temperature range, accepting combined sources only when there was good overlap of experimental data between the sources. Third, we sought data reported at zero ionic strength; when unavailable, we established corrected values by using activity coefficients provided by EQUIL93 itself. The quality of data for the range of complexes in EQUIL93 varied considerably, but a number of internal checks were employed. This led us to believe that the resulting database was, in general, fairly conservative and reliable.

Temperature-dependent fits of stability constants

An expression for variation of stability constants with temperature was derived from the van't Hoff equation using an empirical function for the heat capacity. This gave a six-term expression that could be solved easily using stability constant and enthalpy data. Most stability constants behave monotonically over the temperature range of interest to us, and therefore a six-term expression was more than adequate to describe such data. Constants in EQUIL2 corresponded to various temperatures of determination, mostly 37°C and 25°C, so that calculations performed with EQUIL93, while more accurate, may differ to some extent from those of the previous version. The new version allows the user to bypass the fitted constants altogether and to employ constants from the earlier software to allow comparison of results or to maintain consistency of treatment.

Specialized simulations in the EQUIL93 software

Simulated precipitation of COM

EQUIL93 now includes a subroutine which simulates COM precipitation. For a solution supersaturated with respect to COM, the subroutine incrementally diminishes total calcium and oxalate concentrations until the resulting solution has a relative supersaturation of unity. The results provide a "snapshot" of the solution conditions before and after precipitation. This feature can be useful when knowledge of equilibrium conditions is desired.

Charge balance by pH adjustment

EQUIL93 does not require the user to provide data for input as electrically neutral solutions; instead, the charge balance of the solution is reported in the output. Then, theuser can become aware of those situations where this may be an important consideration. Detailed charge balance calculations allow a priori prediction of pH in experimental solutions from their formulations. This has been used for modeling titrations with good results for simple solutions and with more limited success for whole urine [1]. Such work indicates, however, that if additional components (i.e., urinary solutes, metabolites, and proteins) were incorporated into EQUIL93, the titration behavior of whole urine could be more faithfully described.

Calculation of solutions for desired relative supersaturation

A new feature of EQUIL93 that has found great utility is the ability to predict appropriate formulations necessary to achieve solutions of desired in vitro relative supersaturations. This feature is the functional corollary of the precipitation subroutine discussed above. We and other colleagues have used this feature extensively in the design of crystal growth experiments and inhibition assays. While the only solid phase presently considered in this way is COM, we can expand this capability to other solid phases for which solute interactions are included in the EQUIL93 database.

Typical human urine concentrations

In addition to the discrete chemical species that we have included in the EQUIL93 program, we have now added the first of a series of composite solutions. Our first entry is referred to as human urine 1 (or HU1) in the program. It consists of a list of those substances considered as major ions in EQUIL93 at their typical concentrations in human urine based on the extensive tabulations given in *Documenta Geigy* [18]. While typical values do not apply to any particular human, they may be useful in *gedanken* experiments, or speculative calculations, to evaluate the behavior of whole urine or partial urine in anticipated experimental designs. Input values for this option specify HU1 as a desired percentage of the user's solution. Other composite solutions to be added in the future will include human serum, solute concentrations typical of rat urine, and an artificial urine [8].

Discussion: biophysical applications of the EQUIL93 software

We present this material to describe the program to potential users; readers who desire more mathematical detail may consult Finlayson (1977) and Finlayson (1978), where the applicable physical theory and computational strategy have been explicated more rigorously. Additional

explanation and applications are noted in the text, and an expanded form of this report is available from the authors.

Although virtually every echelon of the urolithiasis problem has received attention, no pathophysiological cause has been verified, with the exception of genetic effects in primary hyperoxaluria. The highly synergistic nature of the problem suggests that broad interdisciplinary approaches offer the greatest hope for success. Such approaches demand a common framework that encourages effective discourse among practitioners from various disciplines. In the physical sciences, communication is achieved through the use of thermodynamics and kinetics. Such computational software as EQUIL93 affords such a framework to relate physical, chemical, and clinically relevant aspects of urolithiasis. Hopefully, EQUIL93 can become a means for chemists and biologists to gain greater understanding of clinical issues and for clinicians to appreciate the underlying chemical issues. As aspects of the problem other than kinetics and thermodynamics yield to standard and quantifiable treatments, they too will become part of the formalized discourse, thereby providing a more satisfying bridge between the basic science and the clinical science of urolithiasis.

EQUIL93 has been employed for sometime to assess kidney stone patients, particularly by Dr. Frederic Coe at the University of Chicago and Dr. Lynwood Smith and associates at the Mayo Clinic. In each of these clinical programs, a computerized patient information system automatically submits clinical chemical values for analysis by EQUIL93. Supersaturation results are then added to patient records. Dr. Charles Y. C. Pak has employed EQUIL93 in risk assessment, and the software provides numerical data analysis for a graphical display of patient risk factors [23]. Appropriate recommendations for altering the patient's diet can then be made. Examining the synergistic effects of dietary and therapeutic protocols in terms of relative supersaturation calculations may also allow more appropriate therapeutic choices, and EQUIL93 provides a rational basis for evaluating a patient's progress during and after treatment. There are limitations, of course, and EQUIL93 permits an accurate evaluation of stone risk only with consideration of the fuller clinical picture. Specifically, it should be kept in mind that EQUIL93 does not purport to simulate stone formation and is based solely on the principles of chemical thermodynamics of the equilibrium state; consequently, the software cannot account for kinetic processes of stone formation, complex solutes (such as urinary macromolecules), or the role and nature of stone matrix.

Even with these limitations, the EQUIL93 software has been designed for easy extensibility. As the significance of known urinary metabolites becomes clear, they can be added to the EQUIL93 database; likewise as new and interesting metabolites are discovered. When such additions are warranted and the altered software has been thoroughly tested, new versions of EQUIL can be made available.

The biophysical basis of urolithiasis has been studied in a wide variety of systems. The success of such studies often hinges on either correctly establishing initial supersaturation conditions or estimating RS on the basis of chemical analyses. In cases where the activity of a free ion or surface action of a complex is relevant, software such as EQUIL93 is essential; complexation often alters the free ions available in a biological system, thereby allowing them to participate in processes of interest. As noted earlier, EQUIL93 allows for good design of such experiments and for more thorough analysis by revealing chemical effects and giving the researcher a direct way of understanding and evaluating them even in the absence of extensive grounding in solution physical chemistry.

We also should note that EQUIL93 has found use beyond urolithiasis in related fields of biomineralization and calcium ion biochemistry. Here again, issues of metal ion complexation and ionic activity have become important in understanding biological phenomena. In one such industrial application, we assisted in estimating the availability of calcium from a calcium-fortified beverage. Similarly, EQUIL93 has been used to evaluate blood calcium levels in a transplant patient [3] and to examine calcium activation during protein polymerization reactions. EQUIL93 has also served as the foundation of a variety of more theoretical and purely physical studies. We have employed EQUIL93 in numerical simulations of precipitating systems [7], and the surface chemical calculations provided by the program have been used as the basis for studying agglomeration processes [2].

While it is a powerful computational tool, attention should be given to the limitations of the EQUIL93 software. This program treats equilibrium processes only, and kinetic matters are not addressed directly. Nevertheless, solution parameters affecting kinetics can be provided by EQUIL93, and these reflect on the instantaneous status of solute concentrations, speciation, relative supersaturation, etc. Reliance on Debye-Hückel solution theory in the EQUIL93 software tacitly chooses decreasing accuracy with increasing ionic strength. Because of the large number of species being evaluated, the investigator's awareness of such limitations is important for very complex solutions at high ionic strengths. EQUIL93 also does not account for the full range of substances found in urine. Provision in the program for certain urinary components will require a sufficiently developed theoretical framework for incorporation of macromolecular species into ionic solution theory. Moreover, in its present stage of development, EQUIL93 will not provide any analysis of cation interactions with isolated phospholipids or intact membranes or vesicles.

Finally, while others have developed programs along the lines of EQUIL93, we should like to say that for us the EQUIL93 software stands as a tribute to the late Professor Birdwell Finlayson, a urologist and biophysicist who strove to understand urolithiasis from the rigorous perspective of a physical chemist [5]. The program and instructional materials are available at a nominal charge upon written request to the authors. The EQUIL93 software is being constantly revised and expanded in our facility, and the authors invite inquiries as to current and

potential capabilities of the program as well as consultation or collaboration in its use. It is our hope that common use of EQUIL93 among the diverse workers of urolithiasis will foster greater and more focused communication to facilitate solutions to problems of common interest. Ultimately, our goal is to increase the scope and sophistication of EQUIL93 to give the active researcher a more useful and complete tool for comprehending the behavior of stone-salts and solutes in physiological environments.

Acknowledgement This work was supported in part by National Institutes of Health Grant AM20586.

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