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Prediction by Computer Modelling of the Precipitation of Stone-forming Solids from Urine

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Abstract

The development and verification of an equilibrium speciation computer model of urine is described. The model is based on critically selected equilibrium constants and solubility products corrected where needed to $T = 37$ °C and $I = 0.2$ mol dm^{-3}. The model represents a slight improvement over previous equilibrium models in that a simpler and more reliable measure is used to represent the degree of supersaturation with respect to a stone-forming salt. A further improvement arises from an implicit allowance being made for certain kinetic factors governing the precipitation of calcium-phosphate solids. The model was verified by comparison with an analogous experimental procedure applied to a standard reference artificial urine. Good predictions were obtained for the precipitation of calcium oxalate monohydrate (COM), dicalcium phosphate dihydrate (DCPD), calcium hydroxyapatite (HAP) and uric acid, but not for struvite. The model indicates that normal urine in the physiological pH range of 5.5 to 7.0 contains precipitates of COM, DCPD and HAP. Precipitates of uric acid and struvite are predicted to occur below and above a pH of 6, respectively. Further computations yield results which are consistent with the view that DCPD may act as a precursor in the precipitation of HAP. Finally, the results indicate that COM precipitation is far more markedly augmented by an increase in oxalate concentration than by an increase in calcium concentration.

Introduction

Urolithiasis constitutes a world-wide medical problem not only in terms of the suffering endured by the individuals afflicted but also because of a widespread economic impact upon society through hospitalization and absenteeism from work [1, 2]. Thus there is abundant justification for research into the causes and control of urinary calculi formation. Whereas clinical and biological studies produce considerable advances in the understanding of urolithiasis, there is no doubt that fundamental bioinorganic–chemical investigations form an essential complement [3]. Moreover, urolithiasis as a topic has pertinence to bioinorganic chemistry in view of the growing general interest in bio-minerals [4].

The most commonly occurring constituents of urinary stones are calcium oxalate, calcium phosphate, magnesium ammonium phosphate, uric acid and cystine [1]. Of these, calcium oxalate is the most frequent constituent, occurring in about 70% of all cases. Cystine is the most infrequent, its presence being observed in about 1% of all cases. The remaining three are found to occur at about the same frequency, namely just below 9%. These five solids therefore account for about 98% of all urinary stones.

The detailed mechanisms of stone formation in urine are not clear but the overall process is expected to proceed through three main steps, namely:

initiation of precipitation ⟶

crystal growth ⟶ aggregation

Two important relevant facts are that the stone-forming salts are usually present in urine at concentrations exceeding their equilibrium solubility values and that most people pass urine that from time to time contains precipitates [3]. It follows that urinary stone disease occurs when a particle moves through the urinary system at a rate much lower than the ordinary flow rate of urine. This requires retention of the particle through adhesion to tissue. Subsequent crystal growth and aggregation can lead to the blocking of a urinary duct.

It seems that a large number of factors may determine whether stone disease will occur [1]. Included are factors affecting the kinetics of crystal growth [5]. Nevertheless, the usefulness of modelling the ionic equilibria in urine by computer simulation has been clearly demonstrated [3, 6, 7]. The computer models are constructed by compiling a list of the formation constants for every cation–ligand–proton complex that potentially can be formed from a selected set of components. Measurements or

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estimates are then made of the pH and the total concentrations of the selected components in the urine or urine-like solution under investigation. All of this information is then used in an appropriate computer program to set up and solve simultaneously the relevant mass balance equations derived from the respective mass action and conservation of mass equations. The speciation results obtained are used in various ways by different authors to calculate a suitable index of the state of supersaturation of the urine sample with respect to a given stone-forming salt. Finlayson asserts that the degree of supersaturation of a stone-forming salt represents a crucial index of a urine sample to form stones and that without supersaturation none of the other stone-forming factors can operate [1]. The index used by Finlayson and his co-workers and also by Robertson and his co-workers is termed the relative saturation ratio. The latter is determined by obtaining from the speciation results for a given urine or urine-like solution the activity product corresponding to the relevant stone-forming salt, e.g., $a_{Ca^{2+}}a_{(COO)_2^{2-}}$ or $a_{Ca^{2+}}a_{HPO_4^{2-}}$ (where $a_{X^{n+}}$ denotes the activity of ion X^{n+} in the solution), and dividing this by the thermodynamic solubility product of the stone-forming salt. The thermodynamic solubility product is determined, in general, from synthetic solutions of known ionic composition.

The main difference between the methods of Finlayson, of Robertson, and of Daniele and Marangella lies in the choice of components used for determining the activity products of the stone-forming salts. There are also differences in the values used for the stability constants of some of the complexes. An alternative parameter that has been proposed as an index of the state of supersaturation of a urine sample is the activity product ratio [8], evaluated by dividing the activity product by the solubility of synthetic stone-forming salt in the individual urine sample.

Incidentally, Pak [8] has adopted an approach to determining the state of saturation of a urine which bears some resemblance to the methods of Finlayson, Robertson, and Daniele and Marangella, but which does not make use of computer modelling. In Pak's method, it is assumed that no complexation occurs and activity products are calculated directly from the measured total concentrations of the ionic components constituting the relevant stone-forming salt.

In contrast with the authors mentioned above who have aimed at determining supersaturation in urines, Rubin *et al.* [2, 9] have applied an approch involving equilibrium modelling of the fluids in successive body compartments. They have used this approach to investigate the therapeutic potential of orally administered disodium nitrilotriacetate in inhibiting the formation of dicalcium phosphate dihydrate (DCPD) and struvite (magnesium ammonium phosphate hexahydrate) calculi or in dissolving calculi present in animals.

In this paper we describe a computed speciation model of urine aimed at examining the effects of various factors which influence the equilibrium precipitation of individual stone-forming salts. Allowance can implicitly be made for certain kinetic factors which govern the precipitate formation of hydroxyapatite and calcium oxalate monohydrate. An additional feature comprises an improved database of complex formation constants including values for the phosphate-magnesium species recently determined by ourselves [10].

The Urine Models

In order to predict the precipitation of solids from urine, we have assembled computer input data consisting of the total concentrations of the components in the standard reference artificial urine composition proposed by Burns and Finlayson [11]. The input database also contains values for the metal–ligand formation constant for every significant complex that can conceivably be formed, the protonation constants for every ligand present, and the solubility product for every partially soluble salt that can potentially precipitate from the components of the solution. The values for these constants were obtained, as far as was possible, from the literature, exercising critical selection where more than one reference to a given constant could be found. As many values as could be found of the enthalpies of the corresponding reactions and heats of solution were also extracted from the literature, to facilitate correcting of the constants, where necessary, to the desired temperature of the model. In cases where needed enthalpy values could not be found, estimates were made through correlation with similar compounds. Where necessary, the formation and protonation constants were corrected for ionic strength by following the procedure of ref. 12. An analogous procedure was adopted for correcting solubility products. Amongst the investigations undertaken with the model was to consider the effect of adding uric acid to the Burns–Finlayson composition. Thus the protonation constant and the solubility product for uric acid had to be included in our database.

The human body temperature, 37 °C, was chosen as the model temperature. In regard to the choice of ionic strength, we were guided by Isaacson [13] who reports having determined an ionic strength of 0.263 ± 0.109 in the urine of 48 normal subjects and of 0.199 ± 0.053 for a group of 15 stone-formers. Noting in addition that the major urinary compo-

nents, sodium and chloride ions, of the Burns–Finlayson composition yield an ionic strength of about 0.195, we settled on a choice of 0.200 as being a representative and convenient value to take for our model.

The complete set of components, together with their respective concentrations, used for our model is listed in Table I. The corrected formation and protonation constants are given in Table II and the corrected solubility products in Table III.

Computational Method

Amongst the appropriate computer programs available [15, 48–53], MINEQL [53] was chosen as the most suitable for the present project owing to its compactness and its ability to handle a large number of solids. Although MINEQL has a built-in database

TABLE I. Total Concentrations of the Components in the Burns–Finlayson Standard Reference Artificial Urine [11] and of Uric Acid in Normal Urine

Component	Concentration × 10^3 (mol dm^{-3})
Na^+	182
K^+	63.7
Ca^{2+}	5.75
Mg^{2+}	3.85
Cl^-	208
PO_4^{3-}	32.3
SO_4^{2-}	20.8
NH_3	45.5
Citrate	3.21
Oxalate	0.318
Uric acid[a]	2.8

[a]Not a component of the Burns–Finlayson composition; concentration value taken from ref. 14.

TABLE II. Stepwise Formation Constants[a] Used in the Computer Simulations Together with Reaction Enthalpies (standard, kJ mol^{-1}), $\Delta H_R^{\ominus}$ and c[b] Values Used to Correct the Formation Constants, where Necessary, to a Temperature of 37 °C and an Ionic Strength of 0.2 mol dm^{-3}

Complex	$\Delta H_R^{\ominus}$	L/E[c]	Reference	c	L/E[c]	Reference	log K[a]	Reference
$H(PO_4)$	−14.64	L	14				11.08	8
$H(HPO_4)$	−4.14	L	14				6.37	8
$H(H_2PO_4)$	7.95	L	15				1.74	8
$Ca(PO_4)$	12.97	L	16	0.165	E	13	4.93	16
$Ca(HPO_4)$	13.81	L	16	0.165	E	13	1.21	17
$Ca(H_2PO_4)$	14.23	L	16	0.165	E	13	0.50	17
$Mg(PO_4)$	12.97	E	16				3.22	8
$Mg(HPO_4)$	13.81	E	16				2.03	8
$Mg(H_2PO_4)$	14.23	E	16				1.61	8
$H(SO_4)$	22.59	L	15	0.051	L	15	1.46	15
$Ca(SO_4)$	−6.90	L	18	−2.731	L	19	2.26	19
$Mg(SO_4)$	20.25	L	20	0.876	L	15	1.92	20
$H(NH_3)$	−52.01	L	21				8.71	8
H(OH)	−56.69	L	15				13.07	8
Ca(OH)	−4.98	L	18	0.165	E	14	−11.32	17
Mg(OH)	8.95	L	22				−9.94	8
H(Cit)[d]	3.35	L	15	0.041	L	23	5.49	24
H(HCit)	−2.43	L	15	1.704	L	23	4.09	24
$H(H_2Cit)$	−4.18	L	15	−1.666	L	23	2.82	24
Ca(Cit)	13.26	L	15	0.165	E	14	3.16	24
Ca(HCit)	13.26	E	15	0.165	E	14	1.74	24
Mg(Cit)	13.35	L	15	−0.190	L	23	3.25	24
Mg(HCit)	13.35	E	15	0.200	E	14	1.54	24
H(Ox)[e]	6.69	L	15	0.206	L	15	3.76	25
H(HOx)	3.77	L	15	0.640	L	15	1.30	25
Ca(Ox)				−1.487	L	26	3.40	27
Ca(CaOx)				−1.487	E	26	1.98	27
Mg(Ox)				−0.286	L	28	3.12	28
K(Ox)				−0.760	L	29	1.00	29
H(UH)[f]				−0.100	E	11	5.21	30

[a]In this table the stepwise formation constant, K, for the general complex, C(L), is defined as the concentration quotient, [C(L)]/[C][L], where C = cation and L = anionic or neutral ligand. [b]The significance of the parameter, c, is discussed in ref. 12. [c]L: literature, E: estimated. [d]Cit = triply charged citrate anion. [e]Ox = doubly charged oxalate anion. [f]UH = singly charged urate anion.

TABLE III. Solubility Products Used in the Computer Simulations Together with Enthalpies of Solution (standard, kJ mol^{-1}), $\Delta H_S^{\ominus}$ and c Values Used to Correct these Constants, where Necessary, to a Temperature of 37 °C and an Ionic Strength of 0.2 mol dm^{-3}

Solid	$\Delta H_S^{\ominus}$	L/E[a]	Reference	c	L/E[a]	Reference	log K	Reference
$Ca(HPO_4)\cdot 2H_2O$ (DCPD)	2.64	L	31	−0.257	L	34	−6.60	32
$Ca_3(PO_4)_2$ (TCP)	42.68	E	33	−0.257	E	34	−24.97	35
$Ca_4H(PO_4)_3\cdot 2.5H_2O$ (OCP)	72.09	E	14	−0.257	E	34	−41.08	36
$Ca_5OH(PO_4)_3$ (HAP)	92.09	L	14	−0.257	E	34	−52.77	37
$Mg(HPO_4)\cdot 3H_2O$	2.64	E	31	−0.257	E	34	−5.56	38
$Mg_3(PO_4)_2\cdot 8H_2O$	42.68	L	33	−0.257	E	34	−21.58	38
$MgNH_4PO_4\cdot 6H_2O$ (Struvite)				−1.257	L	39	−12.42	39
$Ca(SO_4)\cdot 2H_2O$	1.09	L	14	−0.132	L	40	−3.52	41
$Ca(OH)_2$	−17.99	L	15	0.165	E	14	−4.38	15
$Mg(OH)_2$	3.56	L	14	0.200	E	14	−10.21	15
$Ca(Ox)\cdot H_2O$ (COM)	22.30	L	42	−0.748	E	43	−8.65	44
$Ca(Ox)\cdot 2H_2O$ (COD)	22.30	E	42	−0.748	L	43	−8.30	43
$Ca(Ox)\cdot 3H_2O$ (COT)	22.30	E	42	−0.748	E	43	−8.13	44
Mg(Ox)	22.30	E	42	−0.748	E	43	−5.97	45
H(UH)				−0.100	E	11	−8.52	46

[a]L: literature, E: estimated.

of formation constants and solubility products, we preferred to override this in favour of the constants in Tables I and III.

Results and Discussion

Validation of the Urine Models

Investigations aimed at testing the model encompassed by Tables I, II and III were made by comparing predicted results with corresponding experimental observations reported by Rodgers and Wandt [54] on artificial urine solutions. First, Table IV shows our predicted hydrogen ion activity in comparison with the value observed by Rodgers and Wandt on a solution made up according to the Burns–Finlayson composition (refer to Table I; uric acid excluded). Kielland's tables of activity coefficients [55] were used to calculate the predicted hydrogen ion activity from the hydrogen ion concentration computed by MINEQL. The agreement within an order of magnitude between the predicted and observed hydrogen ion activity indicates an acceptable level of validity of the model. Second, Rodgers and Wandt [54] prepared a series of solutions with the Burns–Finlayson composition but with the pH adjusted to various values in the range 3 to 9. After evaporating each solution to half of its original volume, these authors identified the constituents of the individual precipitates that formed. To model the latter series of systems, we doubled the concentrations listed in Table I (excluding uric acid) and used MINEQL to predict which of the solids of Table III would precipitate. The experimental and predicted results are presented in columns 1 to 9 of Table V. It is

TABLE IV. Predicted and Observed [54] Activities of Hydrogen Ions in the Burns–Finlayson Artificial Urine [11]

Quantity	Predicted value	Observed value
H^+ concentration (mol dm^{-3})	1.26×10^{-6}	
H^+ activity	1.04×10^{-6}	0.32×10^{-6} [b]
pH	6.0[a]	6.5

[a]Calculated from $pH = -\log (H^+ \text{ activity})_{calc}$. [b]Calculated from $(H^+ \text{ activity}) = 10^{-(\text{measured pH})}$.

noteworthy that out of the 14 potential solids, our modelling procedure predicts the precipitation of four, in accord with Rodgers and Wandt's observations. Indeed, the predicted and observed patterns of precipitation of calcium oxalate and hydroxypatite (HAP) are in remarkably good agreement. Less satisfactory is the matching of the predicted and observed ranges of precipitation, with respect to pH, of dicalcium phosphate dihydrate (DCPD) and struvite, although the respective trends are similar in the predicted and observed cases. In regard to struvite, the theoretical result implies that precipitation over the pH range 5.5 to 7.0 may be thermodynamically favourable, whereas this is not actually realized amongst the experimental observations. Perhaps factors, such as kinetic ones, which are not understood or included in the model, inhibit the solid phase from forming in the pH range concerned. The discrepancy between the predicted and observed behaviour of DCPD follows an opposite trend, however, and is therefore likely to be of a

TABLE V. Observed *vs.* Predicted Precipitates at Varying pH and the Effect of Removing HAP from the Model. Components as in Table I with omission of uric acid; concentrations are each twice those listed in Table I. Precipitate 1: COM; Precipitate 2: DCPD; Precipitate 3: HAP; Precipitate 4: Struvite

pH	Experimental observations [54]				Long term model (all $Ca-PO_4$ solids)				Short term model (HAP, OCP and TCP omitted)				Intermediate model			
1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
3	1				1				1				1			
4	1				1	2			1	2			1	2		
5	1	2			1	2			1	2			1	2		
5.5	1	2			1	2		4	1	2		4	1	2		4
6	1	2	3		1		3	4	1	2		4	1	2	3	4
6.5	1	2	3				3	4	1	2		4	1	2	3	4
7		2	3				3	4		2		4		2	3	4
8		2	3	4			3	4		2		4		2	3	4

[a]Column number.

different nature. To explain this, we invoke the fact [56, 57] that whereas the thermodynamically most stable calcium phosphate phase precipitating from aqueous solution is HAP, the latter forms slowly and through transformation from more readily precipitated precursors. DCPD and octacalcium phosphate (OCP) are believed to be the most important precursors, particularly at ambient temperatures [58]. Our model predicts precipitation of DCPD at pH values below 6 and of HAP from pH 6 upwards, whereas Rodgers and Wandt observed the precipitation of both DCPD and HAP in the pH range above 6. These results suggest that under the conditions of the present study, DCPD may act as a precursor phase to the kinetically inhibited HAP and that the conversion had not reached completion (equilibrium) at the times that Rodgers and Wandt made their measurements. It is noteworthy that our model predicts no precipitation of OCP, in conformity with Rodgers and Wandt's observations. The rate of conversion of OCP to HAP is known to increase with increasing pH and temperature [59] and this may lend explanation to Rodgers and Wandt's failure to detect OCP.

In order to examine further the postulated role of DCPD as a precursor to HAP precipitation, the computations of columns 1 to 9 of Table V were repeated but with HAP, OCP and tricalcium phosphate (TCP) removed from the model as potential solids. This left DCPD as the only solid calcium phosphate phase. The results, shown in columns 10 to 13 of Table V, show a greatly improved correspondence between the predicted and observed precipitation patterns of DCPD. It is convenient to refer to the first model, which includes HAP, as the 'long term' model and the second, which omits HAP, as the 'short term' model. The 'long term' model may be taken as applying to an equilibrium state of the system, whereas in the 'short term' model we attempt to described a quasi-equilibrium state which takes some account of the kinetic factors which inhibit the conversion of DCPD to HAP. The best fit to the experimental results of Rodgers and Wandt can be obtained by combining the 'long' and 'short term' models to give an 'intermediate' model with the precipitation characteristics represented by columns 14 to 17 of Table V. The matching between observed precipitation and that predicted by the intermediate model is perfect for calcium oxalate monohydrate and HAP, very good for DCPD, but leaves much to be desired in regard to struvite. As pointed out earlier, the factors bringing about supersaturation of the solutions with respect to struvite in the pH range 5.5 to 7.0 are not understood and hence cannot be handled adequately within our modelling procedure.

The 'short term' or 'intermediate' models may be expected to serve as superior predicting systems for DCPD precipitation by comparison with the 'long term' model because the solubility product used in the latter for the slow-forming HAP is derived from measurements made on solutions that had been allowed to equilibrate over periods of several weeks [38, 60]. In contrast, the retention time of urine in the urinary tract is typically a few hours, which is too short a period for equilibrium to be reached between HAP and its precursors.

Predictions Based on Normal Component Concentrations, with the Inclusion of Uric Acid

In order to investigate the precipitation of solids from solutions resembling real urine more closely than those of the previous sections, the concentration values of the components, as listed in Table I and including uric acid, were used as input. Results obtained by applying the 'long term' and the 'short term' models in the pH range 4.0 to 8.0 are presented in Table VI. The pattern of precipitation is essentially

TABLE VI. Predicted Precipitation from Urine-like Solutions with Normal Concentrations of the Components (Table I). Numbering of solids as in Table V, plus Precipitate 5 = Uric acid

pH	Long term model					Short term model				Intermediate model				
1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4.0	1				5	1			5	1				5
5.0	1	2			5	1	2		5	1	2			5
5.5	1		3		5	1	2		5	1	2	3		5
6.0	1		3	4	5	1	2	4	5	1	2	3	4	5
6.5			3	4		1	2	4		1	2	3	4	
7.0			3	4		1	2	4		1	2	3	4	
8.0			3	4			2	4			2	3	4	

[a]Column number.

similar to that in Table V, obtained for the Burns–Finlayson composition with doubled component concentrations, save that uric acid precipitation in the pH range 4.0 to 6.0 is also revealed. Thus our model predicts that under conditions of equilibrium or quasi-equilibrium (*i.e.*, allowing for the slowness of the conversion of DCPD to HAP) normal urine, which has a pH in the range 5.5 to 7.0, contains precipitates of calcium oxalate monohydrate, DCPD and HAP. In addition, if the pH exceeds 6.0, struvite precipitate is present, and if the pH is below 6.0, uric acid precipitate is present. Alternatively, in the event that solid-solution equilibrium is not achieved, normal urine is predicted to be supersaturated with respect to these five solids. Our model, thus, accords with Finlayson's [3] conclusion that most people pass urine that from time to time contains precipitates. More specifically, the results in Table VI corroborate the gneral trends reported by Robertson and Peacock [61] and by Finlayson [3] that particles found in human urine tend to consist of uric acid at the lower physiological pH values, calcium oxalate in the intermediate pH range, and calcium phosphate or struvite at the higher pH values. It must be noted, however, that struvite has been found *in vivo* only in infected urines, the bacteria concerned bringing about hydrolysis of urea and thereby releasing ammonia.

Precipitation of Calcium Oxalate Hydrates

Although calcium oxalate is known to precipitate in three distinct crystalline hydrates, namely the mono- (COM), the di- (COD) and the tri-hydrate (COT), only COM and COD have been identified in urines and only COM in healthy urines [3, 5]. COM is thermodynamically the most stable, followed by COD and then COT. COT has been identified as a precursor which is rapidly transformed to COM [5].

It can be seen from Table V that according to the predictions of our model and the observations of Rodgers and Wandt, COM is the only one of the three calcium oxalate hydrates to precipitate under the pertinent conditions. Thus, to investigate the interrelationship between the three hydrates, we have carried out a series of computations in an analogous manner to our investigation of HAP precipitation with DCPD as a possible precursor ('long' *vs.* 'short' term models).

The series of computations were made on the 'short term' model; in one step COM was removed, and in the subsequent step both COM and COD were removed. The output revealed the ranges of precipitation of the two more soluble calcium oxalate hydrates, namely COD and COT; the relevant results are presented in Table VII. This table indicates that in the absence of COM, COD would precipitate below pH 6.0, and in the absence of both COM and COD, COT would precipitate below pH 5.5. Thus Table VII suggests the plausibility of both COD and COT acting as precursors to the crystallization of COM, although it must be stressed that of the two, only COT has been firmly identified in this role (*vide supra*). Our predicted precipitation of COT is consistent with the successful attempt of Sheehan and Nancollas [5] to crystallize COT under carefully controlled conditions. The likely reason that Rodgers

TABLE VII. Predicted Precipitation of the Calcium Oxalate Hydrates Using the 'Short Term' Model

pH	Calcium oxalate precipitate predicted		
	Step 1[a]	Step 2[b]	Step 3[c]
4.0	COM	COD	COT
5.0	COM	COD	COT
5.5	COM	COD	COT
6.0	COM	COD	
6.5	COM		
7.0	COM		
8.0			

[a]Step 1: as in Table VI. [b]Step 2: COM removed from model. [c]Step 3: COM and COT removed from model.

and Wandt [54] failed to identify COT as a phase in their precipitates lies in the fact that the COT-to-COM transformation is rapid compared with the DCPD-to-HAP conversion.

Effects of the Concentrations of the Major Urinary Components on COM Supersaturation

In computing chemical speciation in a given model solution, the program, MINEQL, performs a sequence of iterations ending when solution–solid equilibrium is reached. At this stage, the amount of each solid phase precipitated from a given volume of the solution is calculated. The values obtained represent the 'concentration' of each solid in equilibrium with the solution and provide a convenient measure of the degree of supersaturation that the original solution would have with respect to each solid, were the system to remain in a metastable single phase state consisting of the solution only. We have made use of this facility in MINEQL to predict the relative degree of supersaturation of the 'long term' model with respect to COM under conditions in which the concentrations of the components, oxalate, calcium ions, magnesium ions, citrate and phosphate, have been adjusted to a variety of values. The first four have been increased in successive steps up to six times their original concentrations. Phosphate has been increased in a single step to twice its original concentration. The results, exhibited in Fig. 1, show a dramatic effect of oxalate in comparison with the other components. Oxalate appears to be about 16 times more effective in increasing the COM supersaturation than calcium or magnesium ions. In contrast with oxalate, calcium and magnesium ions, phosphate and citrate appear to decrease the degree of supersaturation of COM. In this regard, phosphate evidently has a marked effect whereas that of citrate is marginal. These trends corroborate the results of earlier modelling studies using somewhat different databases and different programs [1, 62]. Furthermore, the predictions are consistent with the following clinical and experimental observations. Robertson, Peacock and Nording [63] report that the incidence of calcium oxalate crystalluria is markedly augmented by dietary oxalate but only moderately so by dietary calcium. Brigman and Finlayson [64] found orthophosphate to bring about a substantial reduction in calcium oxalate precipitation by comparison with observations on control animals.

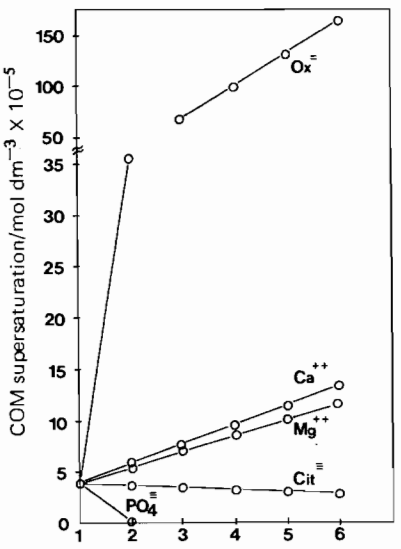

Fig. 1. Effect of increasing component concentrations on the degree of supersaturation of COM.

Our results must also be compared and contrasted with the work of Elliott and Eusebio [65] who report that both citrate and magnesium ions increase calcium oxalate solubility and that the effect of citrate is much greater at pH 7 than at pH 5. With regard to the effect of citrate, it may be noted that our Tables VI and VII indicate the cessation of calcium oxalate precipitation above pH 7, which leads us to suggest that Elliott and Eusebio's observation with respect to citrate may have had superimposed on it the influence of pH on calcium oxalate solubility. Elliott and Eusebio's observation of the effect of magnesium ions contradicts our prediction. It may be possible to seek an explanation in terms of kinetic interference of magnesium with calcium oxalate crystallization, although this suggestion is speculative in that we are not aware of any evidence to support this idea.

Comparison with other Equilibrium Models

In applying computer simulation as a diagnostic aid, other authors [3, 6, 7] have determined the degree of supersaturation with respect to a given stone-forming salt through calculating activity product values of the latter. In contrast, we suggest obtaining a measure of supersaturation through use of the extent of precipitation as computed by MINEQL. It seems that our approach has a small advantage in that it depends to a lesser extent on calculated activity coefficients. Indeed our approach makes use of activity coefficients only for the correction of equilibrium constants which happen not to have been determined at the appropriate ionic strength. Indeed, an ideal database would consist of equilibrium constants all of which have been experimentally determined at the appropriate ionic strength, thereby making the entire computation independent of activity coefficients. One irksome obstacle to this, however, arises from the fact that human urine samples cover a significant range of ionic strengths. Thus the equilibrium constants in the database would need to be determined at several ionic strength values within this range.

Future Development

In spite of the established efficacy of the degree of supersaturation as an index of stone-forming propensity, the diagnostic usefulness of computer simulation could be greatly enhanced by incorporating into the model various additional factors, such as parameters representing the kinetics of nucleation, crystal growth and aggregation, interfacial properties and the role of precursors to the growth of certain crystals. Indeed, Finlayson [66] appears to be developing a simulation program along these lines. In the meantime, our approach represents a step in the desired direction, even if only crudely so, through our attempts to allow for the action of DCPD, COT and COD as precursors to the crystallization of HAP and COM, respectively. An advantage of our approach is that it utilizes a compact program that is easy to use with a database that can be readily updated as more reliable equilibrium constants applicable to the pertinent ionic strength and temperature become available. Moreover, our results, presented above, demonstrate how easily the approach can be used to investigate the effects of various factors, e.g. changing concentrations of components, addition of therapeuticals, etc. Such investigations, of course, cannot realistically be expected to provide definitive solutions to the problem of urolithiasis, but they ought to serve a useful function by indicating directions which are likely to be fruitful in future experimental, physiological and clinical research.

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