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Effect of some organic substances on kinetics of crystallization of calcium oxalate monohydrate and on some bacteria in urine

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Abstract

Effect of some amino phosphonates, in simulated conditions on crystallization rates of calcium oxalate monohydrate crystals (COM) was studied .In the absence of additives , it was found that, the rates of crystallization of prepared COM crystals, were directly proportional to the pH values of medium and inversely proportional to ionic strength of medium. The order of reaction was equal nearly to two and activation energy was 0.144 KJ/mol. In the presence of additives A_1,A_2,A_3,A_4 and A_5, it was found they were inhibited the rates of crystallization of COM seed crystals through adsorption on the surface of the crystals. Langmuir isotherm can be applied and the calculated K_L values in the presence of (A_1,A_2,A_3,A_4 and A_5) were (12.5×10^5 , 11×10^5 , 7×10^5 , 4.167×10^5 , 1.714×10^5) J/mol respectively indicating strong inhibitory effects of these additives. The values of ΔG in the presence of these additives were `(-40.4, -40.0, -39.0,-38.5,-38.2) respectively. Crystallization of prepared COM crystals in presence of 10^{-7} mol dm^{-3} of A_1 ,indicated the adsorption of molecules of A_1 on both kink and terrace sites , but favored kink sites. The percentage of total surface covered by molecules of A_1 additive was 25.6 % which supported the surface-controlled mechanism. These synthesized compounds A_1,A_2,A_3,A_4 and A_5, were screened for their in vitro antibacterial activity against both Gram positive and Gram negative bacteria. A_1 compound showed moderate sensitivity on staph.aureus with slightly activity on klebsiella pneumon.

Keyword: amino phosphonates, Calcium oxalate, Urine, adsorption, crystallization, additives, antibacterial activity.

1. Introduction

Hydrated calcium oxalate ($CaC_2O_4.xH_2O$) commonly occurs as whewellite (monohydrate, COM) and weddellite (dihydrate, COD), rarely also in the trihydrate form – caoxite, COT.[1–3] Industrial usage of oxalate hydrates includes e.g. thermochemical energy storage[4] (the reversible chemical reaction anhydride CaOx ↔ COM is utilized), synthesis of superconducting multicomponent oxides,[5,6] preparation of high purity titanates, stannates, ferrites and zirconates [7–9] or separation of rare earth elements from raw ores by co-precipitation [10] . However, major importance of these minerals lies in the fact that they are the main crystalline components of human urinary stones [11–13].

Urolithiasis or kidney-urinary tract stone disease has emerged as a severe health concern throughout the World [14] With a high recurrence rate in both, males and females as well as affecting around 12% of the population globally, kidney stones or urolithiasis (nephrolithiasis) is marked by the formation of urinary calculi in the urinary tract [15] Urolithiasis is an example of pathogenic mineral formation in the human body. Various exogenous and endogenous factors are considered among the reasons for the development of urolithiasis [16,17] .The more factors act simultaneously, the more difficult the pathogenesis of urolithiasis and the worse its prognosis, which is due to frequent recurrence of the disease and the rapid growth of stones.

Currently, there are many theories explaining the causes and mechanisms of pathogenic stone formation in the human urinary system [18–25] . All theories are based on the complex interaction of biogenic and abiogenic substances, but none of them are exhaustive. The least studied is the bacterial theory [19]

It is well known that the presence of a variety of bacteria in the urine is very likely and bacterial inflammation often accompanies stone formation [26] . Assumptions about the significant effect of microorganisms on the processes of urollithiasis in the human urinary system have been made in a number of works [17–28]. The crystallization system (urine) contains about a dozen bacteria species. Microbiological examination of removed urinary stones'

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microflora shows that more than half of urinary stones are infected, in most cases by several types of bacteria [17,29] The effect of the additives under study (A_1,A_2,A_3,A_4 and A_5) on bacteria present in urine will study.

2. Experimental

2.1. Materials

Calcium chloride, sodium oxalate was prepared from analyzed analytical grade reagents (EL. Nasr pharmaceutical chemicals company, fisher scientific company and Baker chemical company). Ethylene diamine tetra- acetic acid (EDTA) was standardized using magnesium sulphate of suitable concentration using EBT as indicator. Calcium Chloride stock solution was standardized using the standardized EDTA. Concentration of Sodium Oxalate stock solution was determined by titration against standardized potassium permanganate solution .

2.2. Techniques

Energy-dispersive X-ray spectroscopy (EDX) and transmission electron microscope (TEM) measurements were obtained using JEOL-SEM and JEOL TEM-1230 with an acceleration voltage of 80 kV. FTIR spectra for the prepared samples were recorded using Perkin Elmer Fourier transform infrared spectroscopy. X-ray diffraction patterns of the produced solids were determined using a Bruker diffractometer (Bruker D 8 advance target). CuKα radiation source with secondly monochromator (λ= 1.5405˚A) at 40 kV and 40 mA was used. The scanning rate (0.2 min−1) was adjusted for phase identification and line broadening profile analysis. The textural properties of the samples were determined by physical adsorbing nitrogen (N_2) at 77K using using a Quantochrome Nova-Touch 4LX automated gas-sorption apparatus (USA). Before each N2- sorption measurement, samples were degassed at 200 ºC for 2 h. The N_2-adsorption on the samples was used to calculate the specific surface area by means of the Brunauer–Emmett–Teller (BET) equation . The pore size distribution was calculated from desorption branch of the isotherm by the Barrett, Joyner and Halenda (BJH) method. pH measurements were made with a combined pH glass electrode (model 9100 Metrohm AG company). emf measurements were made by calcium ion selective electrode (CH-9101Herisau), in conjugation with a calomel reference electrode (model 90.02 orion Research Incorporated Laboratory products Group). The electrodes were checked before and after each dissolution experiment using the buffer solutions recommended by Bates [30] , pH glass electrode and using calcium chloride solutions with definite concentration in case of selective electrode. In crystallization experiments-using potentiostate, the studies were made at constant emf. Metrohm combi- titrator (model 718 STAT Titrino connected with printer model EPSON LX 300T and stirrer model E649) was used to control the addition of titrant solution consisting of 0.3M sodium chloride solution into the reaction cell .

2.3. -Synthesis of calcium oxalate monohydrate seeds :

One liter of 0.1M calcium chloride solution was added to one liter of 0.1M sodium oxalate solution at 298K at a rate of 500 ml/ per half an hour. The mixture was constantly stirred for one week and then the seed crystals were aged for one month, then, filtered and washed further with deionized distilled water to remove surface contamination due to chloride and oxalate ions and this process was repeated several times. The prepared seed was dried at 40 °C .

2.4. Synthesis of inhibitors

Solutions of (A_1,A_2,A_3,A_4, and A_5) were prepared by taking suitable weights of reagents, dissolved in dimethylsulfoxide(DMSO) (Fluka AG,chem..Fabrik CH-9470 Buchs), and completed with deionized distilled water. The desired concentrations were prepared by diluting the solution.

3. Results and Discussion

3.1. Fourier Transform Infrared (FTIR)

FTIR spectrum of calcium oxalate monohydrate. The spectrum of a pure calcium oxalate monohydrate showed a high absorbance at 1616 -1600 cm-1 and 1314 -1302 cm-1 belonged to C=O and C-O stretching vibration, respectively. The frequency region was 779 -775 cm-1 corresponding to C-H bending. The absorption band observed at 3446 - 3021 cm-1 which happened due to symmetric and asymmetric O-H bending. The absorption band at 1387– 1364 cm-1 was happened due to C-C dan C-O stretching, 891 -874 cm-1 was due to C-C stretching, and 693 -687 cm-1 was due to O-H bending (Fig. 1).

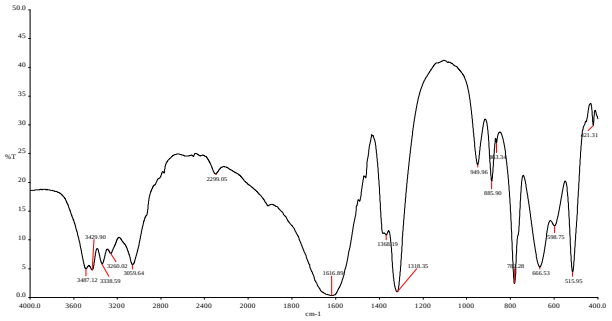


Fig. 1: IR spectrum of prepared crystals

3.2. X-ray Diffraction (XRD) and surface characteristics

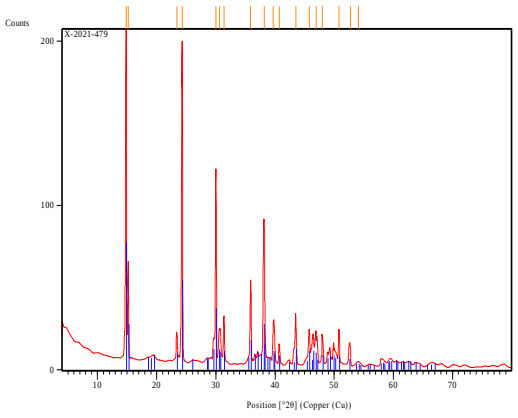


Fig.2: X-ray pattern of the prepared crystals

Fig. 2 reveals that the prepared solid is calcium oxalate monohydrate (JCPDS, 13-0379) with good degree of crystallinity.

3.3. Scanning Electron Microscope (SEM)

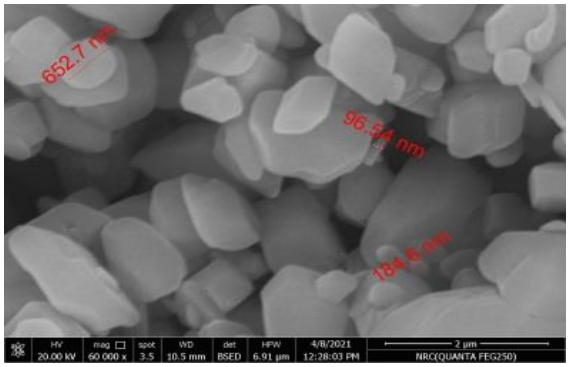


Fig. 3. SEM of the prepared solid

Scanning electron micrographs were taken for the prepared solid (Fig.3) at low magnification. Fig. 3 exhibits the spherical structure of regular shape. No doubt, these results are totally harmonious with the XRD measurements.

3.4. Studying the mechanism of crystallization of COM crystals in absence of additives

3. Various crystal growth systems have been subject to investigation the effects of growth conditions on mineral formation. Growth from solution is profoundly affected by numerous factor – supersaturation (SS), ionic ratios, temperature and pH will all affect nucleation and growth [31]

In the present study , the rate of crystallization of COM crystals at 37 ºC , ionic strength (I) = 0.3 mol dm-3 , pH =5.5 (natural crystal – forming medium) and using 0.01 g of prepared seed crystals were studied .The rates of crystallization were studied at values of degree of supersaturation (ɣ) ranged from 0.3 – 0.8 (Table 1 **)**

Table (1) : Crystallization of calcium oxalate crystals T_{Ca+2} : T_{Ox}-2 = 1:1 at t = 37ºC, I = 0.3 mol dm-3, pH = 5.5 and 0.01g of seed crystals.

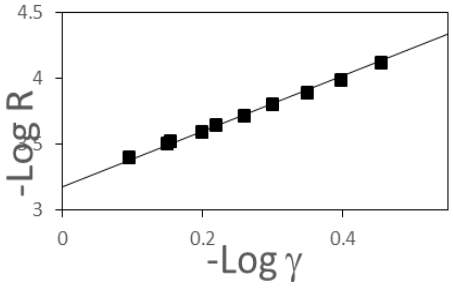
$T_{Ca}^{+2} \times 10^{-4}$ mol dm^{-3}	ɣ x 10^{-2}	-Log ɣ	Rate x 10^{-6} mol $min^{-1}m^{-2}$	-Log R	Wt. of seed Mg
2.592	30	0.56	0.3800	4.42	10
2.692	35	0.456	0.7580	4.12	10
2.791	40	0.398	1.0230	3.99	10
2.891	45	0.35	1.2880	3.89	10
2.993	51	0.30	1.5850	3.80	10
3.090	55	0.26	1.9490	3.71	10
3.190	60	0.22	2.2910	3.64	10
3.249	63	0.20	2.5700	3.59	10
3.389	70	0.155	3.0190	3.52	10
3.409	71	0.15	3.1620	3.50	10
3.589	80	0.096	3.9810	3.40	10
2.791	40a	0.398	1.0230	3.99	10
2.791	40b	0.398	1.0236	3.99	10

a , b : at stirring rates of 300 and 500 rpm

3.4.1. Effect of degree of supersaturation (ɣ) on the rates of crystallization of COM crystals

The order of reaction can be determined by plotting (-log R) against (-log ɣ) (Fig. 4), where R, is the rate of crystallization of COM crystals at certain degree of supersaturation (ɣ). The effective order of reaction at the experimental conditions of t = 37 ºC, pH = 5.5, I = 0.3 mol dm^{-3} and using 0.01 g of prepared seed crystals was ≈ 2 (Fig.4), which suggest surface-controlled mechanism. The assumption of surface-controlled mechanism over a relative supersaturation (ɣ) under study was supported by the observation of the independence of the rates of crystallization of COM crystals on changing the rates of stirring (fluid dynamics). However, this evidence may be inconclusive for such small particles for which changes in the stirring rates may have little influence on the fluid shear forces at crystal surfaces (a and b in Table 1). The particles will tend to move with the fluid flow. The rates of crystallization of COM crystals were also found to be affected by the weight of inoculating seed used to initiate the crystallization process, which may confirm the surface-controlled mechanism.

For surface-controlled crystallization, the rate will be independent on the size of the crystals. Moreover the concentration of electrolyte near the crystal surface will be the same as that in the bulk solution [32] .



4 2: Effect of the values of pH on rates of crystallization of COM crystals:

Urine pH value has been thought to be an important factor that can modulate kidney stone formation. The normal urine is slightly acidic with pH of approximately 6.0 although it can range from 4.5- 8.0. The urine pH has been observed to associated with many diseases: eurothetical carcinoma, metabolic disorders and kidney stone disease.

4. The crystallization rates of COM crystals were studied at 37ºC, I = 0.3 mol dm^{-3}, ɣ = 0.4 and 0.01 g of prepared seed crystals at pH values range of 3-12 as shown in Fig. (5).

5. Inspection of Fig. (5) revealed that the rates of crystallization of COM crystals increase by increasing the value of pH till pH = 7 and began to decrease from pH = 8. Previous studies proved that COM (pathogenic form) was crystallized with greatest size, number and total mass of pH = 4 and least crystallized at pH = 8, whereas COD was crystallized with the vice versa order. Crystal cell-adhesion assay showed the greatest degree of crystal-cell adhesion at the most acidic pH and least at the most basic pH. The crystal internalization into renal tubular cells was maximal at neutral pH = 7. The acidic urine pH may promote C_aO_x kidney stone formation whereas; the basic urine pH (i.e by alkalization) may help to prevent C_aO_x kidney stone diseases .[33]

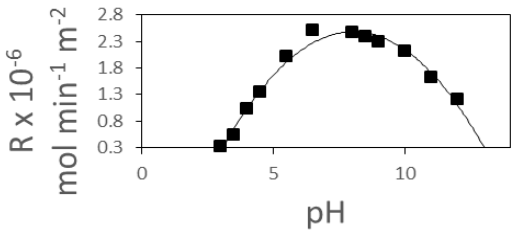


Fig (5): Effect of change of pH on the rates of crystallization of COM crystals at I = 0.3 mol dm^{-3}, ɣ = 0.4, t = 37ºC and 0.01g seed crystals.

3.4.3: Effect of change of ionic strength (I) of the medium on crystallization of COM crystals:

The rates of crystallization of COM crystals at 37ºC, pH=5.5, ɣ = 0.4, weight of seed of 0.01 g and at range of ionic strength from 0.05 – 0.5 mol dm^{-3} corresponding to human urine (using NaCl solution) were studied. It was found that the rates of crystallization of COM crystals were decreased by increasing the ionic strength of the medium, Fig (6). Previous study showed that the rates of crystallization of COM crystals were decreased by increasing the ionic strength of the medium. .

Decreasing of rates of crystallization of COM crystals with increasing the ionic strength of the medium can be attributed to a strong effect of repulsive electrostatic forces between similar ions in high ionic strength medium which inhibit chemical interaction between Ca^{2+} and Ox^{2-} ions [34].

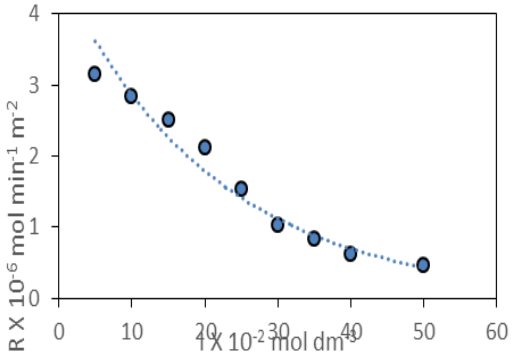


Fig (6). crystallization of COM crystals at t = 37ºC, pH = 5.5, ɣ = 0.4 and 0.01g seed crystals.

3.4.4. Effect of temperature on crystallization rates of COM crystals:

The effect of change of the value of temperature on the rates of crystallization of COM crystals at pH = 5.5, ɣ = 0.4, I = 0.3 mol.dm^{-3}, weight of seed crystal = 0.01 g and at temperature range from 283- 310 K was studied (Fig. 7). Plotting – log R against 1/T, straight line was obtained and the activation energy, Ea., was determined (0.1445 kJ/mol). The order of two, the independence of the rates of crystallization of COM crystals on the fluid dynamics and the low value of Ea. ruled out and confirmed the surface-controlled mechanism of crystallization of COM crystals at the conditions of the present study.

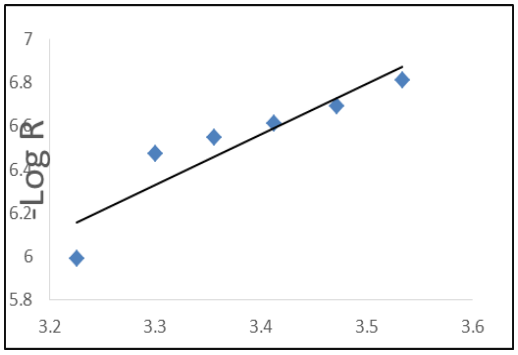
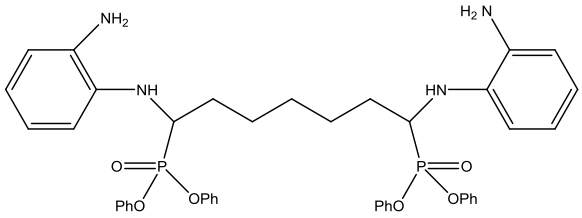
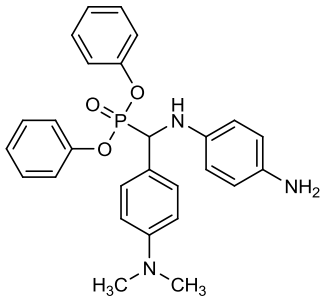


Fig (7): Plot of - log R against 1 / T x 10-3 K-1 at I = 0.3 mol.dm-3, pH = 5.5, ɣ = 0.4 and 0.01 g of seed crystals.

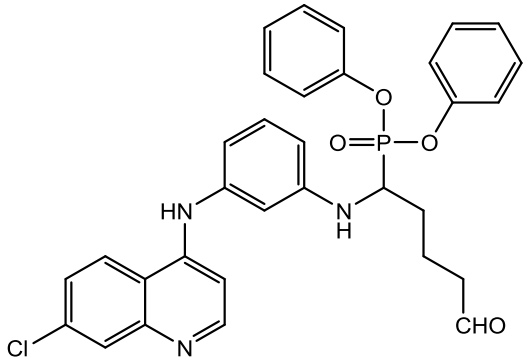
3.5. Studying the mechanism of crystallization of COM crystals in the presence of additives.:



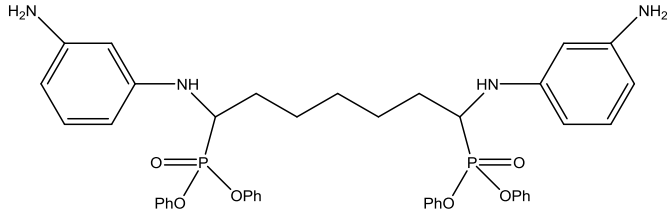
Tetraphenyl(1,5-bis((2-aminophenyl) amino) pentane-1 ,5-diyl)bis(phosphonate (A_1)



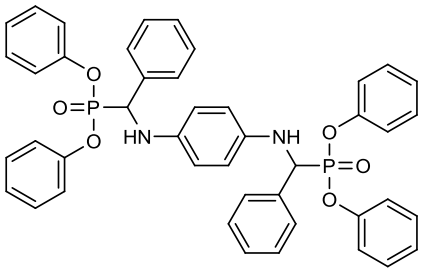
Diphenyl (4-aminophenylamino) (4-(dimethylamino) phenyl)methylphosphonate (A_2)



Diphenyl(1-((3-((7-chloroquinolin-4-yl) amino) phenyl)amino)-5-oxopentyl)phosphonate (A_3)



Tetraphenyl (1 ,5-bis((3-aminophenyl) amino)pentane-1,5-diyl) bis(phosphonate) (A_4)



Tetraphenyl(1,4phenylenebis(azanediyl)) bis(phenylmethylene) diphosphonate (A_5)

3.5.1 The effect of change of concentration of (A_1,A_2,A_3,A_4 and A_5) on the rates of crystallization crystals:

Effect of (A_1,A_2,A_3,A_4 and A_5) on the rates of crystallization crystals, T_{Ca+2} : T $_{Ox-2}$ = 1:1 at t=37oC, I = 0.3 mol dm-3 pH=5.5, ɣ=0.4 and 0.01 g of seed crystals illustrated in fig (9).

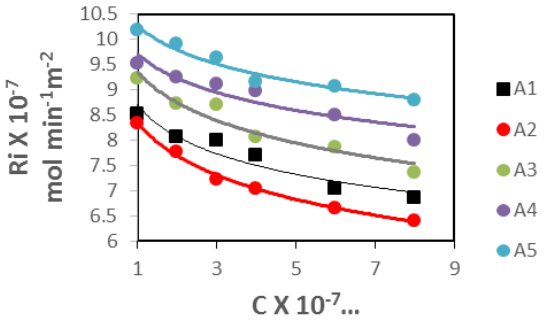


Fig (9):Plot of rates of crystallization of COM crystals against the concentration of A_1 ,A_2, A_3, A_4 ,A_5 at t = 37ºC, I = 0.3 mol dm^{-3}, pH = 5.5, ɣ = 0.4 and 0.01g seed crystals.

From the fig (9), it was found that the order of inhibition of crystallization of COM crystals .followed the order:

$A_1>A_2>A_3>A_4>A_5$

3.5.2: Validity of applying of Langmuir isotherm:

plotting of R_0 / (R_0 – R_i) against 1/C of different additives at the same experimental conditions (fig(10)) it was found that the K_L values in the presence of (A_1,A_2,A_3,A_4 and A_5) ,were (12.5 x 10^5 , 11 x 10^5, 7 x 10^5, 4.167 x 10^5 , 1.714 x 10^5) J/mol respectively. The validity of application of Langmuir – isotherm supported the surface –controlled mechanism and indicated good inhibitory effect of these additives.

The values of ΔG, K_L and K_{ads} in the presence of (A_1,A_2,A_3,A_4 and A_5) (table(3)), supported the order of inhibition of crystallization of COM crystals at the experimental conditions and supported the physical adsorption of the molecules of the additives on the surface of seed crystals and that these additives were good inhibitor.

Table (3) : illustrates the values of ΔG, K_L and K_{ads} in the presence of (A_1,A_2,A_3,A_4 and A_5) .

	A_1	A_2	A_3	A_4	A_5
ΔG	-4.04 x 10^4	-4.00 x 10^4	-3.9x 10^4	-3.85 x 10^4	-3.82x 10^4 J/mol
K_L	12.5 x 10^5	11x 10^5	7x 10^5	4.167x 10^5	1.714x 10^5 J/mol
K_{ads}	1.14 x 10^5	1 x 10^5	7.69 x 10^5	5.6 x 10^5	5 x 10^5 J/mol

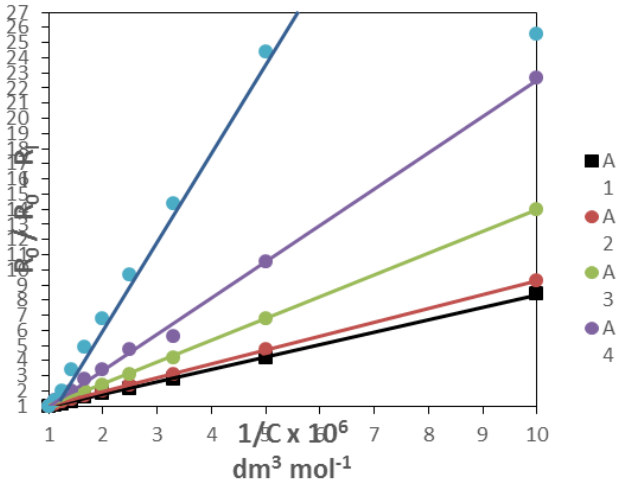


Fig (10) : Plot of R_0 / (R_0 – R_i) against 1/C of different additives .

From this table, it was found that the order of increase of inhibition of the additives on crystallization of COM , at experimental conditions was:

$A_1>A_2>A_3>A_4>A_5$

3.5.3: Effect of concentrations of (10^{-7}-10^{-6}) mol.dm^{-3} of additive A_1 on the rates of crystallization of COM crystals:

The rates of inhibition of COM seed crystals increased by increasing the concentration of A_1 additive. In the surface- controlled mechanism, the molecules of the additive adsorbed at active sites on the surface of COM crystals at slow step. The % of total area covered by A_1 on the surface of COM crystals was 25.6 % , indicating the low numbers of active sites and confirming the surface – controlled mechanism and the adsorption of

molecules of the additive on the active sites of the surface of COM crystals at the rate determining step.

From table (4), it was suggested that the molecules of A_1 were adsorbed on both kink and terrace sites on the surface of COM crystals, but favored kink sites.
Values of K_L,Q_{diff} and K_{ads} in the presence of A_1 at experimental conditions of pH=5.5, I = 0.3 mol dm^{-3}, ɣ = 0.4, t = 37ºC and wt =0.01g seed crystals.

Table (4) : Values of Q_{diff} and K_L in case of the presence of molecules of A_1 .

	Kink site	Terrace site
K_L	9.3×10^5	2.857×10^{-3}
Q_{diff}	2.46×10^{-3}	2.249×10^{-3}

Table (5) illustrated the ΔG, KL and Kads in the presence of A1 at 37oC and 25oC the low value of ΔS of 237.6 J/degree indicated the ordering of A1 molecules on the surface of COM crystals by adsorption on it and A1 is good inhibitor.
Table (5) : Values of ΔG , K_L and K_{ads} in case of the presence of molecules of A_1 at 37ºC and 25ºC .

	37 ºC	25 ºC
ΔG	-4.04×10^4	-4.2929×10^4
K_L	12.5×10^5	3.125×10^5
K_{ads}	1.14×10^5	3.0769×10^5

Antibacterial screening:
The Antibacterial activities of the synthesized compounds were tested against Escherichia Coli and Klebsiella (Gram –ve bacteria), Staphylococcus
Aureus and (Staphylococcus haemolyticus) using nutrient agar medium.
Agar Diffusion Medium:
The synthesized compounds were screened in vitro for their antimicrobial activity against, by agar diffusion method (Cruickshank).0.5ml suspension of each of the aforementioned microorganisms was added to sterile nutrient agar media at 45oC and the mixture was transferred to sterile petri dishes and allowed to solidify.
Holes of 0.9cm in diameter were made using a cork borer. Amounts of 0.05,0.1 and 0.15ml of the synthesized compounds were poured inside the holes. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. the diameters of the inhibition zone of were measured and compared with the values were tabulated. Ciprofloxacin (50 µg/mL) was used as standard for antibacterial (35-37) .The observed zone of inhibition is presented in Table (6).

Table 6: In vitro antimicrobial activity by agar diffusion method of tested Compounds.

Microorganism inhibition zone diameter (mm)				
Compds.	Gram +ve bacteria		Gram –ve bacteria	
	Staphylococcus haemolyticus	Staphylococcus aureus	Escherichia coli	Klebsiella
A1	14	15	-ve	12
A2	13	14	12	10
A3	11	13	-ve	-ve
A4	10	12	-ve	-ve
A5	11	13	-ve	-ve
Ciprofloxacin	26	28	17	14

Highly active (+++) = (inhibition zone > 20 mm)
Moderately active (++) =(inhibition zone 15 - 19 mm)
Slightly active (+) = (inhibition zone 10 - 14 mm)
Inactive (-ve) = (inhibition zone < 10 mm)
This table shows the inhibition zone of different synthetic compounds on gram positive and gram-negative bacteria.
A1 compound show moderate sensitivity on staph.aureus with slightly activity on klebsiella pneumon. While ciprofloxacin show highly sensitivity on gram negative bacteria. Compounds from A2 to A5 shows slightly activity against Gram positive and Gram negative.
Compound A1 can be used as a substitute for ciprofloxacin with minimum side effects.

4. Conclusion :

1-The rates of crystallization of COM crystals at experimental conditions of 37oC , I = 0.3 mol dm-3, pH = 5.5, ɣ = 0.4 and 0.01g seed crystals, were studied.
2-The rates of crystallization of COM crystals at experimental conditions were increased with increasing pH values of medium and decreased with increasing the ionic strength of medium.
3- The order of reaction was approximately two, which suggests surface-controlled mechanism.
4- The low value of Ea and the independence of the rates of crystallization of COM crystals on the fluid dynamics,support the surface mechanism.
5-Effect of some amino phosphonates (A1,A2,A3,A4 and A5) on mechanism of crystallization of COM crystals at experimental conditions was studied.
6-These substances inhibited the crystallization process of COM crystals and the order increase of inhibition of them were: A1>A2>A3>A4>A5
7- The rates of crystallization of COM crystals at 10-7 mol dm-3 of A1 and at experimental conditions were studied.
8-The percentage of total surface covered by A1 was 25.6% ,which supported the surface mechanism.
9-The values of Qdiff for kink and terrace in the presence of A1, indicated that the molecules of A1 adsorbed on both kink and terrace sites on the surface of COM seed crystals but nearly favorite the kink sites.

10-The low value of ΔS in the presence of A1 indicated the adsorption of molecules of A1 on the active sites of surface of COM crystals in ordered manner, and confirmed surface adsorption as rate determining step.

11- The effect of these substance (A1,A2,A3,A4and A5) on gram positive and gram negative bacteria present in urine, indicated that: A1 compound show moderate sensitivity on staph.aureus with slightly activity on klebsiella pneumon.

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