Egypt. J. Chem. **Vol. 65,** No. 10 pp. 577 - 584 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Organosilicon Surfactants as Antitumor Agents

Sahar M. Ahmed, Dina A. Ismail and Dalia E. Mohamed

Petrochemicals Department, Egyptian Petroleum Research Institute, Cairo, 11727, Egypt.

Abstract

Organosilicon surfactants draw scientific attention due to their significant biological action as they offer the real possibility to improve their pharmacological properties because of easier penetration through lipophilic barriers inside the body. Synthesis, structure and spectroscopic characterization of cobalt (II), copper (II) and zinc (II) coordination compounds with N-dodecyl-N-trimethyl silane ammonium iodide are presented in this research. N-dodecyl-N-trimethyl silane ammonium iodide and its complexes with cobalt, copper and zinc chlorides were characterized structurally using Ultraviolet-Visible and Fourier Transform Infra-red spectra. Surface parameters of the prepared surfactants were investigated including, critical micelle concentration, maximum surface excess, minimum surface area, effectiveness, and efficiency. Free energy of micellization and adsorption were also calculated. The cytotoxic activity of various metallomicelle surfactants was tested against five lines of human tumor cells [HEPG2 (liver), MCF-7 (breast), HCT-116 (colon), HEP2 (larynx), and HFB4 (normal)]. The results showed that zinc (II) and cobalt (II) complexes have substantial surface and cytotoxic activity whereas copper (II) complex showed less surface and cytotoxic activity.

Key Words

Cytotoxic Activity; Silicon Surfactant; Metallomicelles and Surface Parameters.

Introduction

Development of new antitumor candidates draws the scientific researchers' attention [1, 2]. Organometallic amphiphiles are important class of surfactants. Various chemical and physical properties of their adsorption and aggregation have been widely investigated in recent years, such as active control of surface tension, cytotoxic activity, selective binding and charge transfer. Research on transition metal complex surfactants chemistry have received a high level of attention [3-5] due to their significance in various redox processes in biological systems as promising agents for antibacterial and anticancer drugs [6], and due to their multiple applications in various fields such as medicine [7], and drug delivery [8].

Transition metal complexes have become increasingly popular as therapeutic compounds. These complexes have a wide variety of activities, including anti-inflammatory, anti-diabetic and anti-infective compounds. Many efforts are established for the development of transition metal complexes as drugs. Despite a range of drawbacks and side effects, transition metal complexes remain the most used chemotherapeutic agents and contribute significantly to medicinal therapeutics [7]. A considerably large number of metal complexes are known to possess antitumor activity [9-10].

Metal based -surfactant complexes are a special kind of surfactants, in which the coordination complex acts as a surfactant. In these surfactants, the head group is the metal complex, since it contains the core metal ion with its primary coordination sphere, while its tail is the hydrophobic chain of one or more ligands. These metallosurfactants, as other surfactants, form micelles in aqueous solution at a specific concentration called critical micelle concentration (CMC) [11].

Organosilicon quaternary salts are cationic surfactants which contain silicon in their hydrophobic tails. In general, this form of surfactant has lower surface tension and lower critical micelle concentration (CMC) than surfactants whose hydrophobic parts are totally hydrocarbon in nature. It exhibits excellent properties such as thermal stability, low-temperature flexibility, low toxicity, anti-static properties, water resistance, low surface energy and antimicrobial activity on Gram-positive and Gram-negative bacteria, yeast, fungi, and mold [12]. These characteristic properties of silicone surfactants are mainly attributed to the low cohesive energy, good

*Corresponding author e-mail: dinaabdlkader@hotmail.com.; (Dina Ismail).
Receive Date: 07 January 2022, Revise Date: 11 February 2022, Accept Date: 23 February 2022
DOI: 10.21608/EJCHEM.2022.114183.5223

flexibility and low glass transition temperature of the siloxane chain [13-14].

Most of the organic compounds which contain platinum, gold, zinc, cobalt, iron and copper are used for treatment of different diseases as cancer, herpes, HIV, diabetes and Alzheimer's disease. These compounds are known as metallodrugs or metal-containing drugs [15].

So, according to all the above-mentioned facts, we aimed in this study, to prepare N-dodecyl-N-trimethyl silane ammonium iodide, with its cobalt, copper and zinc complexes, then investigate the surface properties of their solutions and also evaluate their biological activity as potential selective anticancer prodrugs. N-dodecyl-N-trimethyl silane ammonium iodide (A) was tested in vitro against five human monolayer tumor cell lines: [HEPG2 (liver), MCF-7 (breast), HCT-116 (colon), HEP2 (larynx), and HFB4 (normal)]. In addition, cytotoxicity of the metal complexes (A-Cu, A-Co and A-Zn) was determined against colon cell line.

Materials and Methods

Materials

Dodecyl amine, Iodo trimethyl silane, Zinc chloride, Cobalt chloride and Copper chloride were purchased from Sigma Aldrich.

Preparation of N-dodecyl-N-trimethyl silane ammonium iodide (A)

The quaternary ammonium compound was prepared according to our previous study [16] by dissolving dodecyl amine (0.1mol) in benzene (200 ml) with stirring and then trimethyl iodo silane (0.1mol) was added slowly. The reaction mixture was stirred at room temperature until a white precipitate formed which was recrystallized from acetone to give the quaternary ammonium salt (A) with yield 75% (Scheme 1).

Preparation of the Cationic Metallomicelles

The Co, Cu and Zn complexes of (A) were prepared by slow wise addition of a solution containing (0.2 mol) of quaternary ammonium salt (A) in 10 ml ethanol to a solution of MCL2 (0.1 mol). The resulting precipitate was washed with ether, purified by ethanol-ethyl acetate and dried to give metallomicelles A-Co, A-Cu and A-Zn with yield percentage varies between 80-90% [17] (Scheme 1).

Surface Tension Measurements

Surface tension values of the synthesized cationic silicon-based surfactant solutions (A-Co, A-Cu and A-Zn) were obtained at 25oC using KRUSS K6 type 4851, Du-Nouy Tensiometer with a platinum ring at different concentrations of surfactant. Distilled water of 72 mN/m surface tension was used to prepare the concentrated surfactant solutions. Surface tensions were determined three times for each sample within two min interval between each reading. The obtained data were plotted against -log C, then CMC values were determined from this plot [18-19].

Cytotoxicity Assay

The MTT assay is a sensitive and quantitative method of testing. It is a colorimetric procedure for determining the viability, proliferation and activation of cells [20]. The basis of this assay depends on the capacity of the mitochondrial lactate dehydrogenase enzymes (LDH) in living cells to transform the yellow water-soluble substrate 3-(4, 5- dimethylthiazo1-2-y1)-2, 5-diphenyl tetrazolium bromide (MTT) into a dark blue formazan product that is insoluble in water [21]. The percentage of viable cells was determined from the equation:

% Viable cells (I) = Test O.D x 100 / Control O.D

where: OD is the optical density.

The IC50 is the concentration of treatment required to induce 50% inhibition of cell growth [22].

Results and Discussion

Chemical structure of the prepared surfactants

The chemical structure of N-dodecyl-N-trimethyl silane ammonium iodide (A) and its complexes with Co, Cu and Zn chlorides were confirmed by FTIR and UV-VIS spectra.

FTIR spectra of the synthesized surfactants showed: absorption bands at 2918 and 2849 cm^{-1} characteristic for the asymmetric and symmetric vibrations of the methylene group, respectively. In addition, the characteristic band of the quaternized nitrogen (N^+) appeared at 3131 and 3020 cm^{-1} for both the complexes and the parent surfactant, respectively. C–N_{st} band appeared at 1086 cm^{-1} and Si–C_{st} band appeared at 723 cm^{-1} (Figure 1).

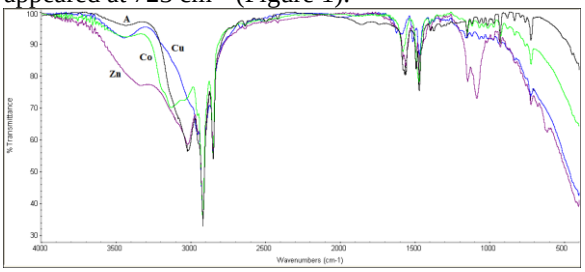


Figure (1) FTIR of cationic surfactant (A) and its complexes with Cu, Co, and Zn

Formation of metallomicelles with Co, Cu and Zn ions are confirmed via UV-VIS spectra. UV-visible absorption spectra are very sensitive to formation of

metal complexes, since metal complexes exhibit intense absorption peaks corresponding to the formation of bond between the metal ions and the ligands. Data in Figure 2 showed two characteristic bands of the parent surfactant A at 210 and 224 nm. Formation of metal complexes was detected through appearance of new absorption bands. These new absorption bands are due to the electronic transition of d-orbitals of the different transition metal ions incorporated in the metal complexes. A new band appeared at 288 nm characteristic for A-Cu. Meanwhile appearance of two bands at 242 and 666 nm which are characteristic for A-Co and those at 242 and 278nm are for A-Zn complex.

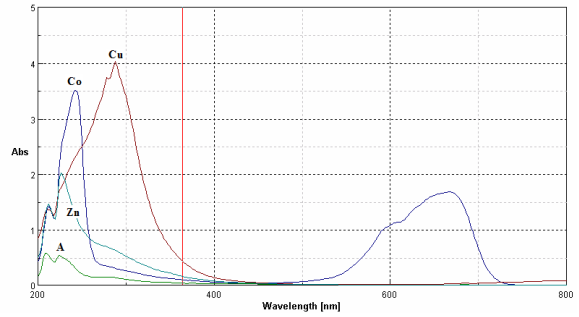
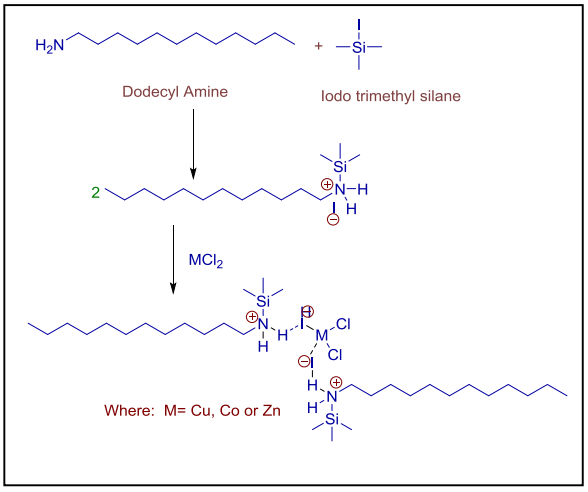


Figure (2) UV-visible spectra of cationic surfactant (A) and its complexes with Cu, Co, and Zn



Scheme 1

Surface Properties

Surface Tension

Figure 3 represents the surface tension versus - Log C relationship of the synthesized cationic parent surfactant (A) and its metal complexes (A-Co, A-Cu & A-Zn) at 25 °C. The surface tension values of the produced cationic complexes (A-Co, A-Cu and A-Zn) were found to be slightly lower than those of the parent surfactant A, possibly due to the enhanced hydrophobicity of these complexes in comparison to their parent. This hydrophobicity may be due to the existence of two ligands coordinated to the metal ion within the huge structure of the complex containing methylene groups, i.e., more non-polar chains, leading to an increase in the interaction between water and surfactant molecules, which forced them to the air water interface [23].

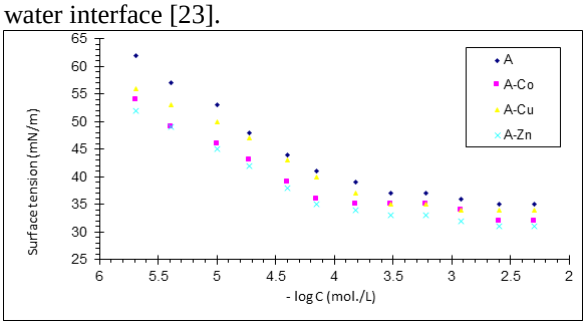


Figure (3) Surface tension vs. – log C of the synthesized surfactants (A, A-Co, A-Cu, A-Zn

Critical micelle concentration CMC

The CMC was determined from the interaction points in the γ versus log C plots. The results in Table (1) show that, there is a depression in CMC value observed due to the complexation of the cationic surfactant (A) with metal ions compared with that of the parent surfactant. Thus, it can be concluded that these metal–surfactant complexes have more tendency to form aggregates compared to the parent surfactant A, which suggests enhancement of the aggregation's ability through the introduction of the metal complex to the hydrophilic part [24]. This may be attributed to the unique property of the metal complexes in water, since the complexes retain their unity in their solutions, leading to an increase in their volume in the aqueous media and then repulsion occurs between water molecules and the hydrophobic chain. That repulsion facilitates two consecutive processes [25], adsorption of the metal complex molecules at the air/ water interface at extremely lower concentrations (below CMC) and micellization of these molecules at concentrations lower than that of their parent cationic. Therefore, we can conclude that the CMC value of A-M complexes were lower than that of the corresponding surfactant-parent due to an increase in hydrophobic character of the molecule in the coordination sphere.

Effectiveness (π_{CMC})

The effectiveness ''π_{CMC}'' can be determined from the difference between the surface tension at CMC ''γ_{CMC}'' and the surface tension of pure water at the appropriate temperature (γ^0). The most efficient surfactant is the one which gives the greatest lowering in surface tension for a critical micelle concentration (CMC). The Zn complex was found to be more efficient than the parent compound (A) and the other complexes as shown in Table (1), since it achieved the maximum reduction of the surface tension at CMC (Figure 3).

Efficiency Pc_{20}

The efficiency (Pc_{20}) was determined by the concentration (mol/l) capable of suppressing the surface tension by 20 mN/m [26]. The larger the Pc_{20} value, the more efficiently the surfactant is adsorbed at the interface and the more efficiently it reduces surface tension. The values of efficiency of adsorption of the prepared surfactants are shown in Table (1). It is clear that efficiency of the complexes under study has the following arrangement A-Zn > A-Co > A-Cu and that the three complexes are more efficient at the interface than the corresponding parent surfactant A.

Maximum surface excess Γ_{max} and Minimum area per molecule A_{min}

The values of (Γmax) have been calculated using the Gibbs adsorption equation,

$$\Gamma_{max} = - (\partial \gamma / \partial \log c)_T / 2.303nRT \quad (1)$$

where $-(\partial \gamma / \partial \log c)_T$ is the slope of γ versus log C plots at constant absolute temperature T and R = 8.314 J $mol^{-1}K^{-1}$.

The average area occupied by the surfactant molecule at the air/ water interface of the surfactant solution i.e., the minimum surface area (Amin) has been calculated using the following equation:

$$A_{min} = 10^{14} / N \Gamma_{max} \quad (2)$$

where N is Avogadro's number. The surface excess, Γmax, and the area per molecule Amin vary with the molecular structure, showing a large area per molecule with metal complex which indicates that the molecule is less tightly packed at the air/ water interface [27].

Thermodynamic Parameters

Standard free energies of micellization and adsorption for the prepared surfactants were calculated at 25°C using the following equations:

$$\Delta G°_{mic} = nRT \ln (CMC) \quad (3)$$

$$\Delta G°_{ads} = \Delta G°_{(mic)} - 6.023 \times 10^{-1} \times \pi_{CMC} \times A_{min} \quad (4)$$

According to Rosen et al. [26], negative values of both $\Delta G°_{mic}$ and $\Delta G°_{ads}$ indicate that adsorption and micellization are two spontaneous processes Table (1). $\Delta G°_{mic}$ and $\Delta G°_{ads}$ become more negative with metallomicelle.

Cytotoxicity of Target Compounds

The in vitro anticancer cytotoxic activity of N-dodecyl-N-trimethyl silane ammonium iodide (A) was investigated by MTT assay against different human cancer cell lines [HEPG2 (liver), MCF-7 (breast), HCT-116 (colon), HEP2 (larynx), and HFB4 (normal)]. In addition, the comparative cytotoxicity of compound A and its metal complexes A-Cu, A-Co, and A-Zn were determined against colon cell line as shown in Tables (2, 3) and Figures (5-6).

The most common methods for treatment of cancer tumors are chemotherapy, surgery and radiation. However, these methods have different adverse-side effects, thus the discovery of new anti-tumor agents that are targeted towards tumor tissues became a must [5]. Surfactants can achieve this required selectivity. So, the main target of cancer therapy is to attain the maximum therapeutic damage of tumor cells using the minimum concentration of the drug. This can be achieved, mainly, via selective antitumor preparations, the cytostatic effects of which would be targeted towards tumor tissue. It is impractical to have 100% selectivity, so achievement of reasonably high selectivity seems to be a feasible aim. The results of the cytotoxic activity of the prepared surfactants on different human tumor cell lines were determined according to the dose values required to reduce survival in the cell lines to 50% (IC_{50}). The experimental results are recorded in Tables (2-3) and Figures (5-6).

Table (2) shows that, the parent surfactant A was able to exert the antiproliferative effects towards the tested human cancer cell lines. The IC_{50} values which is the concentration required for 50% growth inhibition of the synthesized surfactants towards cell lines variety were between 6.8 to 11.4 µg/ml. Comparatively, Doxorubicin (DOX), a drug with antineoplastic activity was used in this study as standard drug, since it is widely used in the treatment of tumor cells. DOX imposed an inhibitory effect on the same cell lines, with an IC_{50} values ranged between 4.4 to 17.4 µg/ ml. The anti-proliferation activity of synthesized compound A inhibited the proliferation of normal tumor cell (HFB4) and Colon tumor cells (HCT116) with IC_{50} values of 8.4 and 6.8 µg/ml respectively, while the DOX inhibited them with IC_{50} values of 17.4 and 4.6 µg/ml, respectively.

Figures (4 & 5) showed that the activity of both DOX and the prepared cationic surfactant A increased with increasing their concentrations. The anticancer activity of A on all cell lines is nearly the same and the difference in IC_{50} is depending on the type of tumor cell line. IC_{50} result indicates that, surfactant (A) affects tumor tissues at very low concentrations (lower than its CMC value), which means that there is a strong relationship between the low value of CMC of this compound and its ability to reach its IC_{50} value using very low concentrations. Where increasing the concentration of cationic surfactant causes an increase in the adsorption process on cell membranes until the CMC is reached; after this the adsorption process slowly decreases and then stops due to the formation of micelles [6].

Colon Carcinoma Cell Line [HCT116]:

Colorectal cancer, also called colon cancer or bowel cancer, includes cancerous growths in the colon, rectum and appendix. It is the third most common form of cancer.

Table 1: Surface parameters of the synthesized surfactants (A, A-Co, A-Cu & A-Zn)

Surfactants	CMC mol./L	γ_{CMC} mN/m	π_{CMC} mN/m	Pc_{20}	$\Gamma_{max}x10^{10}$ mol./ cm^2	A_{min} nm^2	ΔG^o_{mic} KJ/mol	ΔG^o_{ads} KJ/mol
A	1.1 $x10^{-4}$	37	35	5.01	1.005	1.652	-45.11	-45.16
A-Co	8 $x10^{-5}$	36	36	5.41	0.745	2.230	-46.69	-47.18
A-Cu	1 $x10^{-4}$	37	35	5.28	0.752	2.208	-45.64	-45.69
A-Zn	6.8 $x10^{-5}$	35	37	5.65	0.947	1.754	-47.49	-47.58

Table 2: Mortality % of different human cell lines under different concentrations of cationic surfactant A and Doxorubicin DOX

Human cell /Conc.µg/ml	5		12.5		25		50		IC_{50}(µg/ml)	
	A	**DOX**	**A**	**DOX**	**A**	**DOX**	**A**	**DOX**	**A**	**DOX**
HFb4	33.44	30.59	71.39	43.38	92.06	59.91	92.22	74.22	8.4	17.4
MCF7	29.83	57.85	64.95	58.64	91.75	58.91	92.33	55.53	9.4	4.4
HEPG2	10.93	42.91	58.06	58.15	88.57	59.05	90.52	62.09	11.4	8.8
HEP-2	20.65	78.18	64.67	80.62	92.15	77.98	93.75	80.02	10.0	3.3
HCT116	40.14	54.94	81.56	51.50	90.29	67.35	90.92	80.05	6.8	4.6

Table 3: Mortality % of colon human cell line under different concentrations of DOX and cationic surfactants (A, A-Cu, A-Co & A-Zn)

Surfactants/ Conc. µg/ml	5	12.5	25	50	IC_{50}
DOX	54.06	51.49	67.35	80.05	4.6
A	40.14	81.56	90.299	90.92	6.8
A-Co	33.41	64.64	57.24	48.78	8.85
A-Cu	12.79	22.23	38.32	35.47	-
A-Zn	74.24	73.45	53.06	50.0	3.3

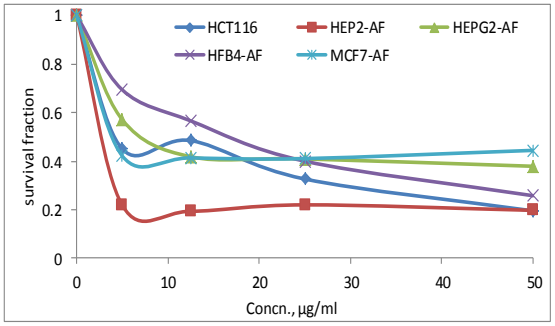


Figure (4) Cytotoxicity of Doxorubicin (DOX) drug on different human cell lines

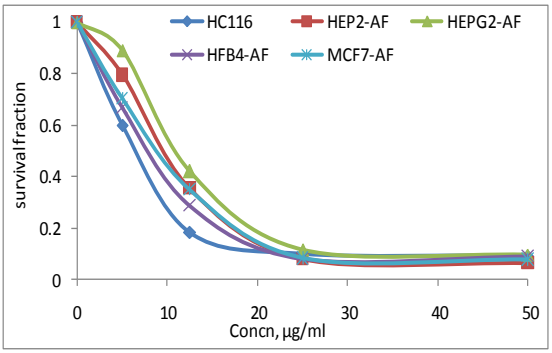


Figure (5) Cytotoxicity of cationic surfactant A on different human cell lines

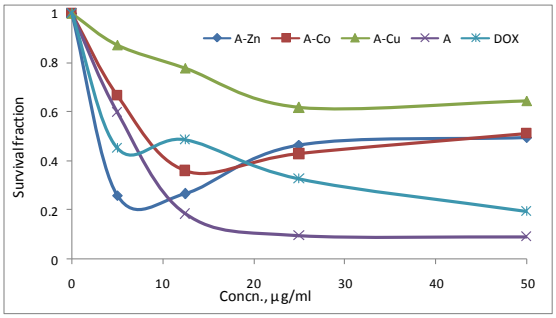


Figure (6) Cytotoxicity of different surfactants (A, A-Cu, A-Co, A-zn & DOX) on Colon human cell line

The anticancer screening test showed that A was highly effective against Colon carcinoma cell line [HCT116]. Therefore, a screening of the cytotoxic activity of the three metal complexes of N-dodecyl-N-trimethyl silane ammonium iodide (A) was performed against colon cell line, the biological assays of the ligand (A) and its metal complexes showed that all of them were active except Cu complex which has no IC_{50}. The percentage of survival versus compound concentration (0–50 µg/mL) was determined. Zn metal coordination compound showed significant activity against HCT-116, Table (3) and Figure (6). In general, the increasing concentration of the prepared compounds was accompanied by progressive increase in the activity. This is due to the fact that by increasing the concentration of the cationic surfactant, the

adsorption of ions on cell membranes increases, leading to an increase in penetration and antitumor activity. The cationic silicon-based surfactants showed good surface properties, their surface tension values were varied between 35 and 37 mN/ m. They exhibit good interaction with the different cell membranes due to their surface activity. The mechanisms, which could be suggested, include interference with the enzyme balance within the tumor, interference with the osmotic balance or increased cell membrane permeability. The antitumor potency of these cationic silicon-based surfactants might be related to the increased charge density around the nitrogen atoms that might possibly disturb the osmotic balance between the tumor cells and the medium.

The most susceptible complex was A-Zn, while for A-Cu the IC_{50} value was not reached, Table (3) revealed that, the lipophilicity of a drug not only affects the membrane permeability, but also the metabolic activity as well [28]. However, compound A-Zn showed a lower CMC (6.8 $x10^{-5}$ mol/l) than the other surfactants which appears probable to facilitate its combination with the tumor cell lipids and interferes with its enzyme balance.

Conclusion

The prepared metallomicelles were confirmed using different techniques. These surfactants have showed good surface activity. The surface tension values of the produced cationic complexes (A-Co, A-Cu and A-Zn) were found to be slightly lower than those of the parent surfactant. Also, from cmc results we can conclude that the prepared metal–surfactant complexes have more tendency to form aggregates compared to the parent surfactant A. The values of efficiency of adsorption of the prepared surfactants showed the following arrangement A-Zn > A-Co > A-Cu and that the three complexes are more efficient at the interface than the corresponding parent surfactant A. Thermodynamic parameters showed that ΔG^{o}_{mic} and ΔG^{o}_{ads} become more negative with metallomicelle. Finally, the cytotoxic activity of these surfactants was evaluated against five human tumor cell lines [HEPG2 (liver), MCF-7 (breast), HCT-116 (colon), HEP2 (larynx), and HFB4 (normal)], where the results showed that zinc (II) and cobalt (II) surfactants have significant cytotoxic activity, where as copper (II) complex showed the least activity.

Acknowledgement

This work has been supported by Egyptian Petroleum Research Institute (EPRI).

Conflicts of interest: The authors declare no competing financial interest.

References:

1. Ali A. A., Khan D., Naqvi A., Al-blewi F.F., Rezki N., Aouad M.R., and Hagar M. (2021) Design, Synthesis, Molecular Modeling, Anticancer Studies, and Density Functional Theory Calculations of 4-(1,2,4-Triazol-3-ylsulfanylmethyl)-1,2,3-triazole Derivatives. ACS Omega, 6, 301-316. https://dx.doi.org/10.1021/acsomega.0c04595
2. Lou Sh-J., Li X-H., Zhou X-L, Fang D-M. and Gao F. (2020) Palladium-Catalyzed Synthesis and Anticancer Activity of Paclitaxel−Dehydroepiandrosterone Hybrids. ACS Omega, 5, 5589-5600. https://dx.doi.org/10.1021/acsomega.0c00558
3. Chandar S.C.N, Sangeetha D., Arumugham M.N. **(**2011) Micellization of Metallosurfactant N-Dodecyl/ Hexadecyl/ Octadecyl Salicylaldimine Cobalt (III) Complexes in Nonaqueous Media**.** Journal of Solution Chemistry, 40, 4: 608-620. DOI https://doi.org/10.1007/s10953-011-9676-4
4. Munteanu C.R. and Suntharalingam K. (2015) Advances in cobalt complexes as anticancer agents Dalton Trans., 44, 13796–13808
5. Anestopoulos I., Kiousi D.E., Klavaris A., Galanis A., Salek K., Euston S.R., Pappa A. and Panayiotidis M.I. (2020) Surface Active Agents and Their Health-Promoting Properties: Molecules of Multifunctional Significance. Pharmaceutics, 12, 688; doi:10.3390/pharmaceutics12070688.
6. Gurpreet K., Sandeep K., Ravi K., Gaurav B., Neeraj D., Santosh K. G., Shashi B. and Sundeep J. (2016) One-step synthesis of silver metallosurfactant as an efficient antibacterial and anticancer material. RSC Adv., 6, 57084–57097. DOI: 10.1039/C6RA09677H.
7. Sodhi R.K. and Paul S. (2019) Metal Complexes in Medicine: An Overview and Update from Drug Design Perspective. Canc. Therapy & Oncol. Int. J., 14(2): CTOIJ.MS.ID.555883.
8. Preeti G., Gurpreet K. and Ganga R. Ch. (2016) Transition metal based single chained surfactants: synthesis, aggregation behavior and enhanced photoluminescence properties of fluorescein. RSC Adv., 6: 108573–108582. DOI: 10.1039/C6RA21811C.
9. Yilmaz V.T., Icsel C., Turgut O.R., Augun M., Erkisa M., Turkdimer M.H. and

Ulukaya E. (2018) Synthesis, structures and anticancer potentials of platinum (II) saccharinate complexes of tertiary phosphines with phenyl and cyclohexyl groups targeting mitochondria and DNA. European Journal of Medicinal Chemistry, 155,609-622. DOI:10.1016/j.ejmech.2018.06.035.

10. Kumaragurua N. and Santhakumar K. (2010) Studies on synthesis, determination of CMC values, kinetics and the mechanism of iron (II) reduction of surfactant–Co (III)–ethylenediamine complexes in aqueous acid medium. Physics and Chemistry of Liquids, 48, 6, 747–763 https://doi.org/10.1080/00319100902962707.
11. Sasikala K. and Arunachalam S. (2013) Antimicrobial activity, Spectral studies and Micellar Properties of some Surfactant-Copper (III) complexes. Chem Sci Trans., 2(S1), S157-S166. DOI:10.7598/cst2013.38
12. Li J., Zhang Q., Wang Y., Zhang W. and Li T., (2012) Synthesis and Properties of Organosilicon Quaternary Salts Surfactants**.** J. Surfact. Deterg., 15, 339-344. DOI: 10.1007/s11743-011-1306-z
13. Hao C., Cui Y., Yang .P, Zhang H., Mao D., Cui X. and Li J., (2015) Colloids Surf. B: Bio interfaces Effect of siloxane spacer length on organosilicon bi-quaternary ammonium amphiphiles., 128, 528-536. doi: 10.1016/j.colsurfb.2015.03.004.
14. Fang L., Tan J., Zheng Y., Yang G. Yu J. and Feng Sh., (2017) Synthesis, aggregation behavior of novel cationic silicone surfactants in aqueous solution and their application in metal extraction. Journal of Molecular Liquids ,231, 134-141. https://doi.org/10.1016/j.molliq.2017.02.017
15. Adamovich S.N. and Favorsky A.E., (2019) New atranes and similar ionic complexes. Synthesis, structure, properties. Applied Organometallic Chemistry, e4940. https://doi.org/10.1002/aoc.4940.
16. Badawi A.M. and Ahmed S.M., (2007) Degradation of Pesticides Wastewater by Silyl Based Cationic Surfactants. J. Surfact. Deterg., 10:103-108. DOI https://doi.org/10.1007/s11743-007-1019-5
17. Badawi A.M. and Ahmed S.M., (2010) Hydrolysis of Pesticides in Wastewater Catalyzed by Cu (II) Complexes of Silyl Based Cationic Micelles. Journal of Dispersion Science and Technology, 31 (4), 577–582. https://doi.org/10.1080/01932690903192804.
18. Cai Z., Gong Y., Liu W., Fu J., O'Reilly S.E., Hao X. and Zhao D. **(2016)** A surface tension based method for measuring oil dispersant concentration in seawater. J. Surfact. Deterg. Marine Pollution Bulletin, 109 (15), 49–54. https://doi.org/10.1016/j.marpolbul.2016.06.028
19. . Ghiaty, E. A, Mohamed, D. E., Badr, E. A, Gad, El. A. M., Soliman El. A. and Aiad. I.A. (2020) Experimental and Computational Study of Ecofriendly Synthesized Imine Cationic Surfactants as Corrosion Inhibitors for Carbon Steel in 1 M HCl. Tenside Surf. Det. 57.
20. Karakas D.; Ari F. and Ulukaya E. (2017) The MTT viability assay yields strikingly false-positive viabilities although the cells are killed by some plant extracts. Turk J Biol, 41, 919-925 doi:10.3906/biy-1703-104
21. Bahuguna A.; Khan I.; Bajpai V. K. and Kang S. Ch. (2017) MTT assay to evaluate the cytotoxic potential of a drug. Bangladesh Journal of Pharmacology, 12, 115-118. DOI: https://doi.org/10.3329/bjp.v12i2.30892.
22. He Y.; Zhu Q.; Chen M.; Huang Q.; Wang W.; Li Q.; Huang Y. and Di W. (2016) The changing 50% inhibitory concentration (IC50) of cisplatin: a pilot study on the artifacts of the MTT assay and the precise measurement of density-dependent chemoresistance in ovarian cancer. Oncotarget. 7(43): 70803–70821. doi: 10.18632/oncotarget.12223
23. El-Dib F.I., Ahmed S.M., Ismail D.A. and Mohamed D.E. (2013) Synthesis and Surface Properties of Novel N-Alkyl Quinoline-Based Cationic Gemini Surfactants. Journal of Dispersion Science and Technology, 34 (4), 596-603. https://doi.org/10.1080/01932691.2012.683979
24. Santhakumar K. , Kumaraguru N., Arunachalam S. and Arumugham M.N. (2006) Studies on Cobalt (III) Metallosurfactants. Kinetics and Mechanism of Reduction of Cobalt (III) by Iron (II) in Aqueous Acid Medium. Transition Metal Chemistry, 31, 62-70. https://doi.org/10.1007/s11243-005-6356-5.
25. Iglesia P.d.l., Jaeger V.W., Xi Y., Pfaendtner J., and Pozzo L.D. (2015) Structure Characterization and Properties of

Metal–Surfactant Complexes Dispersed in Organic Solvents. Langmuir, 31, 33: 9006–9016. https://doi.org/10.1021/acs.langmuir.5b02071.

26. Rosen M. J. and Kunjappu J. T., (2012) Surfactants and Interfacial Phenomena, Fourth Edition New York, John Wiley & Sons, Inc., DOI:10.1002/9781118228920
27. El-Sukkary M.M.A., Shaker N.O., Ismail D.A,, Ahmed S.M., Zaki M.F. and Awad A.I. (2012) Surface parameters, biodegradability and antimicrobial activity of some amide ether carboxylates surfactants. Egyptian Journal of Petroleum**,** 21(1), 37–43. https://doi.org/10.1016/j.ejpe.2012.02.006.
28. Arnott J.A. and Planey S.L. **(2012)** The influence of lipophilicity in drug discovery and design, Journal Expert Opinion on Drug Discovery, 7 (10) ,863-875. DOI: 10.1517/17460441.2012.714363.