

FERROMAGNETIC NANOPARTICLES CONTAINING BIOLOGICALLY ACTIVE ALKANOLAMINES

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Introduction. Ferrofluids composed of fine magnetic particles covered with biologically active molecules are increasingly used as medical remedies for therapy and diagnostics. Today, a number of magnetic iron oxide particle types are known. Within the superparamagnetic iron oxide family, two compounds, foreseen for oncology, are registered and approved: Feridex[®] (Berlex) in the USA or Endorem[®] (Guerbet) in Europe and Resovist[®] (Schering) in Europe and Japan. Recently, ultrasmall superparamagnetic iron oxide particles with citric acid coating have been developed and are under clinical development for the demarcation of coronary arteries [1, 2]. Oral magnetic particles, prepared with non-biodegradable coating matrices composed of siloxane or polystyrene [3, 4] are also available.

The aim of the present study is to investigate the possibility of sorption of model biologically active organosilicon alkanolamines on the surface of ferromagnetic fluids, in order to spread this methodology over preparation of ferromagnetic fluids, containing more complex biologically active N-heterocyclic compounds. The choice of oleic acid for first coating (surfactant 1) is reasonable because of its wide presence in nature and due to the proved fact of its biological activity. Alkanolamine derivatives – biologically active substances, structural analogs of choline and colamine, affecting central nervous system diseases, have been chosen as the second cover (surfactant 2). To overcome the problem of colloid system stability, the compounds have been modified by introduction of organosilicon substituent and by preparing salts of silyl modified substances. Introduction of organosilicon substituent into the molecule of alkanolamine is an attractive and original approach to the lipophilicity increase and better interaction with lipophilic chains of the first coating. The transformation of the compounds synthesised into salts in many cases causes activity increase, but also changes (increases) the solubility of the compounds in water that is very significant for preparing and stabilization of water bilayer colloid systems, used for biological purposes.

1. Experimental procedure.

1.1. General procedure for the preparation of surfactants 2. Hydrosilane and catalytic amount of metallic sodium were added to the solution of equivalent amount of β -dimethylaminoethanol in benzene. The reaction mixture was refluxed under stirring during 6 h. Solvent was evaporated under reduced pressure and the residue was distilled under vacuum to obtain the products, decyldimethyl- (A) or hexadecyldimethyl (β -dimethylaminoethoxy)silane (B), as viscous liquids. The corresponding methiodides (C and D) have been prepared by their interaction with excess of methyl iodide under stirring in hexane at room temperature. The products obtained have been characterized by elemental analysis, ¹H, ¹³C, ²⁹Si NMR and mass-spectroscopy data.

1.2. Preparation of ferromagnetic samples. Initial magnetic particles Fe₃O₄ were prepared by wet synthesis coprecipitating inorganic ferric and ferrous salts

Table 1. Physico-chemical properties of magnetite based samples **1–9**.

No.	surfactant 1	surfactant 2	physical state	magnetization, emu/g	concentration of magnetite, %	particle diameter, nm
1	oleic acid	no	solution	0.44	0.47	9.7
2	oleic acid	no	solution	0.29	0.32	11.1
3	oleic acid	no	solution	1.03	1.1	12.6
4	oleic acid	no	powder	24	25	9.5
5	oleic acid	C	powder	17	18	9.5
6	oleic acid	D	powder	9.9	11	9.3
7	no	no	powder	50	55	10.2
8	no	C	solution	0.003	0.003	12
9	oleic acid	A	solution	0.0061	0.0066	12.9

with sodium hydroxide solution. The results of the investigation of magnetic properties are present in Table 1. The ferromagnetic fluids (**1 – 3**) were obtained by the reaction of oleic acid (surfactant 1) with ferromagnetic by fine stirring of the mixture at 80°C in toluene according to the method [5]. Ferromagnetic solid **4** was isolated from the ferrofluid **3** by treatment with acetone, centrifugation and sediment drying. Ferromagnetic solids **5** and **6** were prepared by addition of surfactant 2, decyldimethyl- or hexadecyldimethyl (β -dimethylaminoethoxy)silane methiodides (C and D), correspondingly, to the ferromagnetic fluid **3** in toluene. The mixtures were stirred under room temperature during 10 h and worked up by the same way as in the case of solid **4**. Ferromagnetic solid **7** was obtained by drying of initial magnetite, prepared by wet method. Ferromagnetic fluid **8** was obtained from solid **7** by later one stirring at room temperature during 18 h with surfactant 2, namely, decyldimethyl (β -dimethylaminoethoxy)silane methiodide (C), in toluene. The fluid **8** was separated from the resulting mixture by centrifugation. Ferromagnetic fluid **9** was prepared from ferromagnetic fluid **3**. To the sediment, obtained after treatment with acetone and centrifugation of fluid **3**, water and surfactant 2, decyldimethyl (β -dimethylaminoethoxy)silane (A), were added. The mixture was stirred at room temperature during 24 h and centrifuged. The solution **9** was separated from surfactant **2** as a slightly brown liquid.

1.3. Study of sorption of surfactants 2. The curves of sorption of surfactants **2**, namely, decyldimethyl (β -dimethylaminoethoxy)silane (A) and its methiodide (C), were obtained using mass-spectroscopy data and a routine method. For this purpose a number of samples of ferrofluids **1** and **2** with various concentrations of surfactant 2 (A or C) were prepared. The samples after stirring at room temperature during 10 h were treated with acetone and centrifuged. The sorption of surfactants **2** was estimated by determination of mass of non adsorbed residual surfactant **2**, which was present in acetone supernatant. The calculations were done with correction, taking into account the mass of free oleic acid and the products of its decomposition, which also were present in acetone solution and were revealed under the same treatment of ferrofluids **1** or **2**.

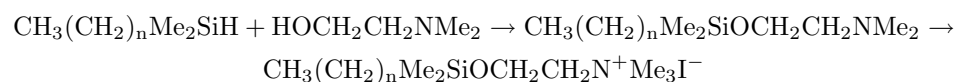
1.4. Determination of magnetic properties of ferromagnetic samples. The dependence of magnetization on an external magnetic field for the samples was determined by using a Vibrating Sample Magnetometer. Such magnetization curves were defined at different steps of the material treatment for the monitoring magnetite concentration and its condition, too. As a rule, we carry out these measurements at room temperature for fields to 10 KOe. The magnetization curves were used for the magnetogranulometry analysis [6] to determine full spontaneous

magnetization and magnetic moment of magnetite particles in the sample from which the concentration and the size of particles in the sample were calculated. In order to do this analysis for the weak magnetic samples, measurements of the matrix (water or toluene) at the same holder were made separately, then matrix magnetization was subtracted from full magnetization.

2. Results and discussion. In this paper we report on the preparation of organosilicon containing biologically active alkanolamines and novel complex model ferromagnetic – oleic acid (surfactant 1) – organosilicon containing biologically active alkanolamine (surfactant 2) nanoparticles, containing biologically active alkanolamine molecules adsorbed at biocompatible magnetic particles, which consist of ferromagnetic particles (ferrite) pre-coated with oleic acid.

Model organosilicon alkanolamines were designed. The compounds contain long lipophilic tails, which are able to deepen inside the oleic acid shell, but also hydrophilic heads, which ease their contact with water.

The desired compounds were synthesised according to the following reaction sequence



Reaction of dehydrocondensation of alkanolamine with hydrosilanes was carried out in the presence of metallic sodium. Thus obtained decyldimethyl(β -di-methylaminoethoxy)silane ($n=9$, compound A) and hexadecyldimethyl(β -di-methylaminoethoxy)silane (n , compound B) were converted to the corresponding methiodides (C and D) by their interaction with methyl iodide.

Magnetic particles Fe_3O_4 were prepared by wet synthesis coprecipitating inorganic ferric and ferrous salts with sodium hydroxide solution and coated further with low molecular oleic acid by the reaction of oleic acid with ferromagnetite under fine stirring of the mixture at 80°C in toluene according to the method [5].

The sorption of surfactant 2 (C) on the surface of ferromagnetite pre-coated with oleic acid has been studied (Fig. 1) in order to show the principal possibility of binding model biologically active organosilicon alkanolamines by the oleic acid shell on the surface of ferromagnetic nanoparticles.

For reproducible production and quality control the nanoparticles have been characterised according to their composition and physical measures. The composition content of powders **4** – **6** was defined exploiting elemental analysis data. The molar ratio $[\text{Fe}_3\text{O}_4] : [\text{C}_{17}\text{H}_{33}\text{COOH}]$ of components in samples **4** – **6** was

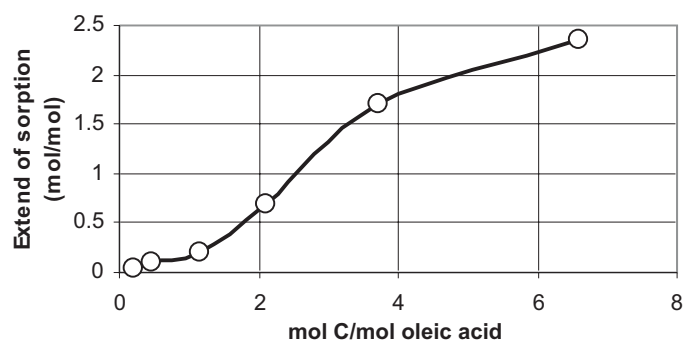


Fig. 1. Adsorption curve of decyldimethyl(β -dimethylaminoethoxy)silane methiodide (C) on ferromagnetite nanoparticles pre-coated with oleic acid.

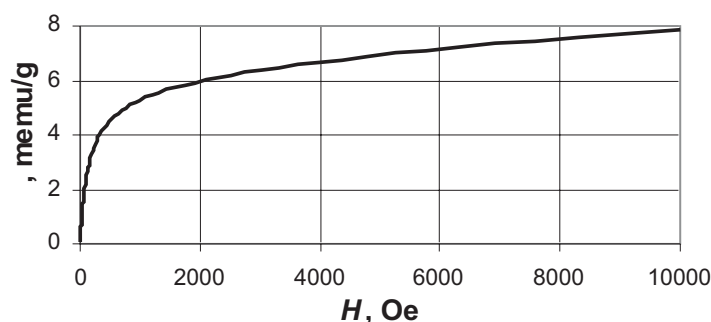


Fig. 2. Magnetization curve of the sample **9** (magnetization of water is subtracted).

estimated as 3 : 1 for sample **4**, $[\text{Fe}_3\text{O}_4] : [\text{C}_{17}\text{H}_{33}\text{COOH}] : [\text{C}] = 3 : 1 : 0.2$ for sample **5** and $[\text{Fe}_3\text{O}_4] : [\text{C}_{17}\text{H}_{33}\text{COOH}] : [\text{D}] = 3 : 1 : 0.4$ for sample **6**. The estimated data are in agreement with the amount of non sorbed surfactant **2** (C and D). Sample **9** represents 3.3% water emulsion of surfactant **2** (A), containing double-coated ferromagnetic nanoparticles, and was obtained by addition of surfactant **2** to the system in threefold molar excess to oleic acid.

The magnetic properties of colloid systems prepared have been studied using the method of magnetogranulometry. The example of magnetization curve of ferrofluid **9** is present in Fig. 2.

The nanoparticle size of samples **1** – **8**, defined as the diameter of ferrite core, was 9.3–12.6 nm, Table 1. Magnetization parameters for ferrofluid samples **1** – **3** were 0.29–1.03 emu/g and are significantly lower than the ones defined for powders **4** – **7**. It was found that the magnetization decreases from 50 to 9.9 emu/g along the samples sequence $\mathbf{7} > \mathbf{4} > \mathbf{5} > \mathbf{6}$. The maximal value, 50 emu/g, corresponds to magnetite **7** itself. The double-coated samples (**5** and **6**) have lower magnetization than a mono-layer sample **4** that indirectly proves the double layer formation in samples **5** and **6**. The attempt to obtain a mono-layer ferrofluid from ferromagnetite and surfactant **2** (C) without the oleic acid pre-coating in toluene resulted in preparation of sample **8**, possessing a low magnetic activity that could be speculated by the fact of low sorption of surfactant **2** on the ferromagnetite surface.

The present results clearly show that there is sorption of the biologically active alkanolamines on the magnetic particles, containing magnetite with oleic acid coating. Besides it is shown that principally it is possible directly to coat the magnetite with biologically active alkanolamines, creating a monolayer cover.

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