stabilization in the present study. At this level, the tablets consistently exhibited the smallest average pore size irrespective of the relative changes in the size and volume of pores resulting from the swelling of starch grains or deposition of salicylic acid in the tablet pores. The role played by subliming salicylic acid and its contribution to the occlusion of the micropores were also evident in this study from the reduction in pore volumes and the size of the pores with increased periods of exposure to water vapor.

SUMMARY AND CONCLUSIONS

Silica I was studied with respect to its physicochemical and surface properties and its ability to stabilize a hydrolabile drug (aspirin) in tablet matrixes. The major findings of the investigation were:

1. Silica I exhibited an adsorption behavior characteristic of adsorbents with limited pore volume. The monolayer capacity and the specific surface area, determined by both water vapor and nitrogen adsorption isotherms employing the BET theory of multilayer adsorption, revealed the superior moisture adsorption capacity of I as compared to the other silicas tested.

2. The void volume of aspirin–silica tablets compressed under constant compressional force was proportional to the silica content of the tablets. Silica contributed approximately six times as much to the void volume as did aspirin on an equal weight basis. Therefore, it was necessary to control the void space of the tablets to eliminate the effect of the void volume variable in the interpretation of stability data.

3. The stability of aspirin tablets containing I at concentration levels of 0–15% was investigated under storage conditions of a continuous moisture supply (82% RH) at 40°. At the end of 120 days, tablets containing up to 5% I exhibited improved aspirin stability in comparison to control tablets. An optimum concentration of 3% silica, however, showed maximum stabilization; the tablets containing 10 and 15% silica showed progressively poorer stability, approaching that of the control tablets at the end of 120 days.

4. Silica I, with superior moisture adsorption properties, proved to be of significant value in enhancing the stability of the hydrolabile test drug (aspirin) by acting as an internal moisture scavenger. This study also demonstrated the importance of controlling the tablet void space in studies involving stability evaluation of drugs prone to moisture hydrolysis in solid drug dosage systems.

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Metal-Binding Abilities of Radioprotective Aminoalkyl Disulfides and Thiosulfates

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Received June 7, 1978, from the *Samuel M. Best Research Laboratory, Massachusetts College of Pharmacy, Boston, MA 02115.* Accepted for publication July 13, 1978.

Abstract □ Metal-binding stability constants for several heterocyclic aminoalkyl disulfides and thiosulfates with Ni(II) and Al(III) were determined. The data obtained indicated that both classes of compounds were acting as bidentate chelating agents and that the heterocyclic rings apparently prevented tridentate behavior of the disulfides because of steric hindrance. The magnitude of the constants indicated that metal complexes of these compounds could exist in a cellular environment, but no correlation with radiation-protective activity was apparent.

Keyphrases □ Disulfides, aminoalkyl—metal-binding stability constants determined, relation to radiation-protective activity □ Thiosulfates, aminoalkyl—metal-binding stability constants determined, relation to radiation-protective activity □ Metal binding—stability constants determined for various aminoalkyl disulfides and thiosulfates, relation to radiation-protective activity □ Binding, metal—stability constants determined for various aminoalkyl disulfides and thiosulfates, relation to radiation-protective activity □ Radiation-protective activity—various aminoalkyl disulfides and thiosulfates, relation to metal-binding stability constants

Aminoalkyl disulfides and thiosulfates have strong radiation-protective properties in animals (1, 2). The fact that the protective compounds all have a two- or three-carbon distance between the amino and sulfur functions, which confers potential metal-chelating ability to them, suggests that metal binding may be important in their

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Table I—Ionization Constants (25°)

Compound	pKa_1	pKa_2
Bis[2-(*N*-piperidyl)ethyl] disulfide	7.78	6.22
Bis[2-(*N*-3-methylpiperidyl)ethyl] disulfide	7.64	6.13
Bis[2-(*N*-4-methylpiperidyl)ethyl] disulfide	7.63	5.86
Bis[2-(*N*-morpholinyl)ethyl] disulfide	5.50	4.26
2-(*N*-Piperidyl)ethanethiosulfuric acid	8.50	2.00
2-(*N*-Morpholinyl)ethanethiosulfuric acid	6.51	2.38
2-[2-(2-Pyridyl)ethylamino]ethanethiosulfuric acid	9.33	2.28

radioprotective mechanism.

Several postulations have related radiation-protective activity to the ability to bind metals (3, 4), and a correlation between the extent of complexation of catalase, an iron-containing protein, and the protective ability in mice was observed (5). Therefore, it was considered important to ascertain the magnitude of the metal-binding ability of such compounds and to compare it to their radiation-protective properties. The role of metal binding in cellular radiation protection is not clear, but several observations indicated that metal ions are involved in both radiation damage and protection (6).

Both the disulfide group and thiosulfate ion bind metals (7), but there are few examples of the metal-complexing avidities of organic disulfides or thiosulfates. Stability constants for a Cu(II) complex of 2,2′-dithiobis(ethylamine) (8) and for Cu(II), Al(III), and Fe(III) complexes of 2-aminoethanethiosulfuric acid and 3-aminopropanethiosulfuric acid (9) have, however, been reported. Also, an X-ray diffraction study of the nickel complex of bis[2-[2-(2-pyridyl)ethyl]aminoethyl] disulfide revealed an extremely stable complex with five coordinate bonds to the nickel ion from one molecule of disulfide (10).

EXPERIMENTAL

Materials—Analytical reagent grade aluminum chloride hexahydrate and nickel chloride hexahydrate were used. Carbonate-free 0.01 *N* KOH was prepared according to Armstrong (11). Solutions of the metal salts were prepared in boiled distilled water and stored in polyethylene bottles under nitrogen; they were diluted quantitatively with carbon dioxide-free water just prior to use. Normalities were checked against potassium biphthalate.

The organic ligands, isolated as the dihydrochlorides of the disulfides or as the zwitterions of the thiosulfates, were prepared as described previously (12), with one exception. Purity was ascertained by TLC. Chromatogram sheets[1] were spotted with approximately 0.1% solutions of the compounds in ethanol, and the sheets were developed with benzene–methanol (9:1). After the sheets were removed from the chamber and dried, spots were detected by UV light. The presence of one spot confirmed the absence of contaminating compounds.

2-[2-(2-Pyridyl)ethylamino]ethanethiosulfuric Acid—To a solution of 2-[2-(2-pyridyl)ethylamino]ethanethiol (12) (8.35 g, 0.046 mole) in 60 ml of methanol were added potassium metabisulfite (11.1 g, 0.05 mole) and 10 ml of water. The resulting mixture was refluxed overnight, cooled to room temperature, and filtered to remove potassium thiosulfate. The filtrate was flash evaporated, and the residue was treated with boiling methanol and filtered. Evaporation of the methanol left an oil, which was triturated several times with anhydrous ether; 5.4 g (45% yield) of a colorless oil was obtained; n = 1.5523; IR (neat): 3450 (NH), 1590 (pyridine ring), 1235 and 1180 ($S_2O_3^-$), 1020, and 760 (NH) cm^{-1}.

Anal.—Calc. for $C_9H_{14}N_2O_3S_2$: C, 41.20; H, 5.39; N, 10.68; S, 24.44. Found: C, 40.95; H, 5.36; N, 10.34; S, 24.16.

Ionization Constants—The method of Albert and Serjeant (13) consisted of titrations of 0.001 *M* aqueous solutions of the compounds with 0.01 *N* KOH in 0.5-ml portions. The pH was recorded[2] after each addition. Each titration thus yielded 10 pH values, giving 10 values for the pKa, which were averaged (Table I). When pH values fell outside the 5–9 range, corrections were made for hydrogen- or hydroxide-ion concentrations.

Stability Constants—Potentiometric titrations were carried out under nitrogen in 95% ethanol at 25° with the described equipment. Volumes of 50 ml of the 0.001 *M* solutions of the organic ligands were titrated with 0.01 *N* KOH in 0.5-ml portions, first in the absence of metal ions and then in the presence of 0.0005 mole of divalent metal salt or 0.00033 mole of trivalent metal salt.

Volumes of 50 ml of the same quantities of the metal salts also were titrated with 0.01 *N* KOH. The pH readings were recorded 2 min after each addition of titrant to allow equilibrium to be reached. Solvent concentration at the end of the titrations was approximately 72% ethanol.

Calculations were performed as previously described (14) with a computer. The log K_1 values for the Ni(II) complexes and the log K_2 and log K_3 values for the Al(III) complexes are recorded in Table II. Values for K_1, K_2, and K_3 were obtained from Eqs. 1–3, according to Flood and Loras (14) and Albert (15):

$$K_1 = \frac{\bar{n}}{(1-\bar{n})[L^-]} \quad \text{(Eq. 1)}$$

$$K_2 = \frac{(\bar{n}-1)}{(2-\bar{n})[L^-]} \quad \text{(Eq. 2)}$$

$$K_3 = \frac{(\bar{n}-2)}{(3-\bar{n})[L^-]} \quad \text{(Eq. 3)}$$

where $\bar{n}$ is the average number of ligand molecules bound by a metal ion at any stage in complex formation and $[L^-]$ is the concentration of the free chelating species.

The K_1 values for the Al(III) complexes were not uncovered, possibly because of nonstepwise complexation (no values for $\bar{n}$ below 1, and in some cases below 2, were obtained). Representative values for the constants obtained for the Al(III) complex of bis[2-(*N*-4-methylpiperidyl)-ethyl] disulfide are shown in Table III. Values of K_2 for the Ni(II) complexes could not be obtained because of the formation of precipitates. Representative titration data for the Ni(II) complex of bis[2-(*N*-piperidyl)ethyl] disulfide are listed in Table IV.

Table II—Stability Constants for Aminoalkyl Disulfides and Thiosulfates

Compound	Al(III) Complexes, log K_2	Al(III) Complexes, log K_3	Ni(II) Complexes, log K_1
Bis[2-(*N*-piperidyl)ethyl] disulfide	—	13.45	4.21
Bis[2-(*N*-4-methylpiperidyl)ethyl] disulfide	11.34	9.65	3.18
Bis[2-(*N*-3-methylpiperidyl)ethyl] disulfide	—	10.36	2.87
Bis[2-(*N*-morpholinyl)ethyl] disulfide	8.03	5.96	4.46
2-(*N*-Piperidyl)ethanethiosulfuric acid	—	—	4.38
2-(*N*-Morpholinyl)ethanethiosulfuric acid	7.36	4.18	—
2-[2-(2-Pyridyl)ethylamino]ethanethiosulfuric acid	—	11.43	5.50

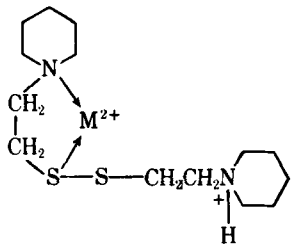
RESULTS AND DISCUSSION

Both nitrogens of the bis(2-aminoethyl) disulfide molecule, as well as the disulfide function, are capable of simultaneous attachment to the

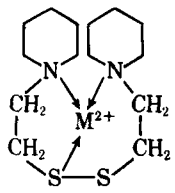
Table III—Potentiometric Titration of Bis[2-(*N*-4-methylpiperidyl)ethyl] Disulfide Dihydrochloride and Aluminum(III) Chloride

pH	log $[L^-]$	$\bar{n}$	log K_2	log K_3
3.20	$\overline{11}.51$	1.76	11.01	—
3.24	$\overline{11}.56$	1.84	11.16	—
3.30	$\overline{11}.67$	1.87	11.18	—
3.34	$\overline{11}.71$	1.96	11.68	—
3.40	$\overline{11}.80$	2.02	—	8.58
3.46	$\overline{11}.88$	2.09	—	9.16
3.50	$\overline{11}.91$	2.19	—	9.49
3.55	$\overline{11}.95$	2.29	—	9.68
3.59	$\overline{11}.96$	2.41	—	9.91
3.63	$\overline{11}.97$	2.49	—	10.03
	log mean of antilogs		11.34	9.65

[1] Eastman.
[2] Beckman research pH meter with glass and calomel electrodes.



I



II

same metal ion (8). This molecule, as well as those titrated in this study, is a complex-forming species of type HLRLH and has the added stabilizing factor of the disulfide group, which would provide chelate rings of five or six members. Complex structures of types I and II, with a divalent metal ion (M^{2+}), are theoretically possible.

Steric hindrance between the heterocyclic rings could prevent the formation of II, however; relevant equilibria in acid solution would then be:

$$M^{2+} + {}^{+}HLRLH^{+} \rightleftharpoons {}^{+}HLRLM^{2+} + H^{+}$$

$$M^{2+} + 2{}^{+}HLRLH^{+} \rightleftharpoons ({}^{+}HLRL)_2M^{2+} + 2H^{+}$$

Scheme I

With a metal having hexacoordinate capacity, a 3:1 complex would also be possible:

$$M^{2+} + 3{}^{+}HLRLH^{+} \rightleftharpoons ({}^{+}HLRL)_3M^{2+} + 3H^{+}$$

Scheme II

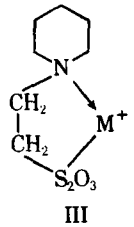
With these compounds, steric hindrance by the heterocyclic rings might prevent formation of a 3:1 complex.

Titration data for the Ni(II) complexes gave values only for K_1. Precipitation generally took place before values of $\bar{n}$ exceeded 1. For the disulfides, log K_1 values ranged from 2.87 to 4.46; the values for the two thiosulfuric acids where constants were obtained were 4.38 and 5.50. These constants were obtained in the pH 5.75–7.20 range where protonation of the nitrogens should not be extensive. Therefore, both the nitrogen and sulfur functions should participate in complex formation, and structures of type III are proposed for these complexes. The thiosulfates are believed to coordinate through the thiosulfate ion (16), in addition to the amino group, as shown previously for 2-aminoethane- and 3-aminopropanethiosulfuric acids (9).

Complexation of the hydrochlorides of the aminoalkyl disulfides with Al(III) generally occurred in the pH 2.8–3.6 range. At this pH range, one nitrogen may be expected to be protonated; coordination to the metal ion would, therefore, take place only through one nitrogen and sulfur. The fact that values for K_1 for the Al(III) complexes were not found, as well as values for K_2 in some cases, indicates that two or three ligands combine in a nonstepwise fashion. If coordination were taking place through both nitrogens and sulfur, the molecules would act as tridentate ligands, and a total of three ligand molecules would be required to give values for K_3, which would exceed the coordination capacity of Al(III).

The stability constants of the 2:1 and 3:1 complexes obtained appear to be too high for binding to either nitrogen or sulfur alone, so complexes involving one nitrogen and one sulfur are proposed. Log K_1 values for the binding of Ag(I) and Cu(II) to piperidine, for instance, are 3.16 (17) and 2.81 (18), respectively. Where a terdentate chelate is involved, as postulated for bis(2-aminoethyl) disulfide, the K' value for the Cu(II) complex is 5.02×10^6 (8). Comparison of the found constants with these values indicates both nitrogen and sulfur coordination to metal.

From the magnitude and nature of the stability constants, it is apparent that steric hindrance by the heterocyclic rings prevents the compounds from acting as terdentate ligands but does not prevent the formation of 2:1 and 3:1 bidentate complexes. However, the lower values for stability



III

Table IV—Potentiometric Titration of Bis[2-(*N*-piperidyl)-ethyl] Disulfide Dihydrochloride with Nickel(II) Chloride

pH	log $[L^-]$	$\bar{n}$	log K_1
6.72	5.81	0.05	2.89
6.78	5.84	0.18	3.50
6.83	5.86	0.31	3.82
6.88	5.85	0.46	4.09
6.92	5.84	0.63	4.41
6.96	5.83	0.76	4.70
	log mean of antilogs		4.21

constants of the morpholine-substituted complexes indicate some interference by the morpholine oxygen. Also, the 3- and 4-methyl groups of the piperidine rings both lower metal-binding avidity, probably sterically. The exceptionally high constant found for 2-[2-(2-pyridyl)ethylamino]ethanethiosulfuric acid in comparison to other organic thiosulfuric acids, *e.g.*, those studied here and in Ref. 9, indicates possible terdentate ligand behavior for Ni(II).

Comparison of the metal-binding strengths of these compounds with the radiation-protective activities in mice (Table V and Ref. 19) showed no apparent correlation. Of the compounds studied here, bis[2-(*N*-morpholinyl)ethyl] disulfide showed the greatest protective effect, giving 50% survival at 30 days, but had the lowest metal-binding constants for Al(III) of the disulfides observed. Its log K_1 for Ni(II) was slightly higher than those values for the other disulfides but did not differ greatly from the log K_1 for 2-(*N*-piperidyl)ethanethiosulfuric acid, which provided only 20% protection to mice. 2-(*N*-Morpholinyl)ethanethiosulfuric acid, however, with somewhat lower binding constants for Al(III), had no radiation-protective ability.

It is unfortunate that radiation-protective data were not obtained for 2-[2-(2-pyridyl)ethylamino]ethanethiosulfuric acid, which had the highest log K_1 for Ni(II). Although a comparison between two different types of compounds, disulfides and thiosulfuric acids, may not be valid, a comparison between the binding ability to catalase and the radiation-protective ability in mice showed a correlation with several varieties of compounds, including dithiocarbamates, trithiocarbonates, and thiols (5).

The magnitude of the metal-binding stability constants observed with these disulfides and thiosulfuric acids is relatively high, particularly for the Al(III) complexes. Since they are equal to or greater than corresponding values for the common amino acids and peptides (15, 20), it may be concluded that these compounds are capable of combining with metal ions in a cellular environment. Since no correlation between the magnitude of the stability constants and radiation-protective ability was evident, any involvement with metal ions in the radiation-protective process would most likely be transient, and formation of relatively stable metal complexes would not be anticipated.

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Table V—Radiation Protective Activities in Mice [a]

Compound	Dose, mg/kg[b]	Route[c]	Survival, %[d]
Bis[2-(*N*-morpholinyl)-ethyl] disulfide	20	Intraperitoneal	50
	100	Intraperitoneal	20
	300	Oral	20
	600	Oral	40
Bis[2-(*N*-3-methylpiperidyl)-ethyl] disulfide	30	Intraperitoneal	10
	60	Intraperitoneal	10
	100	Oral	20
	300	Oral	22[e]
Bis[2-(*N*-piperidyl)ethyl] disulfide	20	Intraperitoneal	0
	20	Intraperitoneal	10
	100	Oral	10
	200	Oral	20
2-(*N*-Piperidyl)ethanethiosulfuric acid	60	Intraperitoneal	20
	180	Oral	0
2-(*N*-Morpholinyl)ethanethiosulfuric acid	100	Intraperitoneal	0
	400	Oral	0

[a] Carried out at the Walter Reed Army Institute of Research. [b] Radiation dosage was 849 rads from a cesium-137 V irradiator given at a rate of 141.5 rads/min. Ten mice were used at each dosage level. [c] Compounds were administered by the indicated route in water, physiological saline, or 0.3% methylcellulose–0.1% polysorbate 80 (Tween 80) vehicle. [d] Calculated from the number of surviving mice at 30 days postirradiation.

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Effect of Microcrystalline Cellulose on Liquid Penetration in and Disintegration of Directly Compressed Tablets

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Received April 25, 1978, from the *Laboratory for Pharmaceutical Technology, University of Groningen, Groningen, The Netherlands.*
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Abstract □ The penetration of isooctane and water into tablets of microcrystalline cellulose, dibasic calcium phosphate dihydrate, spray-crystallized maltose–dextrose, and blends of microcrystalline cellulose with one of the other excipients were studied. The isooctane penetrations occurred according to the Washburn equation and were not affected by the presence of 0.5 or 1.0% magnesium stearate. The inhibition of aqueous penetration into tablets resulting from hydrophobic magnesium stearate was less pronounced for vehicles like dibasic calcium phosphate, which exhibited extensive brittle fracture under compression. Microcrystalline cellulose tablets, both with and without magnesium stearate, exhibited extremely fast aqueous penetration even at low porosities, caused by breaking of the hydrogen bonds and subsequent widening of the pores. Ratios between water uptake and original pore volume up to 20 were obtained for microcrystalline cellulose tablets. This unique property was, however, suppressed by the presence of fast dissolving and highly soluble excipients like dextrose, resulting in an antagonistic disintegration behavior of tablets compressed at pressures over 10,000 N/cm². Improved disintegration properties were obtained by blending microcrystalline cellulose with an insoluble vehicle such as dibasic calcium phosphate dihydrate.

Keyphrases □ Cellulose, microcrystalline—effect on liquid penetration and disintegration of directly compressed tablets □ Penetration, liquid—isooctane and water into directly compressed tablets, effect of microcrystalline cellulose □ Disintegration—directly compressed tablets, effect of microcrystalline cellulose □ Tablets, directly compressed—liquid penetration and disintegration, effect of microcrystalline cellulose □ Excipients, tablet—microcrystalline cellulose, effect on liquid penetration and disintegration of directly compressed tablets

Cellulose was prepared previously in a microcrystalline form having unique properties as a directly compressible tablet vehicle (1). Its disintegration behavior was attributed (2, 3) to the entrance of water into the tablet matrix by capillary forces and subsequent breaking of hydrogen bonds. The hypothesis that hydrogen bonds determine both mechanical strength and disintegration of microcrystalline cellulose tablets was confirmed using a deuterium exchange technique (4).

BACKGROUND

Microcrystalline cellulose was suggested to be useful as a disintegrating agent when used in a proportion of at least 20% (5). One study (6) found that the disintegration properties of microcrystalline cellulose were extremely pressure dependent, and the material was relatively ineffective as a disintegration agent in insoluble, direct compression systems. Microcrystalline cellulose appeared, however, to be a useful complementary disintegrant. The disintegration time of tablets of a cation-exchange resin was reduced significantly in the presence of microcrystalline cellulose (6).

A similar synergistic effect was also reported (7). Tablets containing microcrystalline cellulose and corn starch showed a shorter disintegration time than those containing the disintegrating agent alone. It was suggested that microcrystalline cellulose accelerated water penetration and, thus, swelling of the corn starch.

The penetration rate of a liquid into a porous structure is dependent on the balance between capillary and opposing viscous forces and is given by:

$$L^2 = \frac{2m\,\gamma\cos\theta}{k_0\eta}\,t \qquad \text{(Eq. 1)}$$

where L is the penetrated length at time t, m is the hydraulic pore radius, γ is the surface tension of the liquid, θ is the contact angle between liquid and solid, η is the liquid viscosity, and k_0 is a constant dependent on pore shape. If the total cross-sectional area of the pores does not vary with

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