

STUDY ON THE SYNTHESIS OF POLYSTYRENE-SUPPORTED MACROCYCLIC MERCAPTAL CHELATING RESIN AND ITS PROPERTIES*

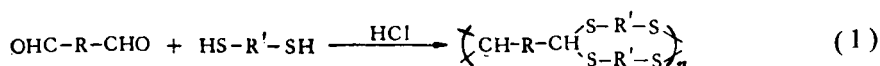
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ABSTRACT

Chelating resin with macrocyclic mercaptal group supported on macroporous polystyrene beads was synthesized, which showed good selectivity to Hg^{2+} : its complexing capacity amounted to 30—60 mg Hg^{2+} /g resin, two orders of magnitude greater than for other metal ions such as Ca^{2+} , Zn^{2+} , Cd^{2+} , Pb^{2+} etc. This resin could restore the activity of urease which had been deactivated by poisoning with Hg^{2+} . Its restoring power was far better than that of the mercapto-resin and common anionic exchange resins. It showed some promising use as an oral polymeric detoxifying drug for mercury poisoning.

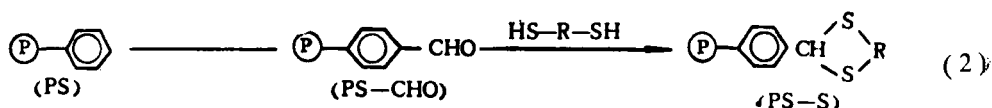
Chelating resins with macrocyclic mercaptal group synthesized so far were products of polycondensation of dialdehydes with di- or tetra-thiol compounds^[1, 2]:



Such resins showed good selectivity to Hg^{2+} and CH_3Hg^+ ions, their complexing capacity being two orders of magnitude higher than that for Ca^{2+} , Mg^{2+} , Zn^{2+} , Cd^{2+} and other metallic ions. They might be used as an oral antidote against mercury poisoning by cutting off the entero-hepatic circulation of mercury in body and excreting mercury through feces. At the same time there were much less harmful side reactions in the chelation and excretion of other metallic ions useful for the body as often happened when mercapto drugs (BAL etc.) were used for the excretion of mercury. The complexing capacity of such resins, however, was limited to 2—6 mg Hg^{2+} /g resin since highly crosslinked resins did not swell in aqueous media and thus had very low specific surface area.

In this work we have synthesized a new chelating resin with macrocyclic mercaptal group attached to a macroporous polystyrene resin support (abbreviated as PS-S) with a complexing capacity of 30—60 mg Hg^{2+} /g resin.

The synthetic route to PS-S proceeded via the following scheme:



The complexing properties of PS-S were studied in some detail and its detoxifying ability for Hg-poisoned urease (mercapto-group containing enzyme) was studied in vitro.

EXPERIMENTAL

1. Synthesis of formylated polystyrene resin (PS-CHO)

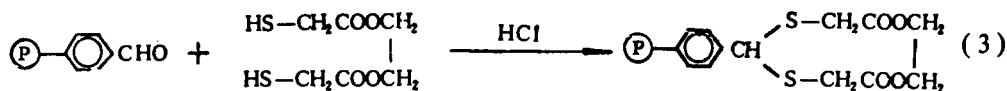
(1) Direct formylation of PS resin^[3]

A mixture of 1.0 g PS resin beads, 2.0 g hexamethylenetetramine and 10 ml of trifluoroacetic acid was reacted at 90°C in nitrogen atmosphere for 24 hrs. After successive washing by water, dioxane, acetone and ethanol, the beads were collected and vacuum dried overnight at 50°C.

(2) Oxidation of chloromethylated PS-resin by dimethylsulfoxide^[4, 5]

Chloromethylated PS resin 4.5 g was stirred with 1.9 g NaHCO₃ in 30 ml DMSO at 155°C for 6 hrs. The beads were collected and washed with DMSO, hot water, dioxane/water (2:1), dioxane, acetone, ethanol, chloroform and benzene successively, and then vacuum dried at 100°C overnight.

2. Synthesis of chelating resin with macrocyclic mercaptal group linked to polystyrene resin support (PS-S)—Mercaptalation of PS-CHO



A mixture of 0.5 g PS-CHO, 1 ml ethylene glycol dithioglycolate^[1] or other thioglycolates and 2 ml conc. HCl was stirred at room temperature for 3 hrs and stood overnight. The resin beads were washed by water until neutral, then further washed by ethanol and acetone. After extraction with absolute alcohol for 48 hrs they were vacuum dried at 50°C overnight.

3. Analysis

The aldehyde group of PS-CHO was analyzed by determining the nitrogen content of its reaction product with hydroxylamine hydrochloride^[6]. The content of CHO group is calculated from the N content of its oxime.

The content of macrocyclic mercaptal group was determined by analysis of sulfur.

Static method for the determination of complexing capacity. PS-S resin 15—50 mg and 10 ml HgCl₂ solution (0.1 mg Hg²⁺/ml) were shaken for 1 hrs and residual Hg²⁺ in solution was determined by a F-732 mercurimeter. In the static method the complexing capacity of resin is dependent upon the amount of resin used, and so the same amount of resin must be used for a given set of experiments.

Dynamic method for the determination of complexing capacity. PS-S resin beads were packed in a small column and HgCl₂ solution was allowed to pass through the column. The elutes were collected and analyzed for Hg²⁺ concentration and the complexing capacity was calculated.

RESULTS AND DISCUSSION

1. *Formylation of PS resin of different structure*

A comparison of the IR spectra of formylated product of gel-type and macroporous PS resin (Fig. 1) showed that the latter can be formylated directly by hexamethylenetetramine in trifluoroacetic acid (characteristic absorption of aldehyde group at 1680 cm^{-1}) to an aldehyde content of 0.70 milliequivalent per gram resin, while for gel-type PS resin the direct formylation was ineffective. After chloromethylation and oxidation with DMSO in the usual way, the aldehyde content was analyzed to be 0.79 milliequivalent per gram.

2. *Mercaptallation of model compound*

Benzaldehyde was reacted with ethylene glycol dithioglycolate in the presence of conc. HCl as catalyst for mercaptallation. IR spectra of reaction product showed very weak absorption at 2560 cm^{-1} (characteristic for —SH group) and in the mass spectra of reaction product there existed a weak M/E 506 peak but very strong M/E 296 peak. Hence the main reaction product must be the cyclic mercaptal;

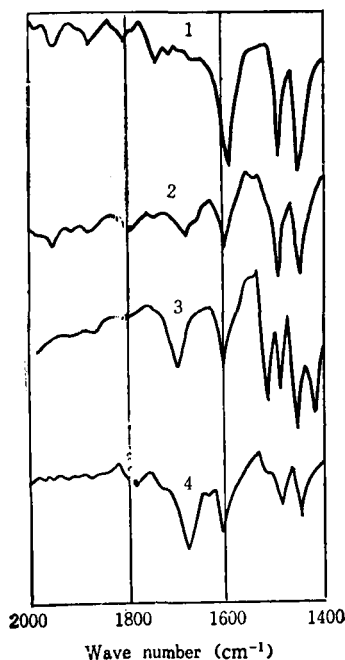


Fig. 1 Comparison of IR spectra of formylated PS resins (PS-CHO) obtained from different PS resins

1. Gel-type PS, DVB 6% direct method;
2. Gel-type PS, DVB 2% direct method;
3. Gel-type PS, DVB 6% formylated by DMSO method;
4. Macroporous PS, direct method.

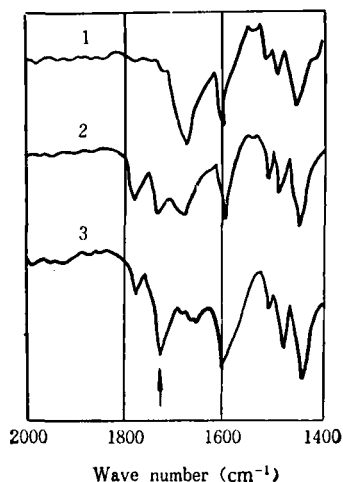
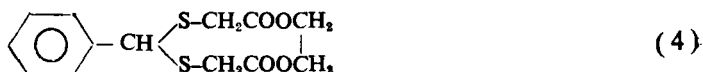
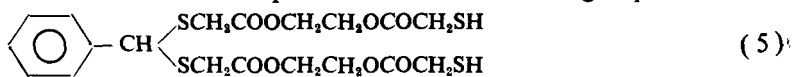


Fig. 2 IR spectra of mercaptallated product of PS-CHO resin

1. Formylated PS resin;
2. Product of mercaptallation in absence of HCl;
3. Product of mercaptallation in presence of HCl.



together with a small amount of disubstituted product with terminal SH groups



(2) Mercaptalation of PS-CHO

A comparison of IR spectra of formylated macroporous PS resin with that of its product of mercaptalation in the presence of HCl (Fig. 2) showed the disappearance of CHO peak and formation of a new ester peak (shown by $\uparrow$). From the IR spectra it could be seen that the mercaptalation process was incomplete in the absence of HCl.

We have used four samples of macroporous PS resin of different specific surface area and pore size and also two samples of gel-type PS resin of different DVB content. After formylation by two different methods and mercaptalation of the aldehyde group with ethyleneglycol-dithioglycolate PS-S resins were obtained. Their specifications and complexing capacity for Hg^{2+} determined by both static and dynamic methods were summarized in Table 1.

Table 1 Comparison of complexing capacity of PS-S resins obtained from different PS resin support by different methods

Type of resin	DVB (%)	Specific surface area (m^2/g)	Av. pore diameter ($\text{\AA}$)	Method of formylation	S content of resin (%)	Complexing capacity ($\text{mgHg}^{2+}/\text{g}$)	
						Static method*	Dynamic method
Macro-porous	40	10—20	2000—4000	Direct method	5.67	38.7	55.6
	40	40—50	1500—2000	Direct method	3.70	48.7	
	40	100	100—1000	Direct method	2.60	64.9	
	40	350—380	50—100	Direct method	3.50	45.4	
Gel-type	2	0.1	Rare network	Direct method	1.05	0	0.73
	6	0.1	Dense network	Direct method	0.20	0	0
	6	0.1	Dense network	DMSO method	5.66	1.7	8.0

* Determined by shaking 15 mg PS-S resin with HgCl_2 solution (0.1 mg Hg^{2+}/ml) for 1 h.

The complexing capacity of PS-S resin from macroporous PS was far greater than that from gel-type PS resin. The macroporous PS-S resin had its optimum capacity when the surface area was about $100 \text{ m}^2/\text{g}$. It seemed reasonable that a greater surface area may adsorb more metal ions, but too large a surface area made the pore size too small for metal ions in solution to penetrate into the depth of the pores.

(3) Comparison of PS-S resins obtained by mercaptalation with different mercapto compounds.

PS-CHO resin was allowed to react separately with five different mercapto compounds to form macrocyclic mercaptal of different size as well as noncyclic mercaptals. Comparison of their complexing capacity for Hg^{2+} (see Table 2) indicated that there was no marked

difference for macrocyclic mercaptals of different ring size, which is in accord with the data obtained in the case of polycondensation type resins^[2]. In Table 2 the capacity of condensation type macrocyclic mercaptal chelating resin was also included for comparison, it was much lower at a much higher sulfur content, i.e., the complexing sites —S— in PS-S resin are utilized much more efficiently than in condensation type resin.

Table 2 Complexing capacity of PS-S resins from different mercapto compounds

Mercapto compounds	S content of PS-S resin (%)	Complexing capacity (mgHg ²⁺ /g)	
		Static method	Dynamic method
Thioglycolic acid	2.64	31.6	68.6
Ethyl thioglycolate		25.8	69.0
Ethylene glycol dithioglycolate	5.67	29.6	55.6
Butylene glycol dithioglycolate	4.40	31.6	70.2
Pentaerythritol tetrathioglycolate	5.78	30.8	156.0
Ethyl mercaptan	2.18	27.6	
Condensation product of terephthaldehyde and pentaerythritol tetrathioglycolate	28	2.5	17.0

3. Complexing properties of macroporous PS-S resin

Dynamic complexing property of PS-S resin to Hg²⁺ and the elution curve of adsorbed Hg²⁺ were shown in Fig. 3. Adsorption of Hg²⁺ on PS-S resin was so firm that it could be eluted only with rather concentrated HCl (HCl/H₂O=9:2). The complexing capacity of PS-S resin appeared not changed after ten cycles of complexation and acid washing, this indicated the excellent stability of PS-S resin.

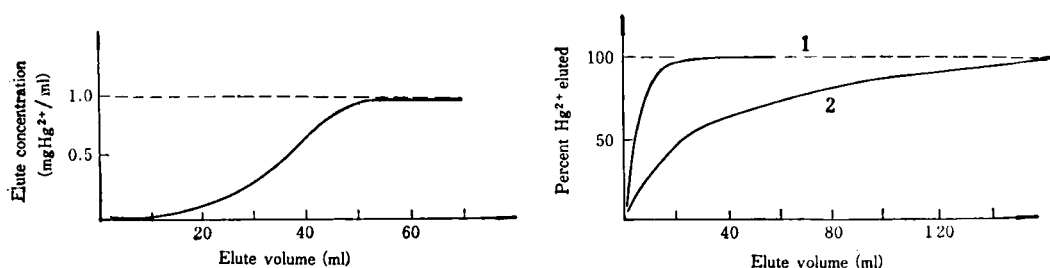


Fig. 3 Dynamic complexation of Hg²⁺ to PS-S resin
Left: complexation onto PS-S column; Right: Hg²⁺ eluted from PS-S column.
1. 9:2 HCl/H₂O; 2. 4N HCl.

Determination of complexing capacity at different pH values showed a somewhat higher value in neutral conditions.

“Blank” experiment indicated that macroporous PS resin and PS-CHO resin showed no complexing ability with Hg²⁺. Macroporous PS resin was also stirred with thioglycolate in the absence of HCl and then the thioglycolate was washed out with a suitable solvent. The

reclaimed resin beads also showed no complexing ability to Hg^{2+} . Thus it might be concluded that the complexing ability of macroporous PS-S resin did not come from physical adsorption or from SH-containing compound possibly adsorbed in the resin pores.

Table 3 Complexing capacity of PS-S resin to various metallic ions

Metallic ion	Complexing capacity (mg/g)		Complexing capacity of condensation type mercaptal resin (mg/g)
	Static	Dynamic	
Pb^{2+}	0.13	0.08	0.16—2.40
Co^{2+}	0.89	0.62	—
Cd^{2+}	0.38		0.04—0.60
Zn^{2+}	0.05		
Ca^{2+}	0.01		0.02—0.05
Hg^{2+}	31.6	68.0	0.50—6.20

From the data in Table 3 it is obvious that macroporous PS-S resin possesses a specific selective complexing property to Hg^{2+} ion.

4. Experiments on the detoxifying power of PS-S resin for urease poisoned by Hg^{2+}

One of the main mechanisms of mercury poisoning in animal body is the deactivation of SH-containing enzymes by reacting with Hg^{2+} . Combination of the mercuric ion with SH side groups in protein is usually connected with other mercury poisoning mechanisms. Detoxifying drugs with stronger restoring power for recovery of SH-containing enzyme activity, which had been Hg-poisoned, can also eliminate Hg from proteinic SH-group more efficiently.

We have selected Hg-poisoned urease for study of detoxifying ability of PS-S resin *in vitro*^[7]. Urease is easily obtained from soybeans by extraction and can decompose urea to

Table 4 Activity restoring ability of different complexing resins for Hg-poisoned urease

Complexing resin	Complexing capacity (mg Hg^{2+} /g)	Percent urease activity restored
Macroporous PS-S resin	32	100
Cation resin (sulfonate type)	200	7.8
Anion resin (quaternary ammonium type)	190	0.0
Mercapto cotton	33	75.0
Mercapto resin (Nankai Univ.)	35	5.2
Sumichelate Q-10R	34	0.0
Gel type PS-S resin	1.7	0.0

ammonia specifically. Thus its activity is determined by the ammoniacal method^[8].

Suitable amount of HgCl_2 solution was added dropwise into the urease solutions until the latter were just deactivated completely. Then various complexing agents were added separately and the corresponding percentage of restoration of activity of urease was determined. In Table 4 the activity-restoring power for Hg-poisoned urease of different complexing resins was compared on an equal-weight basis. It could be seen that macroporous PS-S resin showed the most powerful detoxifying ability. It seemed that the coordination power of mercaptal S atom is somewhat higher than that of S atom in mercapto group. It is interesting to point out that the resin from macroporous PS of large surface area ($380 \text{ m}^2/\text{g}$) but small pore size detoxified poisoned urease less effectively (71 %); this phenomenon could easily be comprehended as the dimension of urease molecule is so large that it can penetrate into small pores only with difficulty.

Detoxifying efficiency in dependence of amount of PS-S resin used is shown in Fig. 4.

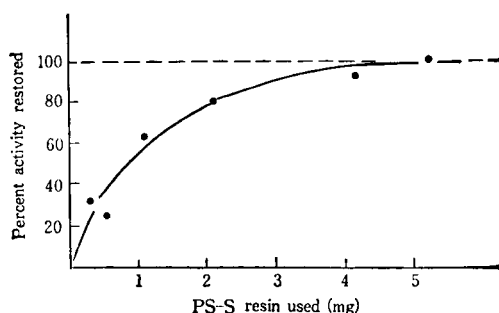


Fig. 4 Restoration of activity of urease with different amount of PS-S resin
(Urease solution: 10 ml; Hg^{2+} added: $20 \mu\text{g}$)

CONCLUSION

Macroporous polystyrene resin when used as support for macrocyclic mercaptal chelating resin has raised its complexing capacity for Hg^{2+} to a level suitable for practical usage. Its high detoxifying power for Hg poisoned urease suggests its possible use as an oral mercury excretion drug.

On the basis of this work we have synthesized further a macrocyclic mercaptal chelating resin supported on a water-soluble polymer and studied its toxicity, detoxifying power, its metabolism in animal body and mercury excretion ability. Results obtained showed the latent possibility of such polymeric mercaptal as an oral mercury excretion drug with very little side reactions, which will be reported elsewhere^[9].

Acknowledgement Macroporous polystyrene resins used in this work were kindly provided by Prof. Shen Jiacong and Bian Fenglan of the Chemistry Department of Jilin University, to whom the authors are very grateful.

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