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Organic Reactions Catalyzed by Copper-Loaded Polymers. Reactivity vs Polymer Structure

F. M. Menger* and T. Tsuno

Contribution from the Department of Chemistry, Emory University, Atlanta, Georgia 30322.
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Abstract: Four types of polymers were constructed: P-M, P-M-H$_1$, P-H$_2$-M, and P-H$_2$-M-H$_1$, where P = polystyrene, M = metal (Cu^{2+}), and H = hydrocarbon chain (H$_1$ = 14 carbons and H$_2$ = six carbons). Thus, P-M is devoid of an aliphatic hydrocarbon, whereas P-M-H$_1$ has a metal interposed between the polymer and a long hydrocarbon chain. With both, however, the metal resides near the polymer backbone. In contrast, P-H$_2$-M and P-H$_2$-M-H$_1$ have a six-carbon spacer separating the metal and polymer. The latter also possesses a 14-carbon outer chain, so that the copper is situated between two hydrocarbon regions. Of the four polymeric types, P-H$_1$-M was found to be the most active in catalyzing the hydrolysis of nerve-agent simulants. Thus, 4-nitrophenyl diphenyl phosphate is rapidly hydrolyzed ($t_{1/2}$ = 2.7 min) with 1.0 mM polymer-bound Cu^{2+} at pH = 8.0 (25.0 °C). The reactions display saturation kinetics and operate via a turnover mechanism. In addition to the rate studies, six synthetically useful copper-promoted reactions (including a Diels–Alder cyclization, an epoxide opening, and an aryl iodide hydrolysis) were examined. Five of these manifest higher yields and shorter reaction times with the metallopolymer as opposed to an equivalent amount of conventional copper salt. Easy reaction workup is another virtue of the polymer-catalyzed processes.

Chemical-warfare agents, such as nerve gas and mustard, owe their potency to a high reactivity toward nucleophiles in body tissues. Consequently, any strategy for chemical defense against these loathsome materials requires the development of compounds for which the agents have an even greater affinity. Notable progress along these lines has appeared recently from the laboratories of Moss and ourselves.[1,2] Moss found that iodosobenzoates destroy phosphorus(V) compounds related to nerve agents.[1] We, on the other hand, exploited "metallomicelles" to inactivate the deadly neurotoxins.[2] Turnover mechanisms with 10^5–10^6 rate enhancements were achieved. The present article is dedicated to rendering nerve agents and their simulants impotent via hydrolyses catalyzed by copper-loaded polymers. Rate studies revealed how the surfaces of the new "metallopolymer" systems interact with small molecules. In addition, the polymers were examined for their ability to promote six synthetically useful organic reactions.[3]

Four types of polymers were constructed (Figure 1): P-M, P-M-H$_1$, P-H$_2$-M, and P-H$_2$-M-H$_1$, where P = polystyrene, M = metal (Cu^{2+}), and H = hydrocarbon chain (H$_1$ = 14 carbons, and H$_2$ = six carbons). Thus, P-M is devoid of hydrocarbon, whereas P-M-H$_1$ has a metal interposed between the polymer surface and a long hydrocarbon chain. With both polymers, however, the metal resides near the polymer backbone. In contrast, P-H$_2$-M and P-H$_2$-M-H$_1$ have a six-carbon spacer separating the metal and polymer. The latter also possesses a 14-carbon outer chain, so that the metal is situated between two hydrocarbon regions.

The polymers were implanted with copper owing to the known ability of this metal to catalyze the hydrolysis of phosphorus(V) compounds.[4] There was, of course, also good reason for incorporating hydrocarbon tails into the polymers. If one is to achieve a high level of catalysis, substrates must bind to the polymer prior to the actual chemistry. Contiguous hydrocarbon tails can provide a means for attracting hydrophobic substrates to the polymer surfaces similar to the action of surfactant chains in micelles. This is not speculation. Many years ago, Cordes et al.[5] showed that small organic molecules bind hydrophobically to poly-4-vinylpyridine quaternized with dodecyl bromide (a "polysoap"). No one has, however, yet investigated the catalytic consequences of embedding Cu^{2+} within nonpolar regions of polymer surfaces.

The catalytic activity of the polymer systems was tested with two substrates: 4-nitrophenyl isopropylphenylphosphinate (I) and 4-nitrophenyl diphenyl phosphate (II). These compounds were selected because: (a) They are easily handled "simulants" of the more relevant but also more toxic nerve agents such as GD. (b) Considerable work, including our metallomicelle experiments,[2] has been carried out on the substrates, so that there exists a large body of data with which to judge the efficacy of the polymeric catalysts.[6] (c) The hydrolysis of the substrates, in contrast to GD, can be monitored spectrophotometrically. (d) Since the

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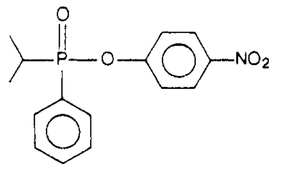

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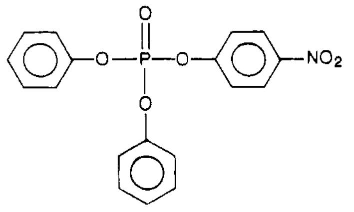

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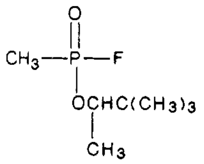


GD

substrates are *less* reactive than GD and other nerve agents, any catalyst that manages to destroy the former will likely be generally effective.

Experimental Section

Synthesis of Polymers. Copper-loaded polymers were prepared by the routes in Scheme I. Specifics are given below; these are followed by information on polymer characterization. "Low" and "high" refer to relative loadings of copper.

P-M(low). Butyllithium (1.3 mL, 1.6 M in hexane, 2.0 mmol) was added slowly with stirring at -5 °C to *N,N,N'*-trimethylethylenediamine (0.21 g in 5 mL of THF, 2.0 mmol). Chloromethylated polystyrene (0.50 g of Bio-Rad Bio-Beads S-X1 resin, 1.33 mequiv/g, 200–400 mesh) that had been swelled in 10 mL of anhydrous THF for 1 h was then added to the diamine solution and kept at about -15 °C for 6 h. The progress of the reaction was monitored via the disappearance of the C–Cl IR band near 705 cm^{-1}. Upon completion of the reaction, the mixture was poured into 30 mL of methanol after which the resin beads were isolated by filtration and washed repeatedly with THF–methanol in an ultrasonic bath. Light yellow beads (0.49 g, 90%) were obtained after 24 h of drying under reduced pressure. The product contained no chlorine according to elemental analysis. The beads (0.25 g swelled in 10 mL of THF for 1 h) were mixed with $\mathrm{CuCl_2}$ (0.07 g, 0.52 mmol in 2 mL of ethanol) with stirring. After 1 h the resin was isolated by filtration, washed with THF/ethanol (ultrasonication), and dried in vacuo for 1 day to produce beautiful green beads (0.28 g, 94% yield).

P-M(high). The preparation of heavily loaded P-M was carried out as just described but with the following modifications: butyllithium (1.6 M, 7.8 mL, 12.4 mmol); *N,N,N'*-trimethylethylenediamine (1.3 g, 12.4 mmol); resin (1.0 g, Bio-Rad, 4.15 mequiv/g, 200–400 mesh); reaction conditions, −15 °C for 6 h. Formation of the copper complex utilized $\mathrm{CuCl_2}$ (0.54 g, 4.0 mmol) and aminated resin (0.50 g); reaction conditions, 22 °C, 1 h (81% overall yield).

***N,N'*-Dimethyl-*N'*-tetradecylethylenediamine (DTEDA).** *N,N'*-Dimethylethylenediamine (10.0 g, 0.113 mol) and 1-bromotetradecane (21.0 g, 0.076 mol) in 40 mL of ethanol were boiled under reflux for 5 min. An aqueous solution of NaOH (3.5 g in 5 mL) was added slowly, and the mixture was further refluxed for 5 h (while periodically monitoring the disappearance of the alkyl bromide by TLC). Most of the solvent was removed under reduced pressure, and the residue was shaken with 100 mL of water and 50 × 3 mL of ethyl acetate. The organic layers were collected, washed with 100 mL of dilute aqueous carbonate and dried over sodium sulfate overnight. A yellow oil (17 g) was produced when the solvent was removed with a rotary evaporator (60 °C). The desired product was isolated from this oil via a vacuum distillation (130–133 °C at 0.2 mmHg) with a 11.0 g (51%) yield and with the correct spectral parameters. Anal. Calcd for $\mathrm{C_{18}H_{40}N_2}$: C, 75.98; H, 14.17; N, 9.85. Found, C, 76.03; H, 14.09; N, 9.77.

P-M-H$_1$(low). This copper polymer was prepared by the procedure given for *P-M*(low) except for the following details: DTEDA (1.3 g, 4.7 mmol); butyllithium (2.9 mL, 1.6 M in hexane, 4.7 mmol); resin suspension (0.70 g of Bio-Rad resin, 1.33 mequiv/g, 200–400 mesh in 15 mL of THF); reaction conditions, -5 °C, 10 h. Formation of the copper complex utilized $\mathrm{CuCl_2}$ (0.30 g, 2.2 mmol in 3 mL of ethanol) and aminated resin (0.61 g, 0.61 mmol, 15 mL of THF); reaction conditions, 22 °C, 1 h; overall yield = 87%.

P-M-H$_1$(high). Prepared as described for the low-copper analogue except for the use of 4.15 mequiv/g of Bio-Rad chloromethylated polystyrene.

***N,N,N'*-Trimethyl-*N'*-(6-hydroxyhexyl)ethylenediamine (THEDA).** Butyllithium (24 mL, 2.5 M in hexane, 60 mmol) was added slowly with stirring to an ice-cooled solution of *N,N,N'*-trimethylethylenediamine (5.8 g, 57 mmol) in 50 mL of THF. This was followed by addition of 1-bromohexanol (9.1 g, 50 mmol) and by continued stirring for 3 h. The reaction mixture (no doubt containing alkoxide) was then concentrated under reduced pressure, shaken with 100 mL of water and 50 × 4 mL of 1-butanol. A yellow oil was formed upon removal of the combined organic layers which was distilled (110–115 °C, 0.3 mmHg) to give 4.7 g (46%) of product with correct spectral properties. Anal. Calcd for $\mathrm{C_{11}H_{26}N_2O}$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.23; H, 12.91; N, 13.60.

***N,N'*-Dimethyl-*N*-(6-hydroxyhexyl)-*N'*-tetradecylethylenediamine (DHTEDA).** Butyllithium (4.0 mL 2.5 M in hexane, 10 mmol) was added to DTEDA (2.0 g, 7.0 mmol) in 15 mL of stirred THF at 0 °C. 1-Bromohexanol (2.2 g, 12 mmol) was then added and the reaction allowed to run for 2 h (TLC monitoring). Thereupon, the reaction mixture was shaken with 100 mL of water and 50 × 3 mL of ethyl acetate. The organic layers were combined, washed with water, dried over sodium sulfate, and the solvent removed and replaced with ether. When HCl gas was bubbled through the ether at 0 °C, hydrochloride salt precipitated and was collected by filtration. Free amine was liberated with aqueous base, producing an oil that solidified on standing. This was crystallized in ether–methanol to give 1.6 g (60%) of a white powder, mp 31.0–32.5 °C, with the expected spectral properties. Anal. Calcd for $\mathrm{C_{24}H_{52}N_2O}$: C, 74.93; H, 13.62; N, 7.28. Found: C, 74.68; H, 13.56; N, 7.25.

P-H$_2$-M(high). Sodium hydride (0.11 g, 80%, 3.8 mmol) was added to THEDA (1.6 g, 7.9 mmol) in 2 mL of anhydrous THF, and the mixture was boiled under reflux with vigorous stirring. After 30 min, 10 mL of THF was added to the slurry and the mixture was further refluxed for 30 min. High-loading type chloromethylated polystryrene (0.20 g, Bio-Rad, 4.15 mequiv/g, 200–400 mesh that had been pretreated with 15 mL of THF for 1 h to induce swelling) was then added, whereupon the mixture was heated to reflux for 10 h (IR monitoring). Resin beads were then filtered, washed, and dried as before to give 0.25 g of product. Copper complexation was carried out as already described for the other polymers.

P-H$_2$-M-H$_1$ (high). The preparation was carried out as given for P-H$_2$-M(high) but with the following changes: DHTEDA (1.6 g, 4.2

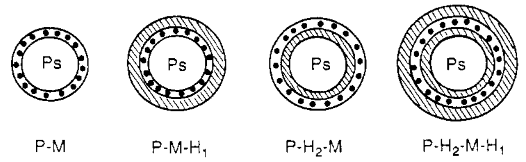


Figure 1. Representations of the four polymer types investigated where Ps = polystyrene beads, heavy dots = Cu^{2+}, and shaded areas = hydrocarbon. The highly schematic diagrams obscure the high porosity of the polymer and the roughness of the polymer surface; the core-shell morphology is, therefore, for illustration purposes only.

Scheme I

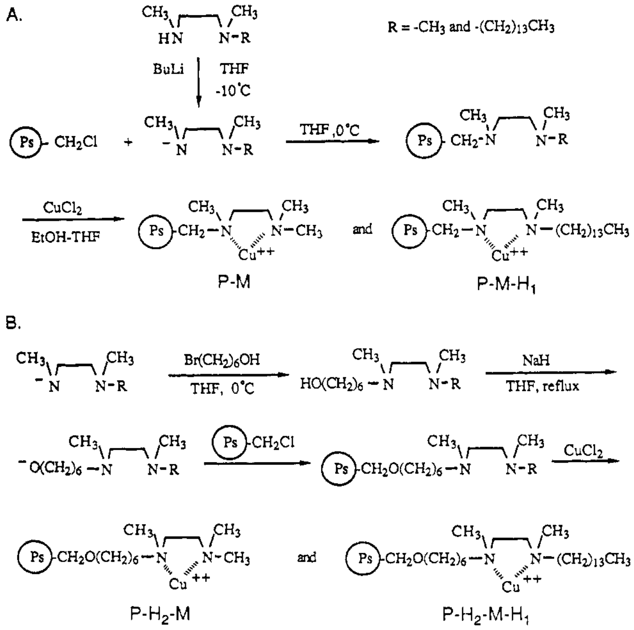


Table I. Fraction *m* of Monomeric Units Bearing a Cu^{2+}

polymer[a]	H_1	H_2	*m*
P-M(low)			0.15
P-M(high)			0.55
P-M-H_1(low)	$(CH_2)_{13}CH_3$		0.15
P-M-H_1(high)	$(CH_2)_{13}CH_3$		0.55
P-H_2-M(high)		$(CH_2)_6$	0.40
P-H_2-M-H_1(high)	$(CH_2)_{13}CH_3$	$(CH_2)_6$	0.33

[a] See Scheme I for the structures of the polymeric types.

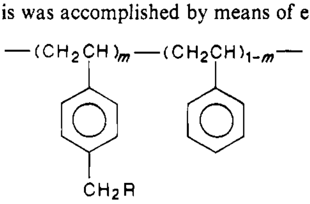
Table II. Calculated[a] and Experimental Elemental Analyses of Copper-Loaded Polymers

polymer		calcd	found	polymer		calcd	found
P-M(low)	C	75.74	75.60	P-M-H_1(high)	C	64.95	64.77
	H	7.20	7.32		H	8.86	8.90
	N	2.94	2.77		N	4.52	4.53
	Cl	7.45	7.55		Cl	11.43	11.44
P-M(high)	C	56.34	56.11	P-H_2-M(high)	C	63.29	63.51
	H	6.57	6.89		H	7.67	7.99
	N	6.40	6.34		N	4.56	4.58
	Cl	16.19	15.99		Cl	11.54	11.71
P-M-H_1(low)	C	77.32	77.58	P-H_2-M-H_1(high)	C	70.56	71.12
	H	8.35	8.29		H	9.11	8.85
	N	2.47	2.24		N	3.19	3.21
	Cl	6.25	6.41		Cl	8.08	8.08

[a] Based on *m* values in Table I (see the text) and two chlorine ligands per copper.

mmol); sodium hydride (0.075 g, 80%, 2.5 mmol in 3 mL of anhydrous THF); resin (0.20 g of Bio-Rad, 4.15 mequiv/g, 200–400 mesh).

Polymer Characterization. The objective was to determine *m*, the fraction of monomeric units within the polystyrene bearing a metallosubstituent R. This was accomplished by means of elemental analyses on the ethylenediamine containing beads with and without copper complexation. Since the latter showed no residual chlorine from unreacted chloromethyl groups, it was assumed for calculation purposes that aromatic substituents either contained an ethylenediamine or else had been converted reductively into methyl groups. Values of *m* are given in Table I. Table II lists the calculated elemental analysis based on these *m* values along with the observed percentages.



4-Nitrophenyl Diphenyl Phosphate (NPDPP). This substrate, prepared according to a literature procedure,[2] melted at 48–49 °C lit.[11] mp 49–51 °C). Anal. Calcd for $C_{18}H_{14}NO_6P$: C, 58.23; H, 3.80; N, 3.77. Found: C, 58.29; H, 3.84; N, 3.75.

4-Nitrophenyl Isopropylphenylphosphinate (NPIPP). The phosphinate ester was kindly supplied by Dr. Dupont Durst of the U.S. Army Chemical Research, Development and Engineering Center.

Kinetics. The following kinetic run is typical of that used throughout. A 1.00-cm cuvette, containing 3.00 mL of 0.05 M *N*-ethylmorpholine buffer (pH = 8.00)[2] and 1.32 mg of P-M(high) (corresponding to 1.00 mM Cu^{2+} if the polymer had dissolved), was stoppered and placed for 1 h in a thermostated bath (25 ± 0.3 °C) seated on a magnetic stirrer. The reaction was initiated by adding 20 μL of 7.50 mM NPIPP dissolved in spectral-grade acetonitrile and by stirring by means of a microbar at the bottom of the cuvette. After 30 min, the stirring was stopped and the polymer was allowed to settle (40–50 s). The UV spectrum was then secured with a Varian DMS 200 UV spectrophotometer. Next the cuvette was returned to the bath and the stirring was resumed for additional 30-min time segments. The decrease in NPIPP (λ = 275 nm) or the increase in 4-nitrophenyl (λ = 400 nm) obeyed the first-order rate equation for 3 half-lives and was used, along with the infinity absorbance, to calculate the rate constants reported herein. A sharp isosbestic point at λ = 335 nm showed the reaction was well-behaved. Reactions ceased when the polymer was separated from the aqueous solution; thus, desorbed Cu^{2+} was not the source of catalysis.

In the case of faster reactions, it was necessary to prepare several cuvettes for a single rate determination. Periodically (e.g. every minute) the contents of one cuvette were rapidly membrane-filtered, and the absorbance of the resulting filtrate was determined to provide, after the usual workup, the required rate constants. Kinetic runs were always run in triplicate to give a reproducibility of ±5%.

Table III. Observed Rate Constants for NPIPP and NPDPP[a] Hydrolysis in Aqueous Buffer at 25 °C[b]

run	substrate	polymer	$10^3 k_{obs}$, s^{-1}	$t_{1/2}$, min
1	NPIPP	None	0.0005	23000
2	NPIPP	P-M(low)	0.002	5500
3	NPIPP	P-M(high)	0.096	120
4	NPIPP	P-M-H_1(low)	0.001	12000
5	NPIPP	P-M-H_1(high)	0.005	2300
6	NPIPP	P-H_2-M(high)	0.73	16
7	NPIPP	P-H_2-M-H_1(high)	0.11	100
8	NPDPP	None	0.012	950
9	NPDPP	P-M(high)	0.42	25
10	NPDPP	P-H_2-M(high)	4.3	2.7
11	NPDPP	P-H_2-M-H_1(high)	2.7	4.3

[a] NPIPP and NPDPP are 4-nitrophenyl isopropylphenylphosphinate and 4-nitrophenyl diphenyl phosphate, respectively (see the text). [b] Substrate concentration = 5.0×10^{-5} M. Polymer weights = 1–3 mg (corresponding to 1.0 mM Cu^{2+} were the polymer soluble). All runs were carried out in 3.00 mL of 0.05 M *N*-ethylmorpholine buffer (pH = 8.00). NPDPP runs contained 10% dioxane (v/v) to assist in the solubilization of the substrate.

Table IV. Pseudo-First-Order Rate Constants for the Hydrolysis of NPDPP at Several "Concentrations" of P-H_2-M(high)[a]

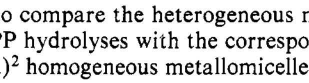
[resin],[b] mM	$10^3 k_{obs}$, s^{-1}	$t_{1/2}$, min	[resin],[b] mM	$10^3 k_{obs}$, s^{-1}	$t_{1/2}$, min
0.55	2.4	4.8	4.00	12.5	0.9
1.00	4.3	2.7	8.00	18.0	0.6
2.00	7.5	1.5	12.00	21.7	0.5

[a] [NPDPP] = 5.0×10^{-5} M. Runs were carried out in 3.00 mL of 0.05 M *N*-ethylmorpholine buffer containing 10% dioxane (v/v) at 25.0 °C. [b] Concentrations represent [Cu^{2+}] that would exist in the buffer if the polymer dissolved. A "concentration" of 1.00 mM represents 1.8 mg of polymer beads.

Results and Discussion

A. Reactions of Phosphorus(V) Compounds. Observed rate constants for the hydrolysis of NPIPP and NPDPP catalyzed by several polymer types are presented in Table III. All polymeric variations are seen to accelerate the hydrolyses of the substrates. For example, hydrolysis of NPIPP proceeds 1460 times faster in the presence of P-H_2-M(high) than in the absence of polymer (run 6 vs 1). (This value increased to 12000 when the reactions were run at pH = 6.0 rather than at the standard pH = 8.0.) The above accelerations refer to only 1–3 mg polymer catalyst per 3.00 mL of reaction solution (corresponding to 1.00 mM Cu^{2+} had the polymer been able to dissolve in the aqueous buffer). Additional polymer further enhances the acceleration (see below). Importantly, run 10, where P-H_2-M(high) destroys NPDPP in 2.7 min, meets the famous McKay criterion for a useful nerve-agent decontaminant: "destruction within a cigarette break".[7] Since NPDPP is deactivated so rapidly and since (as already mentioned) NPDPP is inherently *less* reactive than the agents themselves, P-H_2-M(high) would seem to have potential for practical applications.

It is difficult to compare the heterogeneous metallopolymer-catalyzed NPDPP hydrolyses with the corresponding (and previously published)[2] homogeneous metallomicelle-catalyzed reactions. If the P-H_2-M(high) in run 10 were assumed to dissolve completely in the pH = 8 buffer (25.0 °C), then the resulting Cu^{2+} concentration would be equivalent to that provided by 1.0 mM micellized copper surfactant (III). Under such circumstances,



III

the latter generates a 12-fold greater rate enhancement. Thus,

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[7] This is a frequently voiced but (to our knowledge) unpublished doctrine in circles concerned with nerve-agent decontamination.

Table V. Pseudo-First-Order Rate Constants for NPIPP Hydrolysis at Various pH Values in Aqueous Buffer at 25 °C[a]

pH	resin	$10^4 k_{obs}$, s^{-1}	$t_{1/2}$, min
6.02	P-M(high)	0.41	280
7.00	P-M(high)	0.62	190
7.50	P-M(high)	0.74	160
8.00	P-M(high)	0.96	120
8.50	P-M(high)	1.04	110
6.05	$P\text{-}H_2\text{-}M$(high)	5.32	22
7.00	$P\text{-}H_2\text{-}M$(high)	6.25	19
8.00	$P\text{-}H_2\text{-}M$(high)	7.33	16

[a] All reactions were carried out in 0.05 M *N*-ethylmorpholine buffer and monitored spectrophotometrically at 275 nm. [NPIPP] = 5.00×10^{-5} M, [resin] = 1.00×10^{-3} M.

Table VI. Turnover Experiments[a]

10^4[NPIPP], M	$10^4 k_{obs}$, min^{-1}	% yield[b]
1.00 (1/1)	9.59	100
3.00 (3/1)	6.99	100
10.00 (10/1)	2.72	100

[a] All reactions were carried out in 0.05 M *N*-ethylmorpholine buffer (pH = 7.0, 25.0 °C). [P-M(high)] = 1.00×10^{-4} M. [b] Yield of 4-nitrophenol is based on total amount of substrate.

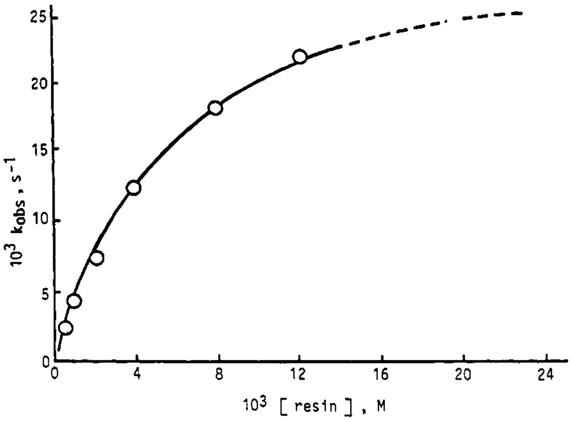
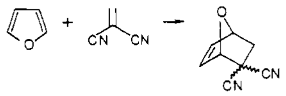
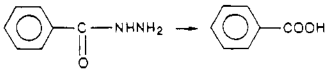
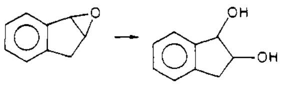
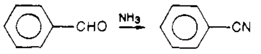
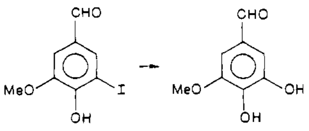
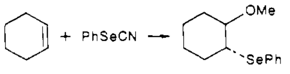


Figure 2. Plot of observed rate constants for hydrolysis of NPDPP (25.0 °C, pH = 8.00) as a function of $P\text{-}H_2\text{-}M$ "concentration". The latter was calculated from the [Cu^{2+}] that the polymer would provide the system were the polymer soluble in the buffer.

the polymer does not quite achieve the rates obtainable with copper micelles. On the other hand, the solid-state nature of the polymeric catalysts permits both catalyst removal by filtration and agent deactivation within a flow reactor, options that are unavailable with water-soluble catalysts.

Table III shows that high metal loadings are more effective than low loadings (compare runs 2 and 3 or 4 and 5). More surprisingly, a long tetradecyl chain on the outer periphery impairs rather than assists the rates (compare runs 3 and 5 or 6 and 7 or 10 and 11). Thus, our original speculation, mentioned in the introduction, that a hydrophobic shell might beneficially "collect" the substrate onto the polymer appears incorrect. Either binding to the outer chains is inefficient (in contrast to the situation with the micellar chains of III) or binding does indeed occur but not at loci sufficiently near the copper to permit enhanced catalysis. Moreover, since $P\text{-}H_2\text{-}M$ is a better catalyst than $P\text{-}H_2\text{-}M\text{-}H_1$, forcing the Cu^{2+} to lie between hydrocarbons H_1 and H_2 clearly does not improve catalytic potency. One might have a priori speculated otherwise; "burying" the Cu^{2+} could conceivably have enhanced metal electrophilicity critical to its interaction with

Table VII. Comparison of Six Reactions Catalyzed Heterogeneously by a Metallopolymer or Homogeneously by a Soluble Copper Salt

reaction[a]	catalyst[b]	catalyst substrate	reaction time	percent conversion[c,d]	% isolated yield[d]
	$Cu(OAc)_2$	0.10	5 days		22 (24)
	P-M	0.10	5 days		35
	$P\text{-}H_2\text{-}M$	0.10	5 days		40
	$Cu(OAc)_2$	0.25	2 h		92 (95)
	$Cu(OAc)_2$	0.025	2 h		79
	P-M	0.25	2 h		93
	P-M	0.025	2 h		93
	$P\text{-}H_2\text{-}M$	0.025	2 h		90
	$CuSO_4$	0.5	8 h	(100)	
	$CuSO_4$	0.05	1 h	59	
	$CuSO_4$	0.05	2 h	80	
	$CuSO_4$	0.05	8 h	90	60
	P-M	0.05	1 h	83	
	P-M	0.05	2 h	100	65
	$P\text{-}H_2\text{-}M$	0.05	0.5 h	61	
	$P\text{-}H_2\text{-}M$	0.05	1 h	100	65
	$CuCl_2$	0.08	6 h	69 (66)	
	P-M	0.08	6 h	66	
	P-M	0.08	14 h	95	80
	$P\text{-}H_2\text{-}M$	0.08	7 h	94	81
	$CuSO_4$	0.60	5 h	100	(65–75)
	$CuSO_4$	0.06	5 h	76	
	P-M	0.60	5 h	100	76
	P-M	0.06	5 h	15	
	$P\text{-}H_2\text{-}M$	0.06	5 h	96	73
	$CuCl_2$	1.0	0.5 h	100 (100)	65 (68)
	$CuCl_2$	0.13	2 h	(80)	
	P-M	1.0	0.5 h	54	
	P-M	0.13	2 h	40	
	$P\text{-}H_2\text{-}M$	0.13	2 h	69	

[a] References to reactions in order of appearance in table: Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700. Tsuji, J.; Nagashima, T.; Qui, N. T.; Takayanagi, H. *Tetrahedron* **1980**, *36*, 1311. Imuta, M.; Zieffer, H. *J. Am. Chem. Soc.* **1979**, *101*, 3990. Brackman, W.; Smit, P. J. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 757. Banerjee, S. K.; Manolopoulo, M.; Pepper, J. M. *Can. J. Chem.* **1962**, *40*, 2175. Toshimitsu, A.; Uemura, S.; Okano, M. *J. Org. Chem.* **1980**, *45*, 1953. [b] The counterion of P-M and $P\text{-}H_2\text{-}M$ was always identical with that of the copper salt to which it was compared. [c] Determined by ^1H NMR. [d] The values in parentheses represent the literature yield under identical conditions.

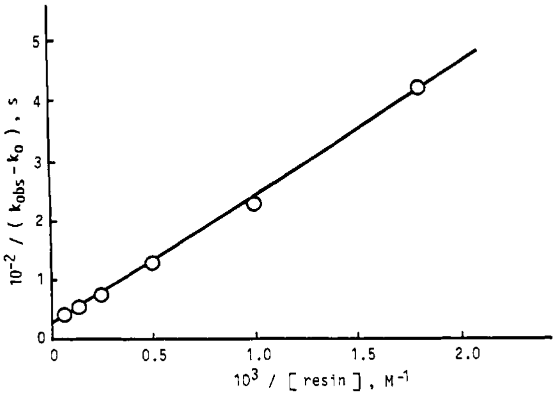


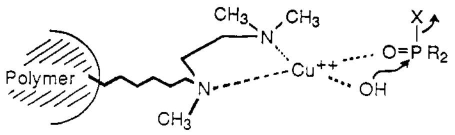
Figure 3. Lineweaver–Burk-type plot based on the data in Figure 2. The k_0 represents the rate of NPDPP hydrolysis in the absence of polymer catalyst.

phosphorus(V) functionalities.[8]

Although an outer hydrocarbon "coat" does not improve catalysis, a hydrocarbon chain between the polymer and metal site definitely does. For example, runs 3 and 6 show that introduction of a six-carbon spacer accelerates NPIPP hydrolysis 8-fold under our standard conditions. Runs 9 and 10 show a similar rate change with NPDPP. Spacer effects arise no doubt from steric factors; substrates have better access to catalytic sites if they are well separated from the polymer backbone.[9]

The rate constants for NPDPP hydrolysis catalyzed by various amounts of P-H_2-M(high) are listed in Table IV. Once again for simplicity we have taken the resin "concentration" as the concentration of Cu^{2+} that would exist in solution were the polymer water-soluble. A plot of k_{obs} vs [resin] curves downward (Figure 2), typical of a preassociation mechanism as found with enzymes. A Lineweaver–Burk-type double reciprocal plot (Figure 3) provided an apparent $K_{assoc} = 114\ M^{-1}$ for NPDPP/polymer binding and a $k_{lim} = 4 \times 10^{-2}\ s^{-1}$ corresponding to the rate of totally bound substrate. In all likelihood, both Cu^{2+}/phosphate interactions and hydrophobic attraction contribute to the overall substrate binding at the polymer surface.

Data in Table V show that hydrolysis rates are pH-insensitive near neutrality (varying only 2.5-fold over 2.5 pH units for NPIPP). Hydroxide ion cannot, therefore, represent the nucleophilic entity that attacks the phosphate or phosphinate ester. Instead, these substrates very likely have their *p*-nitrophenol leaving groups replaced by a metal-bound hydroxyl (drawn below). An identical mechanism was proposed and discussed in connection with metallomicelle-catalyzed hydrolyses.[2]



Catalysts must by definition display "turnover" where each catalyst molecule induces the destruction of multiple substrate units.[10] To test whether turnover is operative in our metallopolymer systems, we measured the yield of 4-nitrophenol when the substrate was in excess over the catalyst. As seen in Table VI, even a 10-fold excess of NPIPP over catalyst leads to a quantitative yield of 4-nitrophenol based on the *total* initial amount of substrate. Thus, reaction between substrate and polymer is not stoichiometric but catalytic in the true sense of the word.

B. Use of Metallopolymers in Organic Synthesis. Having demonstrated the efficacy of the copper-loaded polymers with nerve-agent simulants, we examined their utility in synthetically useful conversions. Six diverse reactions were selected for study (Table VII) including a Diels–Alder, an epoxide ring opening, and an aryl iodide hydrolysis. Exact literature procedures were repeated with both the prescribed soluble copper salt and a heterogeneous metallopolymer catalyst. The data in Table VII show that in all but one case (i.e. the final reaction in the table) copper-loaded polymers either improve the yield or lower the reaction time relative to conventional copper salts. This, plus the ease of metallopolymer removal by filtration, renders the metallopolymers an attractive alternative to current literature methods.

Acknowledgment. This work was supported by the Army Research Office.

Registry No. I, 80751-39-9; II, 10359-36-1; DHTEDA, 120743-24-0; $HN(Me)(CH_2)_2NH(Me)$, 110-70-3; $BrCH_2(CH_2)_8CH_3$, 112-71-0; $Me_2N(CH_2)_2NHMe$, 142-25-6; $CH_3(CH_2)_4CH(Br)OH$, 120743-25-1; $CH_2{=}C(Cl)CN$, 920-37-6; $PhCO(NH)_2H$, 613-94-5; PhCN, 100-47-0; PhSeCN, 2179-79-5; furan, 110-00-9; 5-chloro-5-cyano-7-oxabicyclo[2.2.1]-2-heptene, 84752-04-5; benzoic acid, 65-85-0; 2,3-dihydroindeno[1,2-*b*]oxirene, 768-22-9; 2,3-dihydro-1,2-hydroxyindene, 4370-02-9; benzaldehyde, 100-52-7; 4-hydroxy-3-iodo-5-methoxybenzaldehyde, 5438-36-8; 3,4-dihydroxy-5-methoxybenzaldehyde, 3934-87-0; cyclohexene, 110-83-8; *trans*-1-methoxy-2-phenylselenenylcyclohexane, 51533-22-3.

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Fluorine- versus Methyl-Substituent Effects in the 6-Methylenebicyclo[3.2.0]hept-2-ene–5-Methylenebicyclo[2.2.1]hept-2-ene Thermal Rearrangement

William R. Dolbier, Jr.,* and Otto Phanstiel, IV

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32611. *Received September 19, 1988*

Abstract: It was observed in a study of the thermal rearrangement of the *exo*- and *endo*-7-fluoro-6-methylenebicyclo[3.2.0]hept-2-enes that the fluorine substituent gave induced kinetic and stereochemical effects on the rearrangement which were virtually identical with those reported for a methyl substituent.

Ever since Berson observed the 1,3-sigmatropic rearrangement of *endo*-6-acetoxy-*exo*-7-deuteriobicyclo[3.2.0]hept-2-ene to *exo*-5-acetoxy-*exo*-6-deuteriobicyclo[2.2.1]hept-2-ene,[1] a process which occurs with complete inversion, the stereochemistry of

0002-7863/89/1511-4907$01.50/0