Interpolymeric Reactions. The Fries Rearrangement of Acetoxy and Benzyloxy Derivatives of 4-Hydroxy-3-nitrobenzylated Polystyrene and 5-Polystyrylmethyl-8-quinolinol

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Abstract: The Fries rearrangement of acetoxy and benzyloxy esters of 4-hydroxy-3-nitrobenzylated polystyrene (**14**, gel type, and **15**, macroreticular type) and 5-polystyrylmethyl-8-quinolinol (**16**, macroreticular type), and of a model compound (4-acetoxy-3-nitro)benzylated toluene (**17b**) was investigated in 1.8 M aluminum chloride in nitrobenzene. It was found that with **14b, 15b,** and **17b** the acylium ion is transferred exclusively to the nonphenolic aromatic ring. The evidence for this is provided from mass spectra (of **19b**), IR spectroscopy, and copper complexation studies. Interpolymeric reactions, performed in the presence of a polymeric acceptor, proved that an oxocarbonium ion is an intermediate in the Fries rearrangement.

Polymeric reagents are finding use in a variety of synthetic applications.[1,2] So far, little attention has been given to the use of insoluble polymers in mechanistic studies and for the determination of reaction intermediates.

Blackburn et al.,[3] studying the role of metaphosphate **1** and cyclic trimethylphosphate **2** in phosphorylation reactions in the presence of cyclohexylcarbodiimide, made use of polybenzyl alcohol **3** and its phosphorylated derivative **4**.

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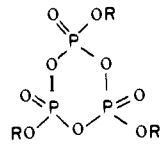

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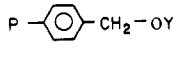
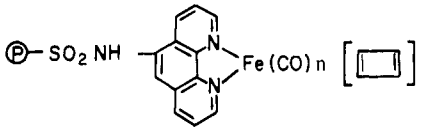


3 Y = H

4 Y = -PO$_3$H$_2$

Multiphase techniques have been used by Rebek et al.,[4] e.g., they have generated cyclobutadiene from a polymer carrying 5-aminophenanthroline groups **5**, and trapped this intermediate with polymaleimide **6**. Efficient peptide synthesis was



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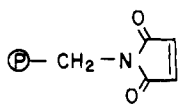

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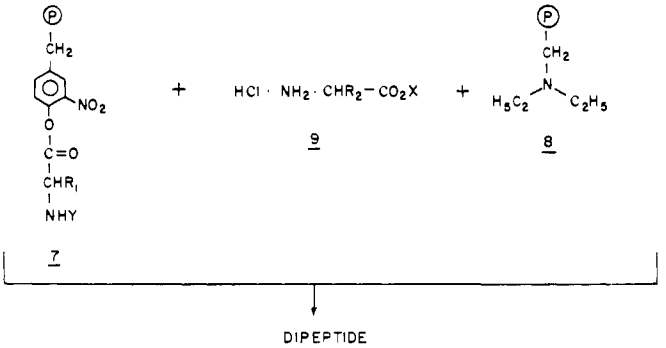
accomplished in this laboratory[5,6] by the simultaneous use of an acylating polymer **7** and a neutralizing polymer **8**.



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8

7

In a different type of application, Janauer[7] has shown that multiple, intrapolymeric reactions occurring inside ion-exchange resins can be used to perform trace level (ppb) analysis of various metal ions. This technique is known as reactive ion exchange (RIEX).

The Fries Reaction. The Fries rearrangement is an acid-catalyzed, acyl transfer reaction of phenolic esters (Scheme I). The mechanistic pathways suggested by product analysis[8] are (1) intramolecular rearrangement leading to *o*-acylphenol **11a** (also called the ortho or 1,2 path); (2) intermolecular rearrangement leading mainly to *p*-acylphenol **11b** (also called the para or 1,4 path); (3) oxocarbonium ion migration leading to both isomers.

The ratio of isomeric products was found to be extremely sensitive to variations in experimental conditions such as temperature,[9] polarity,[10] and catalyst concentration.[8] The critical role of the volatile HCl in the equilibrium expression for the aluminate-free phenol equilibria (Scheme I, part d) was also pointed out.[8] Because of the complexity of the reaction, even recent studies[11] do not offer conclusive evidence for the Fries rearrangement intermediates.

The present study will explore the following points: (1) Can interpolymeric reactions provide conclusive evidence for the oxocarbonium ion as a Fries reaction intermediate? (2) Will the low-chain-mobility of the cross-linked polystyrene eliminate the possibility of a intermolecular rearrangement (path b, Scheme I)?

Results

The Fries rearrangement of the acetyl, benzoyl, *p*-chlorobenzoyl, and *p*-nitrobenzoyl esters of three polymers, (4-hydroxy-3-nitro)benzylated polystyrene (gel structure, type G), (**14**) (4-hydroxy-3-nitro)benzylated polystyrene (macroreticular structure type M) (**15**), and 5-(polystyrylmethyl)-8-quinolinol (**16**), was studied in 1.8 M aluminum chloride in nitrobenzene at 20–75 °C.

The rearrangement of (4-acetoxy-3-nitro)benzylated toluene (**17b**) was studied as a model for a monomeric analogue of polymers **14** and **15**.

In addition (5-acetyl-4-hydroxy-3-nitro)benzylated macroreticular polystyrene (**18**) was prepared by reaction of (5-acetyl-4-hydroxy-3-nitro)benzyl chloride with polystyrene. Polymer **18** represents one of the two possible rearrangement products of **15b**.

The number of active acyl groups attached to the polymer was determined by nonaqueous titrimetry[19] and was in good agreement with results of nitrogen or chlorine analysis of the *p*-nitro- or *p*-chlorobenzoyl derivatives (see Table I).

The progress of the rearrangement was followed by IR

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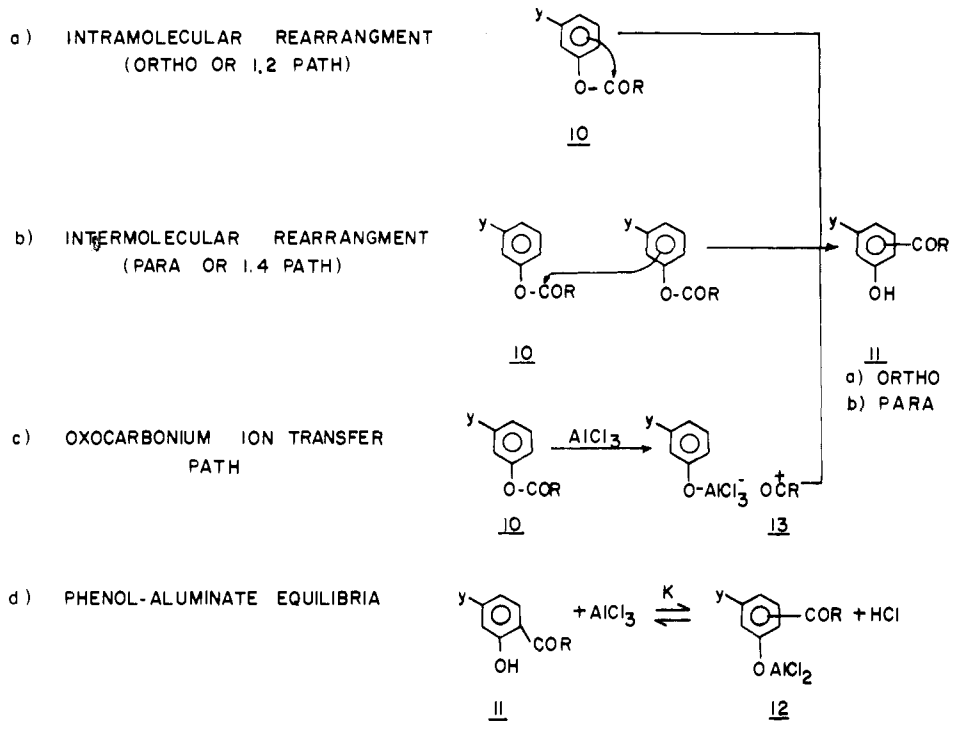
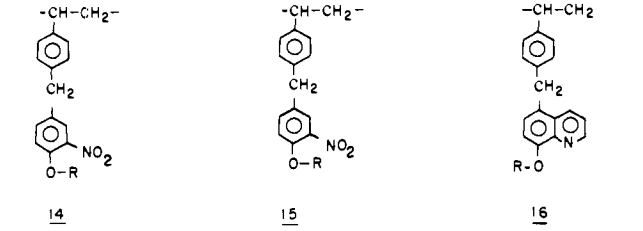
Scheme I



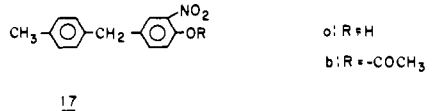
spectroscopy, observing the shift of the carbonyl absorption from the 1750–1790-cm^{-1} range in the starting polymeric esters to the 1650–1690-cm^{-1} range in the ketone products (Figures 1 and 2).



a: R=H
b: R=-COCH3
Polymeric matrix gel type (2% DVB)

a: R=H
b: R=-COCH3
c: R=-CO-C6H5
d: R=-CO-C6H4Cl
e: R=-CO-C6H4NO2
Polymeric matrix MACRORETICULAR (Xe-305)

a: R=H
b: R=-COCH3
c: R=-CO-C6H5
d: R=-CO-C6H4Cl
e: R=-CO-C6H4NO2
Polymeric matrix MACRORETICULAR (Xe-305)

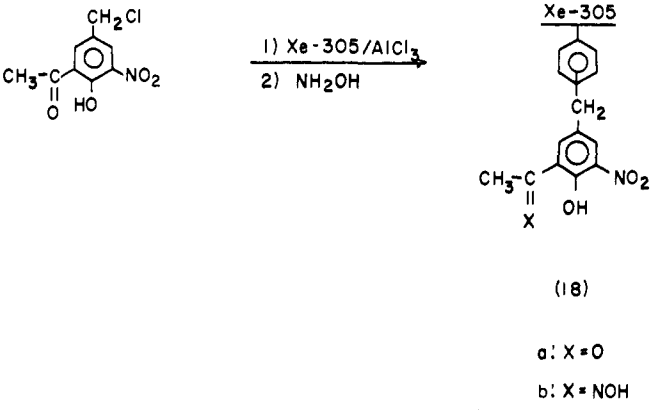


17

a: R=H
b: R=-COCH3

The rearrangement of compound **17b** was followed directly in the reaction. Completion of the rearrangement was observed after 20 h at 45 °C or 96 h at 20 °C for the nitrophenol polymers **14** and **15** and only after 20 h at 75 °C for 8-quinolinol polymers **16.**

The percent transfer of acyl groups was determined directly from chlorine analysis before and after the rearrangement (**15d** and **16d**) or from the analysis of the oxime and DNP derivatives. In the case of **17b,** the percent acyl transfer was calculated from the proton ratio of acetyl to methyl groups in the NMR spectrum. High degrees of acyl transfer were obtained in most cases. However, hydrolysis was also observed in some cases.



(18)

a: X=O

b: X=NOH

The intra- and interpolymeric acyl-transfer experiments were performed under similar conditions, with extra care to exclude moisture and residual traces of acylating agents (see Experimental Section). The band intensities of ketone absorptions of samples of donor and acceptor, taken under identical concentrations (2 mg/100 mg KBr), were measured (see Figure 3). From this the percent transfer was calculated. The accuracy of this method is semiquantitative, but could be possibly improved to analytical accuracy if samples are carefully homogenized and peak areas are compared instead of band intensities.

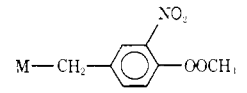
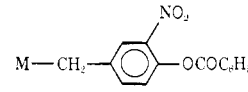
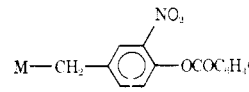
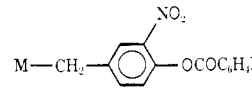
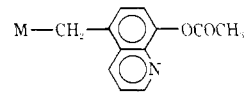
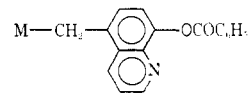
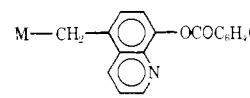
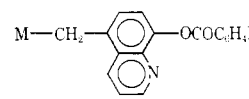
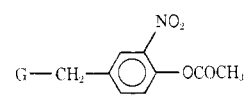
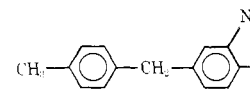
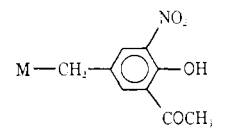
With both gel and macroreticular polymers, high degrees of acyl transfer were recorded (see Table II).

Discussion

Three mechanistic pathways are proposed in Scheme I for the Fries rearrangement in solution, namely,[8] (1) intramolecular (path a); (2) intermolecular (path b); (3) oxocarbonium ion transfer (path c). In the case of the Fries rearrangement performed inside polymeric matrices it is necessary to distinguish between two cases (see Scheme II): (A) when the rearrangement occurs inside a flexible polymer; (B) when the rearrangement occurs inside a rigid polymer.

In a rigid polymer, only intermolecular rearrangement (path a) and oxocarbonium ion transfer via solution may occur. In a flexible polymer, acyl transfer is facilitated by all three mechanistic pathways via chain interactions.

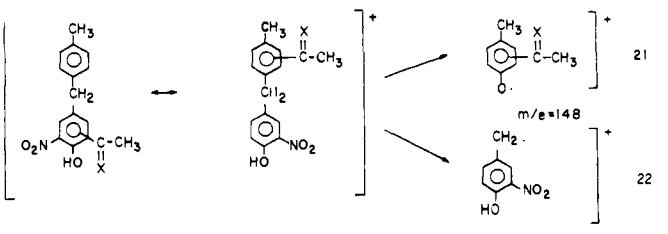
Table I. Rearrangement Conditions, Product Properties, and Derivatives

Compd	Matrix[a]	Structure	Active ester content mmol /g[b]	Rearrangement conditions, °C/h	% N Before rearr	% N After rearr	$\nu_{C=O}$,[c] cm^{-1} Before rearr	$\nu_{C=O}$,[c] cm^{-1} After rearr	Oxime % N	Oxime mmol /g[d]	Dinitrophenyl hydrazone % N	Dinitrophenyl hydrazone mmol /g[d]	% transfer[e]	% hydrolysis
15b	M		1.4	70/20 or 20/96	2.11	2.16	1760	1690	4.28	1.50			*j*	0
15c	M		1.5	70/20, 45/20, or 20/96	1.81	2.10	1750	1660	2.95	0.61	5.89	0.67	43	57
15d	M		1.0	70/20	1.76	1.82	1750	1650			5.84	0.68	68	32
15e	M		1.1	70/20 or 45/20	3.11	3.11	1755	1670	3.94	0.6			54.5	45.5
16b	M		0.75	75/20	1.20	1.10	1750	1670			4.40	0.59	79	21
16c	M		0.27	75.20	1.22	1.25	1740	1660	1.59	0.26	3.53	0.41	*j*	0
16d	M		0.70	75/20	1.17	1.22	1740	1660					60[g]	0
16e	M		0.60	75/20	2.17	2.10	1740	1670			4.35	0.40	67	33
14b	G		1.35	45/20	2.03	2.05	1760	1690	4.13	1.4			*j*	0
17b			3.42	20/96			1792[h]	1692	9.01				55.8[i]	54.2
18a	M		—	—	—	—			1.07					

[a] M = macroreticular Xe-305 containing 1.32 mmol of nitrophenol groups per g of polymer and 1.25 mmol of 8-quinolinol groups per g of polymer. G = gel type 2% divinylbenzene-styrene copolymer containing 1.30 mmol of nitrophenol groups per g of polymer. [b] Nonaqueous titrimetry after ref 19. [c] KBr pellets. [d] Calculated by nitrogen analysis difference relative to rearrangement product. [e] Calculated from DNP and oxime derivatives relative to active ester content of starting polymer. [f] This derivative contained 3.42% Cl before rearrangement and 2.62% Cl after rearrangement. [g] As hydrochloride contained 5.42% Cl (0.36 mmol/g of covalent Cl) before rearrangment and 5.52% Cl after rearrangement (quantitative). [h] In chloroform. [i] From ratio of CH_3Ph to CH_3CO-in the NMR spectra of the rearrangement product. [j] Quantitative transfer within experimental error.

Of the polymers studied, **14b** was chosen to represent a flexible gel polymer of type A and **15** and **16** were chosen to represent a rigid macroreticular polymer of type B. However, this preliminary expectation was not fulfilled as under the reaction conditions both polymers swelled considerably, adsorbing up to five times of their weight, in nitrobenzene solution. This implies that all polymers studied behaved as type A flexible polymer.

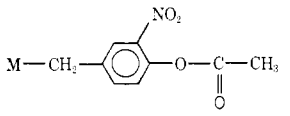
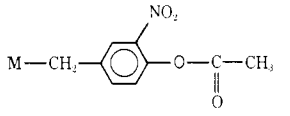
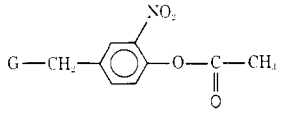
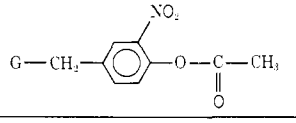
Now, from the considerations discussed above, it was reasonable to expect nondiscriminatory distribution of acyl groups. However, considering classical substituent effect, it seemed obvious to expect the nonphenolic ring (as in **19**) to be the preferred site for the acyl acceptor, rather than the nitrophenol



20
a: X=O
b: X=NOH

19
a: X=O
b: X=NOH

Table II. Intra- and Interpolymeric Acyl Transfer Reactions[a]

Donor Compd	Donor structure	Acceptor compd	Conditions Temp, °C	Conditions Time, h	% acetyl transfer
15b		**14a**[b]	59	48	50
15b		**14a**[b]	57	20	33
14b		Toluene	45	20	48
14b		Toluene	45	20	72

[a] In 1.8 M aluminum chloride in nitrobenzene. [b] Containing 1.5 mmol/g of (4-hydroxy-3-nitro)benzyl groups.

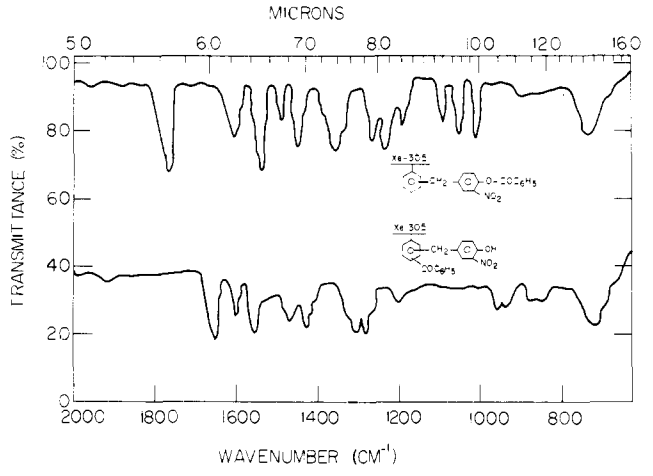


Figure 1.

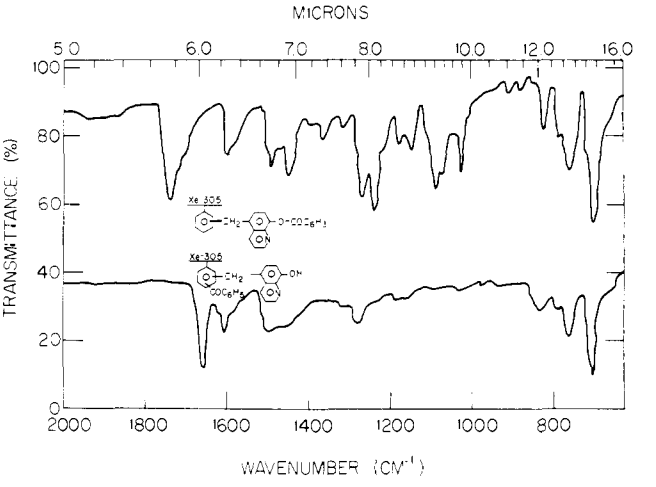
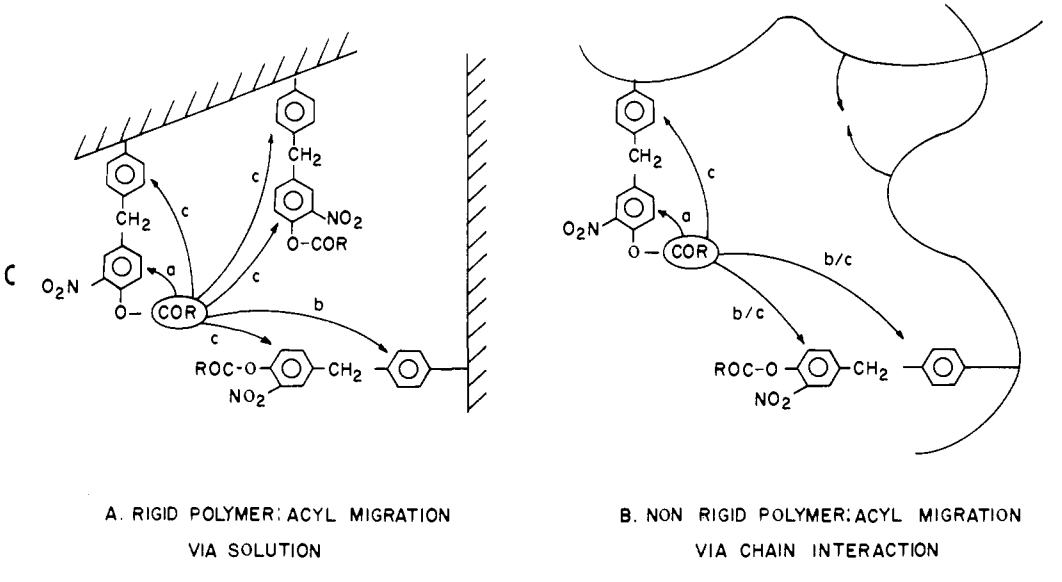


Figure 2.

ring (as in **20**). Evidence for this was sought directly from the studies of the rearrangement products, and especially from their oxime derivatives, and indirectly from the study of model compound **18b** and **23b**. As anticipated, the oxime of the rearrangement product of **17b** has a fragmentation pattern in

Scheme II



A. RIGID POLYMER: ACYL MIGRATION VIA SOLUTION

B. NON RIGID POLYMER: ACYL MIGRATION VIA CHAIN INTERACTION

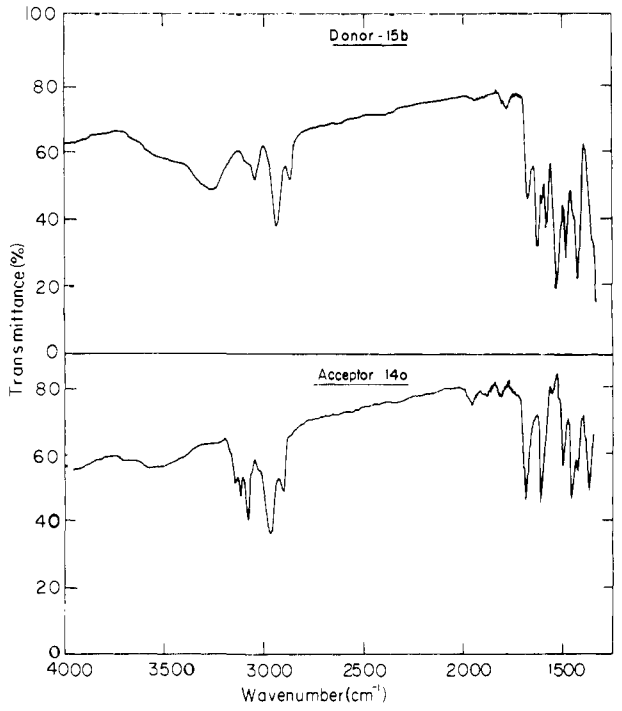
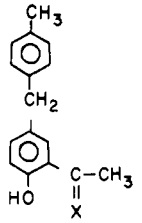


Figure 3.

the mass spectrum that agrees with structure **19b.** No fragmentation patterns corresponding to **20** could be detected.

In the polymers the evidence for the same pattern of acyl transfer was obtained from (1) spectroscopic evidence, carbonyl absorption in the infrared spectra; (2) chemical evidence, copper complexation studies. The infrared spectra of all rearrangement products show carbonyl absorption bands in good agreement with expected absorption bands for acetophenone- or benzophenone-type carbonyls. Furthermore, the rearrangement products of both the nitrophenol polymers **15** and 8-quinolinol polymers **16** adsorb similarly.

Chemical evidence was obtained from metal complexation studies. Since it is known that *o*-ketoximephenols complex copper(II) ions, several oximes were prepared and their complexation with copper(II) was studied. Oximes **18b** and **23b**,[12]



23

a: X = O

b: X = NOH

incorporating phenol oxime in the ortho relationship, were specially prepared and show a good copper complexation ability (0.33 mmol g^{-1} Cu(II) at pH 4.0). On the other hand, none of the oximes of the rearrangement products of **15, 16,** and **17** show any capacity for copper, suggesting strongly that the oxime and phenol groups are *not* in the ortho relationship, and therefore must be located on the two different aromatic rings.

This conclusion rules out the possibility of intramolecular rearrangement path a (see Scheme II). In the case of a flexible polymer (we assume that to be the case at hand) the possibilities of intermolecular path b and oxocarbonium ion transfer, path c, are still open. Since an oxocarbonium ion, in the presence of hydrogen ions and tetrachloroaluminum anions, is free to dissociate from the polymer and diffuse into the bulk of the solution, it could be trapped by an acyl acceptor. Hence, the intrapolymeric experiments using toluene, and interpolymeric experiments using a second polymer acceptor, were designed to test this point. The high yields of acyl transfer to toluene in the intrapolymeric experiment provide strong evidence in favor of oxocarbonium-transfer path c. However, it could be argued that the transfer takes place *inside* the polymer channels and that toluene is a more susceptible acyl acceptor, in comparison with the sterically hindered, nonphenolic aromatic ring of the polymers (see Table II).

The interpolymeric experiments carried out between two insoluble polymers offer conclusive evidence that an oxocarbonium ion was involved in the acylation of the polymeric acceptor. Oxocarbonium ions were postulated as intermediates in Friedel-Crafts acylations[13] and recently oxocarbonium ions derived from ketocarboxylic acids were isolated in fluorosulfuric acid as antimony pentafluoride salts.[14] Our findings prove the existence of oxocarbonium ion as the acylating species under typical Fries rearrangement reaction conditions.

Experimental Section

Gel polymer (type G), 2% divinylbenzene-styrene copolymer of mesh size 100-200, was obtained from Bio-Rad Laboratories. Macroreticular polymer (type M), Amberlite XE-305 4% divinybenzene-styrene copolymer of mesh size 20-50, was obtained by courtesy of Rohm & Haas. The polymers were washed with 1 N sodium hydroxide, water, then 1 N hydrochloric acid, dimethylformamide, and finally with methanol, then dried at 60-80 °C for 24 h.

(4-Hydroxy-3-nitro)benzylated Polystyrene (14a, 15a) and 5-Polystyrylmethyl-8-quinolinol (16a). These polymers were prepared by the Friedel-Crafts alkylation procedure described elsewhere.[16,17] The polymers were characterized by nitrogen analysis and were found to contain the following amount of phenol groups: **14a** and **15a**, 1.32 mmol/g (1.85% N, Table I) and 1.50 mmol/g (2.11% N, Table II); **16a**, 1.25 mmol/g.

(4-Acetoxy-3-nitro)benzylated Polystyrene (14b, 15b) and 8-Acetoxy-5-polystyrylmethylquinoline (16b). One gram of the hydroxy polymers **14a, 15a,** and **16a** was refluxed in 10 mL of chloroform containing 2 g of acetic anhydride and 0.1 mL of pyridine (in the case of **16a**, excess pyridine (1.0 mL) was necessary to neutralize the quinoline base) until the yellow color of the phenol changed to colorless, indicating that the acetylation was completed (usually 1-3 h was sufficient). In the interpolymeric experiments equimolar amounts of acetic anhydride and polymer were refluxed for 20 h. The polymers were filtered and washed thoroughly, on the filter funnel, with a large excess of fresh chloroform. The last filtrate was collected and distilled in order to make sure that the polymer did not contain any more adsorbed compounds, particularly acetic acid or acetic anhydride. The polymers were then dried over P_2O_5 under high vacuum for 20 h. The P_2O_5 trap was then changed and drying was continued until complete dryness has been achieved.[18] This point was reached when the last P_2O_5 portion remained dry for 24 h.

For the analytical and spectroscopic properties of the acetoxy derivatives, see Table I.

Benzyloxy Derivatives of (4-Hydroxy-3-nitro)benzylated Polystyrene (15c, 15d, 15e) and 5-Polystyrylmethyl-8-quinolinol (16c, 16d, 16e). One gram of the hydroxy polymers **15a** and **16a** was reacted with 3 mmol of benzoyl chloride, *p*-chlorobenzoyl chloride, and *p*-nitrobenzoyl chloride in the presence of 1 mL of pyridine in 10 mL of chloroform at reflux temperature for 4 h. The polymers were filtered, washed with chloroform, methanol, and chloroform, and dried as described earlier. For the analytical and spectroscopic properties, see Table I.

(5-Acetyl-4-hydroxy-3-nitro)benzylated Polystyrene (18a). (5-Acetyl-4-hydroxy-3-nitro)benzyl chloride (15 g) was reacted with 10 g of XE-305 in 100 mL of 1.8 M aluminum chloride in nitrobenzene at 60 °C for 48 h. The polymer was filtered, washed with 100 mL of CH_3OH-HCl (1:1), CH_3OH, and ether, and dried at 60-80 °C for 20 h. **18a** (16 g) was obtained, containing 1.94 mmol of nitrogen per

g of polymer. The oxime **18b** was prepared containing 1.07 mmol of oxime per g of polymer.

4-Acetoxy-4'-methyl-3-nitrodiphenylmethane (17b) [(4-Acetoxy-3-nitro)benzylated Toluene]. (4-Hydroxy-3-nitro)benzyl chloride (30 g) was reacted with 100 mL of toluene at 80 °C for 4 h, in the presence of 2 g of aluminum chloride. The organic layer was washed with 50 mL of 32% HCl and 2 × 100 mL of water and dried over Na_2SO_4. The excess toluene was removed by distillation under vacuum to yield 36 g of yellow oil which crystallizes upon standing. The product **17a** is an isomeric mixture of approximately 1:1 ratio, as indicated from thin layer chromatography (CH_2Cl_2–hexane, 1:1) and NMR spectrum.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.10; H, 5.35; N, 5.75. Found: C, 68.70; H, 5.26; N, 5.40; Cl, 0.

NMR ($CDCl_3$): 8.0–7.8, 7.70–7.0 (7 H), 3.92, 3.88 (s, 2 H), 2.28, 2.20 ppm (s, 3 H).

This isomeric mixture of **17a** was reacted with 50 g of acetic anhydride and 2 mL of pyridine in 150 mL of chloroform for 4 h. The acetyl derivative **17b** was obtained in quantitative yield as an oil.

NMR ($CDCl_3$): 8.0–7.8, 7.5–7.0 (7 H), 3.9, 3.86 (s, 2 H), 2.25, 2.17 ppm (s, 6 H). NMR (nitrobenzene): 3.99 (2 H, 2.35 (3 H), 2.18, 2.14 ppm (3 H). IR (nitrobenzene): ν_{CO} 1790 (strong), ν_{OH} 3580 cm^{-1} (very weak).

Analytical Characterization of the Polymeric Esters by Nonaqueous Titrimetry.[19] Duplicate samples of 100 mg of polymeric esters **14b**, **15b–e**, and **16b–e** were reacted with excess 0.1 N benzylamine in toluene for 1 h. The excess amine was then back-titrated with 0.1 N $HClO_4$ in acetic acid, thymol blue serving as indicator. The number of acyl groups per g of polymer are reported in Table I.

Fries Rearrangement of Polymers 14b, 15b–e, and 16b–e. Aluminum chloride obtained from freshly opened ampules of AR grade material was dissolved in nitrobenzene (AR), which was standing over $CaCl_2$ or CaH_2 to give 1.8 M solution. Polymer samples (1.0 g) were left in 10 mL of 1.8 M aluminum chloride–nitrobenzene solution without agitation or stirring in Erlenmeyers equipped with $CaCl_2$ drying tubes. In the case of macroreticular polymers **15** and **16**, about half of the solution was swallowed by the polymer. The reaction was studied at 20, 45 and 70 °C. Polymer samples were withdrawn at various intervals, poured on CH_3OH–HCl (1:1), filtered, washed with methanol, and refluxed in CH_3OH or $CHCl_3$ to remove any traces of nitrobenzene, filtered again, and washed with ether, then dried out at 60–80 °C for 20 h. The final product was also worked up in the same way. Polymer samples were crushed to fine powder and KBr pellets (2 mg/100 mg KBr) were prepared and IR spectra taken. The progress of the reaction and its completion could be easily followed by the disappearance of the carbonyl absorption of the ester (~1750 cm^{-1}) and the appearance of the ketone absorption (1650–1690 cm^{-1}). Typical IR spectra of **15c** and **16c** are given in Figures 1 and 2.

Standard conditions for the rearrangement of all polymeric esters studied were 20 h at 70 °C. Nitrophenol polymers **14** and **15** rearrange at 20 °C (see Table I) but quinolinol polymers **16** required 70 °C for efficient rearrangement to occur.

Interpolymeric Fries Rearrangement Experiments. Control Experiments. Since the Fries reaction is very sensitive to hydrolysis, absolute dryness is necessary. However, prolonged drying of the polymers under high vacuum causes the pores to collapse and close, preventing the penetration of the aluminum chloride solution and causing the rearrangement to fail. Control experiments were conducted with polymeric ester alone to check for a high degree of acyl transfer and low hydrolysis. If this was satisfactory, the interpolymeric experiment was conducted.

Rearrangement of (4-Acetoxy-3-nitro)benzylated Polystyrene 15b in the Presence of Toluene. (4-Acetoxy-3-nitro)polystyrene **15b** (0.5 g), of mesh size 20–50, containing 0.68 mmol of active acetyl groups was rearranged in 10 mL of 1.8 M aluminum chloride in nitrobenzene containing 5 mL of sodium-dry toluene at 45 °C for 20 h. The polymer was filtered off and the concentration of methylacetophenone was determined in the nitrobenzene solution by measuring the increase of the acetyl signal in the NMR spectrum after addition of a known amount of authentic methylacetophenone (internal standard method). A 0.33-mmol quantity of acetyl groups was found representing 48% of acetyl groups transferred: $\nu_{C=O}$ 1690 cm^{-1}.

In an analogous experiment, 0.5 g of (4-acetoxy-3-nitro)polystyrene **16b**, of mesh size 100–200, containing 0.7 mmol of acetyl groups was rearranged under the same conditions in the presence of 5 mL of toluene; 72% of acetyl groups were transferred. $\nu_{C=O}$ 1690 cm^{-1}.

Rearrangement of (4-Acetoxy-3-nitro)benzylated Polystyrene 15b in Presence of Polystyrene (Containing 1.5 mmol/g of Phenol Groups). (4-Acetoxy-3-nitro)polystyrene **15b** (6 g), of mesh size 20–50 (2.11% N), containing 9.3 mmol of active acetyl groups was reacted in 50 mL of 1.8 M aluminum chloride in nitrobenzene with 3 g of (4-hydroxy-3-nitro)polystyrene **14a** of mesh size 100–200, containing 1.5 mmol of phenol groups per g, at 57 °C for 20 h. Methanol (100 mL) was added and the polymers were filtered and washed with warm methanol, $CHCl_3$, and ether. The polymers **15b** and **14a** were separated by sieving, according to their sites. KBr pellets containing 2 mg of crushed polymer per 100 mg of KBr were prepared and IR spectra taken (see Figure 3). The 1690-cm^{-1} ketone absorption band was the only carbonyl band present in both polymers. The percent acetyl transfer was calculated from the absorption intensities (band height) of 1690-cm^{-1} bands of the donor and acceptor, according to the relationship

$$\% \text{ transfer} = \frac{I \text{ acceptor}}{I \text{ acceptor} + 2I \text{ donor}}$$

(the factor of 2 relates the weight ratios). Percent acetyl transfer = 33% (see Table II).

Oxime derivatives were prepared and analyzed. (4-Hydroxy-3-nitro)acetylbenzylated polystyrene (5.5 g) (derived from **15b**): 4.28% N corresponding to 1.55 mmol of oxime groups per g of polymer.

Oxime of (4-hydroxy-3-nitro)acetylbenzylated polystyrene (2.45 g) (derived from **14a**): 3.19% N corresponding to 0.77 mmol of oxime groups per g of polymer. In a second experiment under similar conditions 0.2 g of **15b** was reacted in 1.0 mL of 1.8 M aluminum chloride in nitrobenzene at 59 °C for 48 h in the presence of 0.1 g of **14a** (mesh size 100–200). The polymers were isolated as before. Their IR spectra (2 mg of polymer/100 mg of KBr) revealed 1670-cm^{-1} absorption bands on both polymers. Again the percent transfer was calculated from the adsorption intensities, as described above, and was found as 50% (see Table II).

Fries Rearrangement of (4-Acetoxy-3-nitro)benzylated Toluene 17b. Samples (0.4 g) of **17b** in 2 mL of 1.8 M aluminum chloride in nitrobenzene were reacted under the following conditions: 20 °C for 96 h or 45 °C for 20 h. Samples were washed with 32% HCl and water and reaction progress was followed by IR spectroscopy (carbonyl shift from 1790 to 1690 cm^{-1}) and NMR spectroscopy (acetyl shift from 2.35 to 2.58 ppm).

The reaction was repeated on a preparative scale, using 20 g of **17b** in 50 mL of 1.8 M aluminum chloride in nitrobenzene at 25 °C for 20 h. The nitrobenzene was removed by steam distillation, the residue was dissolved in 200 mL of $CHCl_3$, washed with water, and dried over Na_2SO_4, and the solvent was removed. The product **19a** was reacted directly with 10 g of hydroxylamine hydrochloride in methanol at reflux temperature for 4 h. The solvent was evaporated, the residue was dissolved in chloroform and washed with water, then dried over Na_2SO_4, and the solvent was removed, yield: 65% of **19b**: mp 170–172 °C; mass spectrum *m/e* 300 (M^+, rel abundance 1.0), 152 (ion **22**, rel abundance 0.34), 148 (ion **23**, rel abundance 0.21).

Anal. Calcd for $C_{16}H_{16}N_2O_4$: N, 9.33. Found: N, 9.01.

A solution of 5.0 g of **19b** per L of $CHCl_3$ was prepared and shaken with 3.0 g/L of copper sulfate at pH 4.0 for 5 min. The copper was analyzed in this solution before and after the extraction. No change in concentration was found.

Oxime Derivatives. General Procedure. (Hydroxylamine hydrochloride + triethylamine) solution (1 M) in methanol was prepared. One-gram polymer samples (**14b**, **15b–e**, **16b–e**) in 10 mL were refluxed for 20 h. The polymers were filtered, washed with methanol and ether, and dried at 60–80 °C for 20 h. For nitrogen analysis, see Table II.

Copper Complexation Tests. Polymeric oximes (10 g) were shaken with 10 mL of 3.0 g/L of copper sulfate at pH 4 for 20 h. The polymers were filtered and the copper uptake was determined by difference in metal concentration. All the polymers showed zero uptake of copper except **18b**, which showed 35% capacity (0.37 mol of Cu per 1.07 mol of oxime groups per g of polymer).

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Solvent Effects on Stacking. A Kinetic and Spectroscopic Study of Thionine Association in Aqueous Alcohol Solutions

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Abstract: Rate constants for the self-association of thionine in aqueous solutions of methanol, ethanol, 1-propanol, urea, and formamide have been determined with the Raman laser temperature jump technique. The forward rates in aqueous ethanol and 1-propanol solutions are about a factor of 10 slower than the others. This is interpreted in terms of a specific alcohol–dye interaction. Absorption and fluorescence titrations are consistent with this interpretation. The results suggest that specific solvation properties are important in understanding stacking reactions.

Molecular associations via stacking are important in many areas of chemistry, ranging from dyes to nucleic acids.[1,2] At present, there is controversy over the driving forces for these reactions, particularly the role of solvent in determining stability.[1-6] One of the problems is a lack of experimental data with which to test various theories. The use of dyes as simple models for this process has been suggested by Hammes.[7] Thionine dimerization (see Figure 1) is a particularly attractive system because it combines a large spectral change with a high equilibrium constant.[8] There is also renewed interest in thionine solution chemistry because of its potential use in photogalvanic cells.[9] This paper reports the kinetics of thionine stacking as a function of solvent, and presents evidence for specific dye–solvent interaction.

Experimental Section

Materials. Thionine, 3,7-diaminophenazothionium chloride, was obtained from Eastman, and recrystallized from water as the perchlorate salt. The crystals contained 1 mol of water per mol of thionine, and concentrations were determined using a molecular weight of 344.6. Water was doubly distilled, and absolute ethanol was used. Methanol was spectral grade from Mallinckrodt, 1-propanol "distilled in glass" from Burdick and Jackson, formamide "Baker analyzed" 99%, and urea "ultrapure" grade from Schwarz/Mann.

Spectra. NMR spectra were taken on a 100-MHz JEOL PFT 100 Fourier transform spectrometer with a JEOL EC 100 computer. The WEFT pulse sequence was used to eliminate the residual HDO resonance.[10,11]

Absorption titrations were performed on a Cary 14 spectrophotometer, using a 10-cm path length cell. Fluorescence titrations were performed on the same solutions in 1-cm path length cells using a Perkin-Elmer MPF-2A or MPF-44A fluorimeter. The fluorescence was excited at 570 nm where the absorbance of the solutions is less than 0.05, and changes by less than 10% as the solvent composition is varied. A linear correction was applied for this absorbance change.

Kinetics. The self-association of thionine occurs in less than 1 μs, thus requiring use of the Raman laser temperature-jump method described previously.[12] The probe beam was filtered with a Corning CS3-66 filter, and monitored at 605 nm, which is near the absorption peak of the monomer. As a control to check for photochemical effects, a 4.77×10^{-3} M solution in D_2O was tested. The temperature jump in D_2O is over 100 times smaller than in H_2O, and a negligible signal was observed. Relaxation curves were photographed on 35-mm film, projected and digitized with a Tektronix 4662 plotter and 4051 terminal. The points were then analyzed with a nonlinear least-squares fit to a single exponential. Each lifetime represents the average of at least 12 shots. The estimated error in the rate constants is ±25%. All solutions contained 0.01 M KH_2PO_4. As a control, rate constants were determined in 1 mol % ethanol with no added salt. They are 0.52×10^9 M^{-1} s^{-1} and 0.8×10^6 s^{-1} for k_1 and k_{-1}, respectively. These agree with those measured in the presence of salt, within experimental error.

Results

The stacking of planar dye molecules is known to result in an upfield shift in the NMR peaks of the ring protons, owing to increased shielding.[13-15] The best evidence for stacking is to follow this shift as the concentration of the dye is increased from a point where only monomers exist to a point where mainly associated species are present. Unfortunately, the high equilibrium constant for thionine dimerization, coupled with the low sensitivity of NMR, makes this experiment impractical. Instead, the NMR spectrum of 4 mM thionine has been measured at 25 and 50 °C. The higher association constant at 25 °C predicts that the proton resonance should shift upfield at the lower temperature if the equilibrium is due to stacking. Figure 2 shows that this is the case. This evidence combined with absorption spectra measured previously confirms the thionine association as a stacking equilibrium.[8]

Kinetic experiments were performed in aqueous mixtures, since dye stacking has not been observed in nonaqueous solvents.[16] A typical relaxation is shown in Figure 3. The relaxations observed are due to the monomer-dimer equilibrium:

$$T + T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T_2 \qquad (1)$$

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