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THE EFFECT OF POLYMER-SUPPORTED REAGENT STRUCTURE ON BROMINATION OF ORGANIC MOLECULES

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Abstract - Crosslinked poly(styrene-*co*-4-vinylpyridine) reacted with hydrogen bromide or various alkyl bromides to pyridinium salts, which were further converted with chlorine to polymer supported reagents (1) containing up to 34% of chlorine, while substantial loss of bromide was observed during chlorination, debromination being diminished with increase in the length of the alkyl chain in the pyridinium salt. Polymeric reagents (1) converted 1,1-diphenylethene to 2-bromo-1-chloro-1,1--diphenylethane and 2-bromo-1,1-diphenylethene, the structure of 1 influencing both the reactivity and the ratio of the addition to elimination process. The brominating capacity of reagents 1 was determined with an excess of 1,1-diphenylethene and varied, according to the structure of 1, in the range of 0.4 - 1.4 mmol per gram of polymeric reagent.Bromochlorination of various cis and trans-phenylalkenes with polymeric reagent 1d proceeded anti stereospecifically and followed the Markovnikov type of regioselectivity, the only exception being (Z)-1-phenylpropene, where 9% of regioisomer was formed, while vicinal bromide chlorides were accompanied with up to 7% of vicinal dibromides. The rate of bromination in isopropylbenzene depended on the structure of the reagent 1, as well as the para/ortho regiospecifity, being in the range of 3.6 - 4.0.

It is known that several polymeric resins can be chemically transformed so that they can act as reagents or catalysts, and besides offering simpler experimental techniques, the chemical reactivity can also be influenced when the reagent is attached to the polymeric support[1]. The crosslinked copolymers of styrene with vinylpyridine[2] have received much less attention for the preparation of reagents and catalysts, in spite of the known fact that pyridine has a wide application in organic synthesis by itself, or in conjunction with other reagents. It has already been demonstrated that crosslinked poly(styrene-*co*-4-vinylpyridine) formed various types of complexes with bromine, which were able to brominate alkenes[3] and side chains in alkyl substituted aromatic molecules[4]. Crosslinked poly[styrene-*co*-(1-methyl-4-vinylpyridinium iodide)] was transformed by chlorine to a reagent which chlorinated or iodinated various organic molecules[5].

Preparation of vicinal bromide chlorides from alkenes has been studied several times[6] with various reagents, with the following being the most extensively studied: bromochloride[7-10], pyridinium bromochloride[10,11], tetrabutylammonium dichlorobromate[12-14], and Me_4NBr_2Cl[9].

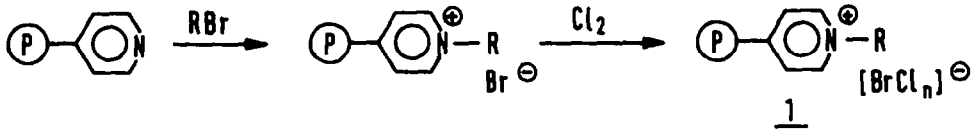
Results and Discussion

In order to get more information about the effect of the polymeric backbone on the reactivity of polymer-supported reagents, we decided to study the reactions of chlorine with several poly[styrene-*co*-(1-alkyl-4-vinylpyridinium bromides)], which were prepared in the reactions of poly(styrene-*co*-4-vinylpyridine) (40 - 42% of pyridine rings, 2% of DVB)[3], with hydrogen bromide or alkyl bromides. In a typical experiment, the poly[styrene-*co*-(4-vinylpyridinium salt)] was suspended in chloroform, and under stirring at 0°C, chlorine gas was introduced until the yellow colour persisted for half an hour, stirred at room temperature for an additional five hours, the polymer resin filtered off and washed with chloroform. Elemental analysis of both halogens showed substantial loss of bromine content and a

very high amount of chlorine, and following compositions were determined: 1a: %Br: 5.6; %Cl: 34.0; 1b: %Br: 10.1; %Cl: 31.5; 1c: %Br: 11.5; %Cl: 31.6; 1d: %Br: 10.8; %Cl: 30.1; 1e: %Br: 9.6; %Cl: 30.4. It is evident that the debromination process was inhibited by the increasing length of the alkyl chain in the pyridinium salt. It is now known that the elemental composition of polymeric reagents does not represent the real potential activity of the reagent, and for this reason we first studied the halogenating capacity of the new reagents 1: 1 g of the reagent was suspended in 50 ml of methanol and 2.5 mmol of 1,1-diphenylethene was added, the reaction mixture stirred at room temperature for 20 hours, the crude reaction mixture, containing 2-bromo-1-methoxy- 1,1-diphenylethane and the excess of 1,1-diphenylethene analyzed by ^{1}H nmr spectroscopy, and the following brominating capacities were established: a mmol of Br per gram of air-dried reagent: 1a (R = H): 0.4; 1b (R = C_2H_5): 1.0; 1c (R = n-C_4H_9): 1.4; 1d (R = n-C_6H_{13}): 1.4; 1e (R = n-$C_{12}H_{25}$): 1.2.

Further, we studied the effect of the structure of the reagent 1 on the reactivity and product distribution in reactions with 1,1-diphenylethene in an aprotic solvent, i.e. chloroform. As evident from Scheme, reagents with a longer alkyl chain were more reactive, and the relative ratio of addition to elimination was also influenced by the structure of the reagent, while Markovnikov type of regioselectivity of bromochlorination was observed. 2-Bromo-1-chloro-1,1-diphenylethane was very unstable under various isolation conditions (glc, tlc) and two conversions, i.e. elimination to 2-bromo-1,1-diphenylethene, and conversion with methanol to 2-bromo-1-methoxy-1,1-diphenylethane, were performed.

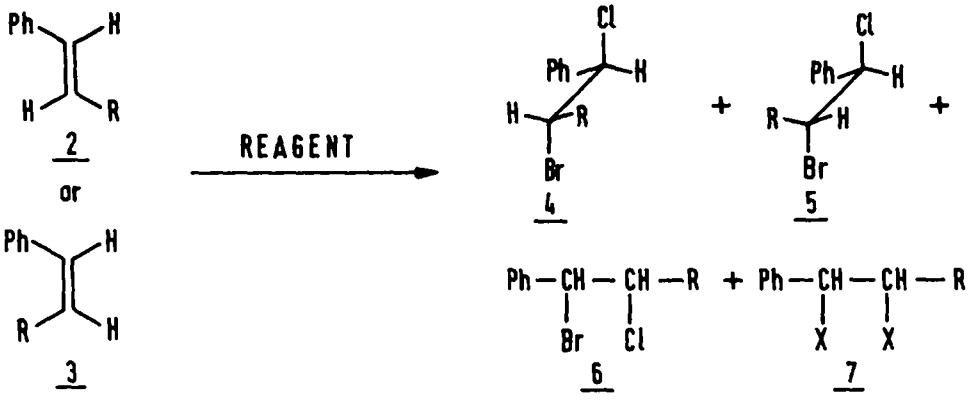
The regioselectivity and stereoselectivity of bromochlorination of alkenes markedly depends both on the reagent and the structure of the alkene. Tetrabutylammonium dichlorobromate reacted with (E)-1-phenyl-1-propene and followed 95% Markovnikov type of regioselectivity (*erythro*-2-bromo-1-chloro-1-phenylpropane)[13], while with 3,3-dimethyl-1-butene, 100% anti-Markovnikovtype of regioselectivity was observed (1-chloro-2-bromo-3,3-dimethylbutane)[14]. According to our findings that polymeric reagents 1 are able to convert alkenes to vicinal bromide chlorides, we found it instructive to study the stereochemistry of addition to various cis and trans-phenylalkenes.



Effect of the Structure of the Reagent on Conversion and Product Distribution in Reactions with 1,1-Diphenylethylene[a]

REAGENT	CONVERSION OF ALKENE /%/[b]	ELIMINATION /%/[b]
1a: R = H	18	39
1b: R = C_2H_5	80	54
1c: R = n - C_4H_5	100	35
1d: R = n - C_6H_{13}	100	28
1e: R = n - $C_{12}H_{25}$	100	28

a/ 1 mmol of 1,1-diphenylethylene; solvent: chloroform (20 ml); reagent 1: 1 g; reaction temperature: 23°C; reaction time: 24 h
b/ 2-bromo-1-chloro-1,1-diphenylethane and 2-bromo-1,1-diphenylethene were formed and their distribution determined by ^{1}H nmr.



a : R = Ph ; b : R = $COOCH_3$; c : R = CH_3

The Effect of the Reagent and Alkene on Stereoselectivity and Regioselectivity of Bromochlorination

ALKENE	REAGENT[a]	PRODUCT DISTRIBUTION[b] VICINAL BROMIDE CHLORIDES 4	5	6	VICINAL DIHALIDES 7
2a	A	52			14(X = Cl)
2a	B	97			
2a	E	67			
2a	1d	95			5(X = Br)
2b	B	85			
2b	1d	93			7(X = Br)
2c	A[c]	90.2	9.8		5-10(X = Cl);12-20(X = Br)
2c	B	94.5		5.5	
2c	C	29			71(X = Br)
2c	D	100			
2c	1d	94			6(X = Br)
3a	A	5.5	68		
3a	B		95		
3a	E	14	47		
3a	1d		93		7(X = Br)
3c	A[c]	24.8	75.2		5-10(X = Cl);12-20(X = Br)
3c	B		76	24	
3c	C		28		72(X = Br)
3c	D		100		
3c	1d		84	9	7(X = Br)

a/ REAGENT: A: $BrCl$[7,8,9,13]; B: $(n\text{-}C_4H_9)_4NBrCl_2$[12,13]; C: $(CH_3)_4NBr_2Cl$[9]; D: PyBrCl[9]; E: N-bromoacetamide/HCl[7]
b/ the ratio of products 4, 5, and 6, is normalized to 100%; where not, the data represent yields of isolated products
c/ the ratio of bromide chlorides only is normalized to 100%

Bromochlorination of trans- (2a) and cis- (3a) stilbene with 1d in dichloromethane at room temperature gave a crude reaction mixture in high yield, which was analyzed by ^{1}H nmr spectroscopy and tlc. On the basis of the spectroscopic data and comparison with those in the literature, we found that anti addition took place (Table), while in the case of trans-alkene 5%, and in the case of the cis isomer 7% of vicinal dibromide (7a: X = Br, relative yields), accompanied the vicinal bromide chloride (4a, 5a). The effect of the reagent on the stereoselectivity of bromochlorination of cis- and trans-stilbene is presented in the Table, and it is evident that reaction with all cited reagents occurred anti with the trans isomer, but in the case of BrCl, vicinal bromide chlorides were accompanied by vicinal dichlorides; however, anti selectivity was diminished in the case of the cis isomer. Bromochlorination of (E)-1-phenyl-2-(methoxycarbonyl)ethene (2b) occurred anti and followed Markovnikov type of regioselectivity (4b). *trans*-1-Phenyl-1-propene (2c) was bromochlorinated with 1d in an anti manner and with Markovnikov type of regioselectivity, with 6% of vicinal dibromides (7c) accompanying 4c. In the case of cis-1-phenyl-1-propene (3c), besides vicinal bromide chlorides formed in an anti attack, following Markovnikov type of regioselectivity (5c), 9% of anti Markovnikov type of regioselectivity (6c) and 7% of dibromide 7c was observed. The effect of the structure of the reagent on the stereochemistry and regioselectivity is presented in the Table.

Finally, we tested the possibility of the use of polymeric reagents 1 for the bromination of the benzene nucleus. We found that reactions proceeded in a mixture of acetic acid and water at 85°C. After 5-hours reaction of 1 mmol of isopropylbenzene with 1.8 g of the reagent 1b, or 1d, or 1e, the conversions were 49%, 70%, and 67%, respectively. The structure of the reagent does not play any important role in the regiospecifity of benzene ring bromination and the para to ortho ratios were found to be 3.6 (1b), 4.0 (1d), and 3.8 (1e).

Experimental Section

Ir spectra were recorded with a Perkin Elmer 727 B spectrometer, ^{1}H nmr spectra with a Jeol-JNM-PS-100 and ^{13}C with Jeol JNM FX 90Q instruments, with Me$_4$Si, as internal reference. Mass spectra and high resolution measurements were taken on a CEC-21-110 spectrometer. Gas liquid partition chromatography was carried out on Varian Aerograph Models 2700 and 3700, and tlc on Merck PSC Fertigplatten silica gel or aluminium oxide F-254. Elemental analysis was carried out in the Pascher microanalytical laboratory in Bonn. Melting points were determined on a Kofler apparatus and are uncorrected. Poly(styrene-*co*-4-vinyl- pyridine)[3], containing 42 - 44% of pyridine moieties, was prepared according to the literature. Solvents were purified[15] before use.

Synthesis of Polymeric Reagent 1a from Poly(Styrene-*co*-4-Vinylpyridine)

4 g of poly(styrene-*co*-4-vinylpyridine) were suspended in 40 ml of chloroform, swelled at room temperature (23°C) for three hours, 8 ml of hydrogen bromide (47%) was slowly added, and the reaction mixture stirred at room temperature for 20 hours. The insoluble resin was filtered off, washed with methanol (twice), chloroform (three times), suspended in 50 ml of chloroform, swelled at room temperature for 24 hours, cooled to 0°C and under stirring chlorine gas was introduced until the yellow colour of the reaction mixture persisted after 30 minutes of stirring at 23°C, stirred for an additional five hours, the insoluble resins filtered off, washed with chloroform (three times), and after drying at 23°C for 20 hours, 6.750 g of product 1a was obtained. For elemental analysis, 1a was dried at 65°C for 4 hours, and 5.6% of Br and 34.0% of Cl was found.

Synthesis of Polymeric Reagents 1b - 1e from Poly(Styrene-*co*-4-Vinylpyridine)

4 g of poly(styrene-*co*-4-vinylpyridine) were suspended in 20 ml of methanol, and after swelling at room temperature (23°C) for 3 hours, 3 - 6 mmols of alkyl bromide (ethyl: 1b, butyl: 1c, hexyl: 1d, or dodecyl bromide: 1e) per mmol of pyridine rings were slowly added. The reaction mixture was refluxed for 20 hours, the insoluble residue filtered off, washed with methanol (twice), chloroform (three times) (complete quarternization is reflected in the disappearance of the IR vibration at 1580 cm^{-1}, corresponding to $\nu_{C=N}$

in the starting polymer), suspended in a given amount of chloroform, and under stirring at 0°C chlorine gas was introduced until the yellow colour of the reaction mixture persisted after 30 minutes of stirring at room temperature (23°C). The reaction mixture was stirred for an additional five hours, the insoluble resin filtered off, washed with chloroform (three times), and dried at 23°C for 20 hours. For elemental analysis, the polymeric resins were dried at 65°C for 4 hours.

Polymeric reagent 1b : $CHCl_3$: 50 ml; isolation of 7.13 g of 1b: %Br: 10.1; %Cl: 31.5.

Polymeric reagent 1c: $CHCl_3$: 75 ml; isolation of 7.60 g of 1c: %Br: 11.5; %Cl: 31.6.

Polymeric reagent 1d: $CHCl_3$: 80 ml; isolation of 7.97 g of 1d: %Br: 10.8; %Cl: 30.1.

Polymeric reagent 1e: $CHCl_3$: 95 ml; isolation of 9.63 g of 1e: %Br: 9.6; %Cl: 30.4.

Reactions of Polymeric Reagents 1 with 1,1-Diphenylethene

1 g of polymeric reagent 1a - 1d was suspended in 20 ml of purified chloroform, 1 mmol of 1,1-diphenylethene was added, the reaction mixture stirred at room temperature (23°C) for 24 hours, the insoluble polymeric residue filtered off and washed with chloroform (twice). The solvent was evaporated, the crude reaction mixtures were analyzed by ^1H nmr spectroscopy. The effect of the structure of the reagent on the conversion and product distribution is presented in Scheme. Besides 2-bromo-1,1-diphenylethene, 2-bromo-1-chloro-1,1-diphenylethane was formed: ^1H nmr ($CDCl_3$): 4.18 ppm (s, 2H); 7.1 ppm (m, 5H); mass spectrum: M^+ at m/z 294, 296, 298 (100 : 135 : 38); calcd. for $C_{14}H_{12}BrCl$ m/z 293.9811, found m/z 293.9820. All attempts to isolate it in pure form either by glc or tlc were unsuccessful, affording only 2-bromo-1,1-diphenylethene, which was also the only product obtained when the crude reaction mixtures resulting in reactions of 1,1-diphenylethene with reagents 1a - 1d were heated; dilution of the crude reaction mixtures with methanol led at room temperature after 3 hours to complete conversion of 2-bromo-1-chloro-1,1-diphenylethane to 2-bromo-1-methoxy-1,1-diphenylethane[16].

Bromochlorination of Phenylalkenes (2a - 2c, 3a, or 3c)

1 mmol of alkene (2a - 2c, 3a, or 3c) was dissolved in 20 ml of distilled dichloromethane and a given amount of polymeric reagent 1d was added. After stirring at 23°C for a given time, the insoluble beads were filtered off, washed with 20 ml of dichloromethane and the solvent evaporated in vacuo. The crude reaction mixtures were analyzed by ^1H nmr spectroscopy, and by ^{13}C nmr spectroscopy and glc, where stated, with the product distributions presented in the Table.

Reaction of trans-Stilbene (2a) with 1d

Reagent 1d: 1.5 g; reaction time: 20 hours; isolation of 288 mg (98%) of the crude reaction mixture, analyzed by ^1H nmr; crystallization from ethanol and from benzene/ethanol yielded 204 mg (70%) of *erythro*-1-bromo-2-chloro-1,2-diphenylethane *(4a)*, mp = 219 - 222°C (mp^{12} = 218 - 221°C). MS M^+ at m/z 294, 296, 298 (100 : 131 : 33). The ^1H nmr spectrum is in agreement with the literature[12].

Reaction of cis-Stilbene (3a) with 1d

Reagent 1d: 1.5 g; reaction time: 4.5 hours; isolation of 278 mg (94%) of the crude reaction mixture, analyzed by ^1H nmr; crystallization from petroleum ether/dichloromethane yielded 230 mg (78%) of *threo*-1-bromo-2-chloro-1,2-diphenylethane *(5a)*, mp = 100 - 101°C (mp^{12} = 102.5 - 103°C). MS M^+ at m/z 294, 296, 298 (100 : 127 : 32). The ^1H nmr spectrum is in agreement with the literature[12].

Reaction of Methyl trans-Cinnamate (2b) with 1d

Reagent 1d: 3 g; reaction time: 30 hours; isolation of 269.4 mg (97%) of the crude reaction mixture, analyzed by ^1H nmr; crystallization from pentane/dichloromethane yielded 230 mg (83%) of methyl *erythro*-2-bromo-3-chloro-3-phenylpropanoate *(4b)*, mp = 115 - 116°C (mp^{12} = 118 - 120°C). MS M^+ at m/z 276, 278, 280 (100 : 129 : 33). The ^1H nmr spectrum is in agreement with the literature[12].

Reaction of trans-1-Phenyl-1-propene (2c) with 1d

Reagent 1d: 1.3 g; reaction time: 45 minutes; isolation of 220 mg (95%) of the crude reaction mixture, analyzed by ^{1}H and ^{13}C nmr and glc (OV 17 3%, Chromosorb W AW 80/100, 130°C); purification by preparative tlc (Al_2O_3, isooctane) afforded 83 mg (71%) of *erythro*-2-bromo-1-chloro-1-phenylpropane *(4c)*, mp = 35 - 36.5°C (recrystallized from isooctane), mass spectrum: m/z 236 (M^+ + 4, 3%), 234 (M^+ + 2, 14), 232 (M^+, 11), 199 (17), 197 (17), 155 (6), 153 (18), 127 (29), 125 (100), 118 (21), 117 (30), 115 (20), 91 (23), 51 (16). ^{1}H and ^{13}C nmr spectra are in agreement with those reported in the literature[13].

Reaction of cis-1-Phenyl-1-propene (3c) with 1d

Reagent 1d: 1.3 g; reaction time: 45 minutes; isolation of 223 mg (96%) of the reaction mixture analyzed by ^{1}H and ^{13}C nmr and glc (OV 17 3%, Chromosorb W AW 80/100, 130°C). The crude reaction mixture contained 84% of *threo*-2-bromo-1-chloro-1-phenylpropane 5c, 9% of *threo*-1-bromo-2-chloro-1-phenylpropane 6c, and 7% of 1,2-dibromo-1-phenylpropane 7c, and their presence was confirmed by comparison with the literature[13].

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