Communications to the Editor

Reaction of Cross-linked Chloromethyl Polystyrene with 1,4-Butanedithiol: Site–Site Interactions and Their Control

Sir:

One of the attractive features which has often been associated with the use of solid phases was their ability to provide isolation of reactive sites which afforded a good alternative to the use of high dilution in the study of reactions involving symmetrical bifunctional molecules or in the study of highly reactive species. A number of reports[1,2] have confirmed that solid supports provide much *more* isolation of reactive sites than would normally be obtained in solution chemistry. Indeed, very reactive species have been successfully isolated[3] on highly cross-linked polymer supports when the number of reactive sites was kept low (<0.5 mequiv/g). In contrast, several reports show that, with lightly cross-linked polymer matrices, intraresin site isolation is generally not achieved.[4,5]

We have designed a probe for intraresin site isolation in 1% cross-linked polystyrene which provides a measure of the extent of site–site interactions and we have devised a system in which these interactions are reduced drastically by simple variations in the reaction conditions. Our probe consists of the reaction of a chloromethylated resin with a symmetrical dithiol in the presence of a base to effect nucleophilic displacement of chloride by sulfur. In such a system, it is expected that, should the reactive sites be isolated on the polymer, each chlorine atom would be replaced by a species containing two atoms of sulfur, while reaction at both extremities of the thiol would lead to a polymer in which each chlorine atom would be replaced by a single atom of sulfur (Scheme I). Thus, a measure of the sulfur content of the polymer after complete removal of chlorine will allow for a calculation of the extent of site–site interactions. Our work was carried out with a 1% cross-linked polystyrene resin having a relatively high degree of functionalization,[6] since it has been shown that site–site interactions increase as cross-linking decreases[5] and as functionalization increases.[1]

In a first experiment, the reactivity of the polymer with sulfur nucleophiles was ascertained by displacement of chloride using butanethiol in basic medium; as expected this reaction was quantitative. When the reaction was carried out with 1,4-butanedithiol using a molar ratio of polymer functional groups:base:dithiol of 0.8:1:4.6 (expt 1, Table I) in DMF at

Scheme I
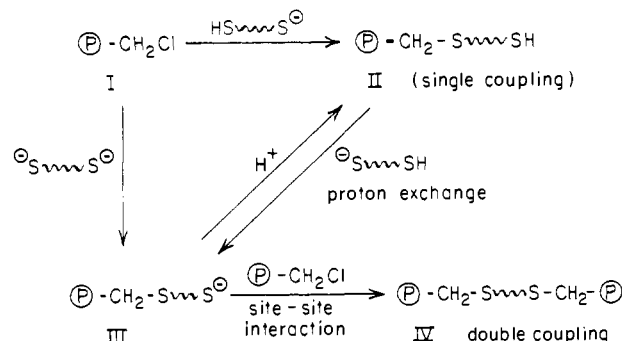
room temperature, the polymer which was isolated contained no chlorine and had a sulfur content corresponding to 62% double coupling[7] to yield IV (Scheme I) and 38% single coupling to yield II. An increase in the amount of base with respect to dithiol[8] resulted in an increase in the amount of double coupling, while a decrease in the ratio of base:dithiol had the opposite effect (Table I, expt 2 and 3, respectively). These experiments clearly confirm that site–site interactions are extensive in chloromethylated 1% cross-linked polystyrene and correlate with the results of Digenis et al.[9] for the reaction of symmetrical diamines with "popcorn" chloromethyl polystyrene in which 80–100% doubly bound species were formed.

The problem which practitioners of solid-phase synthesis must therefore face is how can site–site interactions be avoided in the reaction of a difunctional substrate with a functional polymer. The answer to this question will of course vary depending on the type of reaction being considered. In our case, a solution can be found through consideration of the reactive species which may be involved in the formation of II and IV. A casual inspection of the reactions leading to II and IV would suggest that reaction of the monothiolate with the polymer would lead to single coupling, while reaction of the dithiolate would be responsible for the double coupling. Obviously, this explanation is not satisfactory as shown in expt 3 in which 26% double coupling is obtained even though the high ratio of dithiol:base ensures that few dithiolate species are present. An alternate route leading to the doubly bound IV could proceed through proton transfer involving II and free monothiolate ion

Table I

expt no.	molar ratio,[a] ⓟ-CH₂Cl:base:dithiol	no. of phases	product analysis[b] %S	product analysis[b] mequiv/g	% double coupling,[c] ⓟ-CH₂S(CH₂)₄SCH₂-ⓟ	% single coupling,[c] ⓟ-CH₂S(CH₂)₄SH
1	0.8:1:4.6	2[d]	8.45	2.64	62	38
2	0.2:1:0.69	2[d]	6.76	2.11	94	6
3	0.73:1:11.7	2[d]	10.21	3.19	26	74
4	0.05:1:0.5	3[e]	7.13	2.23	87	13
5[f]	0.11:1:0.68	3[e]	9.62	3.01	39	61
6[f]	0.11:1:0.68	3[e]	9.60	3.00	39	61
7	0.15:1:1.3	3[e]	10.34	3.23	23	77
8[g]	0.15:1:2.6	3[e]	11.21	3.50	5	95

[a] Calculated using the number of milliequivalents of Cl in ⓟ-CH₂Cl. [b] Analyses carried out in our laboratory using 200–300-mg samples to increase accuracy, and by NHW Laboratories. [c] See ref 7 for calculation; these results are estimated to be accurate within ~3%. [d] ~1.5 g of ⓟ-CH₂Cl in 15 mL of DMF with dithiol and NaOCH₃ at room temperature for 24 h, under inert atmosphere. [e] Three-phase reaction under phase transfer conditions with ~1.5 g of ⓟ-CH₂Cl in 15 mL of benzene with 0.13 g of (Bu)₄NOH (40% in water),¦NaOH¦1,4-butanedithiol, and 6 mL of water with vigorous stirring under inert atmosphere for 24 h. [f] Duplicate experiments given to show the consistency of the results. [g] See note 10 for experimental details.

to yield III which, by reaction with a second chloromethyl site, can produce IV.

In order to limit the formation of doubly bound species, the formation of III has to be prevented through control of both the number of dithiolate units present in the medium and the proton exchange reaction. It was thought that such control could be achieved through the use of a three-phase system[10] in which most of the reactive species would be kept from the polymer to limit the proton exchange reaction. Our system consists of a polymer phase swollen in benzene with an aqueous solution of NaOH to which 1,4-butanedithiol is added. The reactive thiolate and dithiolate species are present in the aqueous phase and can be carried to the polymer through the use of a phase transfer catalyst. Using this approach, only a small amount of thiolate can ever be present in the organic phases, and, in addition, since it is known that dianions are transported less easily than monoanions[11] under phase transfer conditions, the influence of the dithiolate on the reaction should be reduced. Our results seem to confirm this expectation as illustrated by the data for expt 2 and 5, in which a drastic reduction of the amount of double coupling is observed with the three-phase system (39 vs. 94%). Double coupling can be reduced to $\simeq$5% by a modest increase[12] in the ratio of dithiol:base which produces an increase in the relative concentration of the monoanion vs. dianion in the aqueous phase (expt 7 and 8). Similarly, double coupling can be increased to $\simeq$87% by ensuring that all dithiol is converted into the dianion (expt 4).

We are presently exploring the application of phase transfer catalysis to the control of site–site interactions in other reactions involving polyfunctional molecules.

References and Notes

(1) A. Patchornik and M. A. Kraus, *J. Am. Chem. Soc.*, **92**, 7587 (1970); R. H. Grubbs, C. Gibbons, L. C. Kroll, W. J. Bonds, Jr., and C. H. Brubaker, Jr., *ibid.*, **95**, 2373 (1973); S. L. Regen and D. P. Lee, *ibid.*, **96**, 294 (1974); J. F. Burlitch and R. C. Winterton, *ibid.*, **97**, 5605 (1975); G. A. Crosby, N. M. Weinshenker, and H. S. Uh, *ibid.*, **97**, 2232 (1975).
(2) C. C. Leznoff and D. M. Dixit, *Can. J. Chem.*, **55**, 3351 (1977); T. M. Fyles, C. C.Leznoff, and J. Weatherston, *ibid.*, **56**, 1031 (1978).
(3) P. Jayalekshmy and S. Mazur, *J. Am. Chem. Soc.*, **98**, 6710 (1976); R. Grubbs, C. P. Lau, R. Cukier, and C. Brubaker, Jr., *ibid.*, **99**, 4517 (1977); G. Gubitosa, M. Boldt, and H. H. Brintzinger, *ibid.*, **99**, 5174 (1977).
(4) J. I. Crowley and H. Rapoport, *Acc. Chem. Res.*, **135** (1975); J. I. Crowley, T. B. Harvey, and H. Rapoport, *J. Macromol. Sci. Chem.*, **7**, 1118 (1973); G. A. Crosby and M. Kato, *J. Am. Chem. Soc.*, **99**, 625 (1977).
(5) L. T. Scott, J. Rebek, L. Ovsyanko, and C. L. Sims, *J. Am. Chem. Soc.*, **99**, 625 (1977).
(6) Chloromethylated resin prepared from Bio-Beads SX-1 (Bio-Rad Laboratories), capacity 2.10 mequiv of Cl/g, or degree of functionalization = 0.244.
(7) The percent double coupling can be calculated as follows. Polymer (1000 g) contains T styrene units, of which X are unsubstituted (mol wt 104), Y are singly bound (mol wt 238), and Z are doubly bound (mol wt 177)

$$1000 = X(104) + Y(238) + Z(177) \qquad (1)$$

and $X + Y + Z = T$. Since the degree of functionalization is 0.244, $Y + Z = 0.244\, T$ and $X = 0.756\, T$. From the sulfur analysis (S expressed in milliequivalents/gram, one gets $S = 2Y + Z$; thus $T = (S - Y)/0.244$. Substituting for X, Z, and T in eq 1, $1000 = 499\, S - 438\, Y$, or $Y = (1000 - 499 S)/438$ and percent double coupling = $100\, Z/(Y + Z)$.
(8) Our experience with the reaction has shown that the ratios of Cl:base or Cl:dithiol have little bearing on the end result of the reaction provided that the nucleophile is always present in excess.
(9) M. B. Shambhu, M. C. Theodorakis, and G. A. Digenis, *J. Polym. Sci.*, **15**, 525 (1977).
(10) A typical three-phase reaction was carried out as follows. To a suspension of 1.40 g of chloromethylated polymer (2.1 mequiv/g) in 15 mL of benzene were added 0.8 g of NaOH in 6 mL of H₂O, 0.13 g of a 40% aqueous solution of tetrabutylammonium hydroxide, and 6 mL of 1,4-butanedithiol. The mixture was stirred vigorously under nitrogen at room temperature for 22 h and filtered, and the polymer was washed with THF–HCl–H₂O (2:1:1), H₂O, THF, acetone, dichloromethane, and methanol. After drying in vacuo, the polymer weighed 1.57 g and contained a trace of chlorine and 11.21% (3.50 mequiv/g) sulfur.
(11) For an excellent review, see E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*,

16, 493 (1977).
(12) Phase-transfer reactions are best carried out with fairly concentrated aqueous ionic solutions. For this reason it was not practical to test the reaction under conditions in which the dithiol:base ratio would approach the 12:1 value of expt 3. Under such conditions essentially no double coupling would be observed. Unfortunately, when the amount of base is reduced drastically, the phase transfer reaction becomes very slow and after 24 h the polymer still contains appreciable amounts of chlorine.

M. Jean Farrall, Jean M. J. Fréchet*
Department of Chemistry, University of Ottawa
Ottawa, Ontario K1N 9B4, Canada

Complete Syn Selectivity in the Alkylation of Lithiated Ketimines

Sir:

The pioneering work of Stork[1] and Wittig[2] on the metalation of ketimines and their subsequent reaction with a variety of electrophiles has proven extremely useful for controlled aldol condensation and also for regioselective functionalization of ketones.[3] Recently reactions of chiral lithiated ketimines[4,5] and aldimines[6] have been established as an important method of asymmetric synthesis, producing chiral ketones in optical yields as high as 95%.[5a] Work in many laboratories on the lithiation and alkylation of other cyclohexanone derivatives, including dimethylhydrazones,[7] oximes and substituted oximes,[8] and also on the structurally related nitrosamines,[9] and N,N-dimethylbenzamides[10] has, in every case, revealed a surprisingly large stereoselectivity with the syn product being formed almost exclusively. Alkylation of conformationally fixed lithiated derivatives with methyl iodide gave in each series a single product (>99%) whose methyl group was shown to possess the syn and axial orientation.[8c,9a] In view of the current conflict as to the origin of this stereoselectivity[11] in these synthetically useful reactions, we have undertaken an investigation of the stereochemistry of lithiation and alkylation of a number of ketimines by direct examination of the products of ¹³C NMR. We report that this sequence of reactions on ketimines also gives *only* syn and *only* axial (in cyclohexanones) alkylation products, a result of major theoretical and practical significance.

Our initial experiments to test for any difference in syn–anti anion stabilities involved a study of the base-catalyzed H–D exchange of acetone-*N*-benzylketimine[13] (1). Only in Me₂SO-d_6 (*tert*-butyl alcohol-*O*-d, 0.03 M in potassium *tert*-butoxide) was the basicity of the medium sufficiently strong to effect an isotopic exchange. The relative rates of syn vs. anti exchange at the two methyl groups[14] was determined to be 50:1 at 20 °C. Since exchange of the anti protons may occur by syn deuteration and then base-catalyzed inversion, the 50:1 rate ratio represents a lower limit for this selectivity.

Lacking other solvent systems sufficiently basic to promote isotopic exchange, we turned our attention to the determination of the stereochemistry of the products of lithiation and alkylation of ketimines. Using standard aprotic conditions, i.e., addition of 1 equiv of ketimine to 1.05 equiv of lithium diisopropylamide (LDA) in THF at −20 °C, then at 0 °C for 1 h, and then cooling to −78 °C, followed by addition of 1.1 equiv of methyl iodide and reaction for 1 h at −78 °C, rapid concentration at <0 °C, and dissolution in CDCl₃, gave a sample whose ¹³C NMR was immediately recorded at −2 °C. The results of alkylation of a number of ketimines **2a**, summarized in Table I, demonstrate the reaction to be totally stereoselective, yielding syn product only.[15,16] Subsequent isomerization to the thermodynamically more stable anti configuration could be followed by ¹³C NMR and the position of this equilibrium is also given in Table I.