Communications to the Editor

On the Rate of Site–Site Interactions in Functionalized Polystyrenes

Sir:

Reagents attached to insoluble, cross-linked polystyrene supports must experience reduced mobility with respect to their counterparts in bulk solution. Evidence for[1] and against[2] this site–site insulation or pseudodilution leaves questions regarding the rates at which intrapolymeric encounters occur. Here we report experiments which bear on this issue.

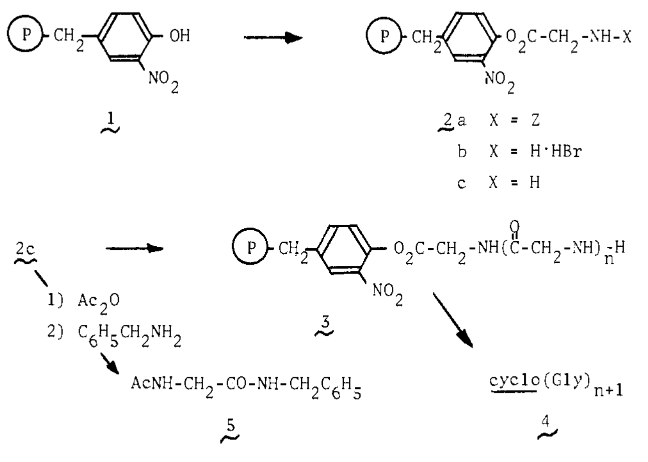
Our technique involves generating a self-destructive species on a given support and determining its rate of disappearance. Specifically, we examined the polymer-bound acylating agent—nucleophile system **2c.** Glycyl transfers within the resin produce peptides of glycine **3,** bound as their C-terminal nitrophenyl esters; cyclization then releases peptides **4** into solution.[3] See Scheme I.

Polymer-bound nitrophenol **1,** 1 mequiv/g was prepared by Patchornik's procedure[4] from 4% cross-linked polystyrene (Rohm & Haas XE-305). Radioactive glycine was attached as its benzyloxycarbonyl (Z) derivative **2a,** 0.8 mequiv/g, using carbodiimide. N deblocking with HBr–HOAc gave the stable salt **2b.**

Suspensions of **2b** in DMF were treated with excess Et_3N or *N*-methylmorpholine to ensure that the generation of **2c** was rapid and complete.[5] Radioactivity was quickly released into solution during the first 30 min (50%) and then more slowly[6] (~65% after 2 days). Isotope dilution established that 20% of the activity released was diketopiperazine (**4,** $n = 1$) and <2% was glycine (little, if any, hydrolysis occurs). The remaining activity in solution was presumably in the form of cyclic oligomers of glycine (**4,** $n > 1$) since the ninhydrin test proved negative.

The extent of disappearance of monomer **2c** could be determined by quenching the intrapolymeric acyl transfers with Ac_2O. Subsequent treatment with benzylamine releases any remaining **2c** in the form of the *N*-benzylamide of aceturic acid **5.** Isotope dilution for **5** revealed that, 30 min after Et_3N was added, <5% of the original activity on the solid phase was the monomer **2c,** whereas, after 5 min, 20% was the monomer. When **2b** was treated simultaneously with Et_3N and Ac_2O, followed by benzylamine, 80% monomer **2c** was trapped.[7] This demonstrates that glycyl transfers within the polymer occur even in the presence of excess acylating agents in solution.

Scheme I



Initially, the disappearance of monomer **2c** should resemble a second-order process. Interaction of two sites gives **3** ($n = 1$) which can cyclize and release diketopiperazine into solution. However, **3** ($n = 1$) may also engage in further reactions with monomer sites, acting either as a nucleophile or as an acylating agent. Evidence that these secondary processes occur may be inferred from the low yield of diketopiperazine. The ensemble of polymer-bound acylating agents and nucleophiles thus generated and the large numbers of their possible intrapolymeric reactions preclude kinetic analysis. The empirical value of 1–2 min for the half-life of **2c,** assuming a second-order process for its disappearance, can be derived from the quenching experiments. If acyl transfers between sites of **2c** do not occur at every encounter, this half-life corresponds to a lower limit for the encounter frequencies of reagents attached to such polymers. Remarkably, this figure agrees well with that derived independently by Mazur[8] for the dimerization rate of polymer-bound benzyne.

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References and Notes

(1) W. D. Bonds, C. H. Brubaker, Jr., E. S. Chandrasekaran, C. Gibbons, R. H. Grubbs, and L. Kroll, *J. Am. Chem. Soc.*, **97,** 2128 (1975); P. Jayalekshmy and S. Mazur, *ibid.*, **98,** 6710 (1976); C. C. Leznoff and J. M. Goldwasser, *Tetrahedron Lett.*, 1875 (1977); C. C. Leznoff and S. Greensburg, *Can. J. Chem.*, **54,** 3824, 935 (1976); M. A. Kraus and A. Patchornik, *J. Am. Chem. Soc.*, **93,** 7325 (1971).

(2) J. I. Crowley, T. B. Harvey, III, and H. Rapoport, *J. Macromol. Sci. Chem.*, **7,** 1118 (1973); J. P. Collman, L. S. Hegedus, M. P. Cooke, J. R. Norton, G. Dolcetti, and D. N. Marquardt, *J. Am. Chem. Soc.*, **94,** 1789 (1972); L. T. Scott, J. Rebek, L. Ovsyanko, and C. L. Sims, *ibid.*, **99,** 625 (1977); J. I. Crowley and H. Rapoport, *Acc. Chem. Res.*, **9,** 135 (1976).

(3) M. Fridkin, A. Patchornik, and E. Katchalski, *J. Am. Chem. Soc.*, **87,** 4646 (1965). Azlactone formation may also release the polyglycines from the resin, but this also requires at least one intrapolymeric acyl transfer of **2c.**

(4) L. Kalir, M. Fridkin, and A. Patchornik, *Eur. J. Biochem.*, **42,** 151 (1974).

(5) Control experiments with **2a** established that these bases did not act as nucleophilic catalysts under these conditions; cf. J. Rebek, D. Brown, and S. Zimmerman, *J. Am. Chem. Soc.*, **97,** 454 (1975).

(6) Unlike **2a** which reacted readily and completely (>95%) with benzylamine in solution, samples of **2b** which had been exposed to Et_3N for this time failed to release additional radioactive material, even under forcing conditions.

(7) Experiments using lower levels of polymer loading (0.01 mequiv/g) gave similar results. The "mobility" of groups on such supports has been shown to decrease with increased cross-linking (S. L. Regen, *J. Am. Chem. Soc.*, **96,** 5275 (1974)), and with charge type (G. Crosby and M. Kato, *ibid.*, **99,** 278 (1977)).

(8) S. Mazur and P. Jayalekshmy, *J. Am. Chem. Soc.*, elsewhere in this issue.

Julius Rebek, Jr.,* John E. Trend
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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Synthesis and Characterization of (Pentafluorosulfur)acetylenes

Sir:

The synthesis and properties of compounds containing pentafluorosulfur groups have been a matter of concern for some time,[1] and renewed interest in such materials is evident from recent publications.[2] As an extension of earlier work in

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