

comparison purposes a polymer with randomly distributed amino groups was prepared from 3.

To investigate the distance accuracy both polymers were equilibrated with an equimolar mixture of the three dialdehydes 4, 5, and 6, requiring for a two-point binding a distance of the amino groups in the polymer of 0.72, 1.14, and 1.56 nm, respectively. With other distances only a one-point binding is expected.

In Table I the apparent binding constants obtained under the conditions used are given. Polymers A-1 and A-2 showed the highest uptake for the dialdehyde with the same distance of the functional groups as the template. The selectivity was calculated as the selectivity factor α and corrected for the different nonspecific adsorption to the polymer with statistically distributed amino groups; e.g.,

$$\alpha'_{4,5} = \frac{K_4/K_{4\text{stat}}}{K_5/K_{5\text{stat}}} \quad (1)$$

where K_4 = apparent binding constant for substance 4 on P A-1 or P A-2 and $K_{4\text{stat}}$ = apparent binding constant for substance 4 on P A-3.

The observed selectivity is astonishingly high in the case of P A-1 with $\alpha'_{4,6} = 5.37$. Even a distance difference of only 0.42 nm (4.2 Å) shows a selectivity of $\alpha'_{4,5} = 4.60$. The polymer prepared from 2 with larger distance between the groups (1.56 nm) was less selective but still showed $\alpha'_{6,5} = 1.69$ and $\alpha'_{6,4} = 1.81$ which indicates a strong preference for its own template. This shows that the functional groups at the polymer remain in a given position since distances of 0.42 nm can be clearly recognized by the added dialdehydes.⁷

Aside from a selective two-point binding, the foregoing example might contain some shape selectivity as well. To avoid any shape selectivity, two amino groups were attached to the surface of silica at a distinct distance from one another using the template monomers 7 and 8.⁵ In this case the attachment to the surface occurs by condensation through siloxane bonds between the methoxy silane groups of 7 and 8 and the silanol groups on the surface of the silica.⁸ Most of the remaining silanol groups were afterwards blocked by reaction with hexamethyldisilazane to avoid nonspecific adsorption. The templates could be split off to more than 95% (see Figure 1). In this case the position of the two amino groups should not be changed by chain mobility, swelling, or shrinking as in a polymer. The distance can only be altered by conformational changes within the functional group part.

The selectivity was determined by equilibration with an equimolar mixture of the two template dialdehydes 4 and 10 (see Table II). Both silicas showed a significant difference in binding preferring their own templates with α -values of 1.74 and 1.67. So only by the distance selectivity and with differences of only 0.33 nm (between 4 and 10) could selectivity be obtained.

Imprinting on the surface of silica is thus a further extension of the original imprinting method.^{2,3} The method appears to be applicable for a wide range of examples, some of them have already been verified.⁹

Acknowledgment. We thank "Fonds der Chemischen Industrie" and the "Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen" for financial support.

(7) For related work using diketals for the introduction of each two diol groupings, see: Shea, K. J.; Dougherty, T. K. *J. Am. Chem. Soc.*, following paper in this issue. We are grateful to professor Shea for an exchange of information prior to publication.

(8) Wide-pore silica Fractosil 500, Merck, Darmstadt) was used. An amount of monomers 7 and 8 was used that would be expected to cover around 20% of the surface (2×10^{-5} and 9×10^{-6} mol/g, respectively) and to attain site isolation of each two groups. Condensation was effected by boiling in xylene for 40 h, similar to methods for binding substances via one siloxane group (see, e.g., Evans, M. B.; Dale, A. D.; Little, C. J. *Chromatographia* 1980, 13, 5. Practically all monomer had been taken up by a two-point binding. After this time an excess of hexamethyldisilazane was added and again refluxed for 20 h.

(9) Wulff, G.; Heide, B., unpublished results.

Molecular Recognition on Synthetic Amorphous Surfaces. The Influence of Functional Group Positioning on the Effectiveness of Molecular Recognition

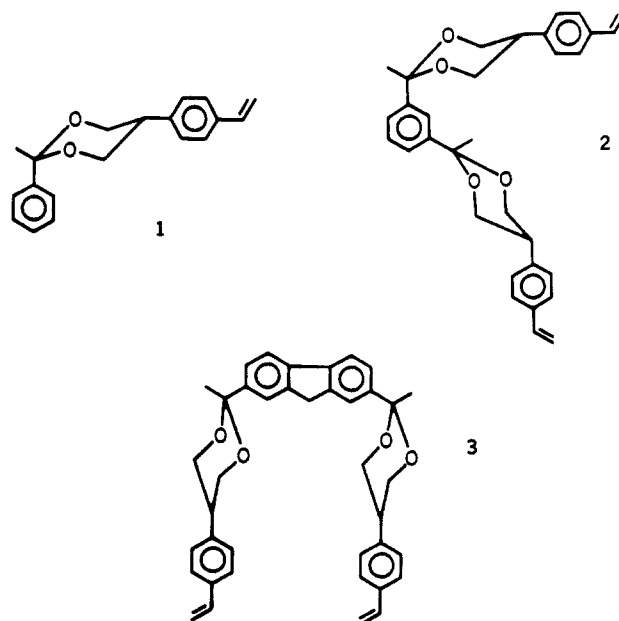
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The template synthesis method is used to prepare macroreticular polymers containing sites of organic functional groups. The spatial relationship of the functional groups at each site is determined, in part, by the spacer used to introduce the functionality and by the mobility of functional groups on the polymer surface. Sites prepared by this method have been shown to exhibit molecular recognition. The technique employed for the construction of these sites was developed by Wulff¹ and co-workers and has also been applied by ourselves² and others³ for the preparation of selectively functionalized network polymers. This paper reports the results of an investigation of how molecular recognition is influenced by the initial positioning of the functional groups at the binding site.

The system chosen for study is outlined in Scheme I. Aromatic ketones are used for spacer or template molecules. Ketals 1-3⁴



(1-2 mol %), prepared from 2-(p-vinylphenyl)-1,3-propanediol,⁵

(1) (a) Wulff, G.; Sarhan, A.; Zabrocki, A. *Tetrahedron Lett.* 1973, 4329. (b) Wulff, G.; Vesper, W.; Grobe-Ensler, R.; Sarhan, A. *Makromol. Chem.* 1977, 178, 2799. (c) Wulff, G.; Zabrocki, K.; Hohn, J. *Angew. Chem., Int. Ed. Engl.* 1978, 17, 535. (d) Sarhan, A.; Wulff, G., *Makromol. Chem.*, 1982, 183, 1603. (e) Wulff, G.; Best, W.; Akelah, A. *React. Polym. Ion Exchn., Sorbents* 1984, 2, 167. (f) Wulff, G.; Dederichs, W.; Grotstollen, R.; Jupe, C. In "Affinity Chromatography and Related Techniques"; Gribnau, T. C. J., Nivard, R. J. F., Eds.; Elsevier: Amsterdam, 1982; p 207.

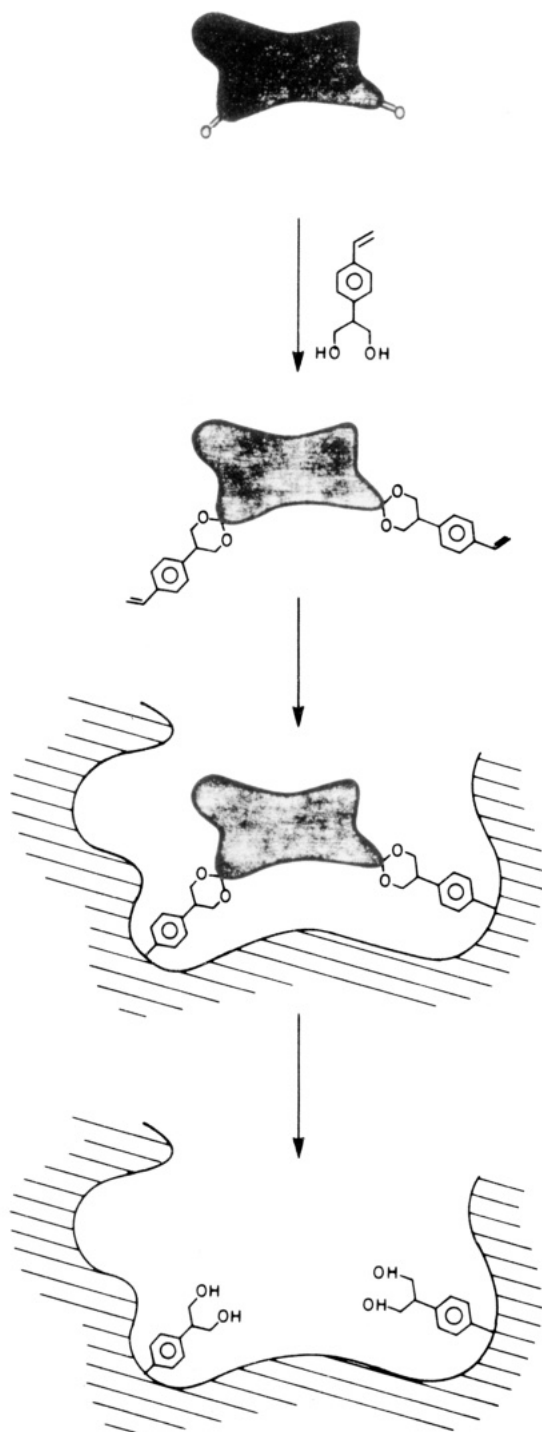
(2) (a) Shea, K. J.; Thompson, E. A. *J. Org. Chem.* 1978, 43, 4255. (b) Shea, K. J.; Thompson, E. A.; Pandey, S. D.; Beauchamp, P. D. *J. Am. Chem. Soc.* 1980, 102, 3149. (c) Shea, K. J.; Thompson, E. A. *Macromolecules* 1985, 18, 814.

(3) (a) Damen, J.; Neckers, D. C. *Tetrahedron Lett.* 1980, 1913. (b) Damen, J.; Neckers, D. C. *J. Am. Chem. Soc.* 1980, 102, 3265. (c) Anderson, B.; Sellergren, B.; Mosbach, K. *Tetrahedron Lett.* 1984, 25, 5211.

(4) Single stereoisomers (cis) of the bis-ketal template assemblies were used for these experiments. Their stereochemistry was assigned on the basis of NMR and X-ray crystallographic studies of model 1,3-dioxanes; Shea, K. J.; Dougherty, T. K. *J. Org. Chem.* 1985, 50, 4439.

(5) All new compounds gave spectral properties and analytical data consistent with the assigned structure.

Scheme I



are individually copolymerized with either technical grade divinylbenzene (DVB) or styrene-1,3-diisopropenylbenzene (S-DIP), using acetonitrile as diluent.⁶ Hydrolysis of these materials (MeOH/H₂O/H₂SO₄) results in liberation of the template molecule and formation of a functionalized site on the macro-molecule containing 1,3-diol groups.⁷ Hydrolysis yields and typical loadings are summarized in Table I.

(6) Polymerizations were run in bulk using AIBN as initiator. A description of the experimental procedures for polymerization and complete characterization of macroreticular DVB is given in ref 2b.

(7) For earlier work regarding the preparation and synthetic applications of polymer-bound ketalizing groups, see: (a) Fyles, M. T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935. (b) Leznoff, C. C.; Greenberg, S. *Can. J. Chem.* **1976**, *54*, 3824. (c) Frechet, J. M. J.; Bald, E.; Svec, F. *React. Polym., Ion Exch., Sorbents* **1982**, *1*, 21.

The S-DIP matrix, which was found to result in significantly greater hydrolysis yields, was used for all subsequent investigations.⁸ Rebinding experiments revealed that the template molecules (aromatic ketones) quantitatively reketalyze at vacated sites.⁹

The criterion used to evaluate the efficiency of molecular recognition is the preference for functionalized sites to rebind the original template. The results of competitive rebinding experiments are given in Table II. The ratios represent the relative molar amounts of ketones obtained from a subsequent hydrolysis. In all cases the combined yield of rebound diketone is equivalent to the number of vacant sites on the material ($\pm 3\%$). The rebinding ratios are also adjusted for the intrinsic affinity of the individual ketones for polymers that contain a single 1,3-diol group at each site (template 1). These corrected rebinding selectivities (α) are also included in Table 2.¹⁰

The rebinding studies reveal that changes in selectivity can result from either small changes in diketone carbonyl spacing or from the initial positioning of the 1,3-diol groups. For example, upon exposure of polymers prepared from a template of 1,3-diacetylbenzene (i.e., 2) to a mixture of 1,3- and 1,4-diacetylbenzene, preferential uptake of the original template, 1,3-diacetylbenzene, is observed. In this example the "intrinsic" selectivity for 1,4-diacetylbenzene is reversed ($\alpha_{1,3/1,4} = 1.69$) in spite of the fact that the spacing of the two carbonyl groups differs by less than 1 Å.

It is important to note that under the reaction conditions for rebinding, the selectivities are *kinetic*; exchange of bound ketones with those in bulk solution does not take place.

One of the more interesting examples of molecular discrimination is found in competition between 1,3-diacetylbenzene and 2,7-diacetylfluorene. The carbonyl separation between those two compounds differs by 5.1 Å. With acetophenone as the template, (1), 1,3-diacetylbenzene and 2,7-diacetylfluorene rebind in a 60:40 ratio. When the template is changed to 1,3-diacetylbenzene (2), the selectivity for 1,3-diketone is 85:15 ($\alpha_{1,3/1,4} = 3.8$). Note, however, that when 2,7-diacetylfluorene is used as the template (3) the selectivity is not reversed, rather 1,3-(or 1,4-)diacetylbenzene is still preferred in rebinding ($\alpha_{1,3/1,4} = 0.64$, $\alpha_{1,4/1,3} = 0.62$).



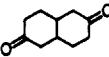
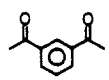
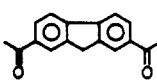
These results permit several general observations to be made. First, changes in rebinding selectivity are brought about by changes in the positioning of the functionality at the binding site. Optimal selectivity is observed at approximately 5-Å separation of 1,3-diol groups, selectivity falls off at greater separations. It is also clear, however, that other factors are at play in determining the kinetic selectivity. The sites may be viewed as hydrophilic regions on a hydrocarbon surface. Substrate rebinding will be dependent not only upon spacing of the 1,3-diol groups but also on a hydrophilic attraction. For small diketones this hydrophilic attraction is expected to be very important but is expected to diminish for larger diketones. The combined influence of hydrophilic interactions coupled with a general trend of reduced selectivity as the distance between binding groups is increased may account for the high selectivities observed with template 2 and for the failure of polymers with 2,7-diacetylfluorene templates (3) to exhibit a preference for the original template.

(8) The characterization of S-DIP copolymers and an analysis of the origins of the differences in chemical properties between S-DIP and DVB networks will be described in a forthcoming paper. Shea, K. J.; Dougherty, T. K., manuscript in preparation.



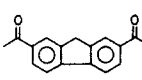
(9) Rebinding of *original* template molecules produced polymers for which no evidence for carbonyl absorption could be found (FT-IR). These results indicate that diketones were rebound to both carbonyls.

(10) Selectivities (α) were calculated from the experimentally measured rebinding ratios corrected for the intrinsic affinity of each substrate for randomly distributed 1,3-diol groups introduced by template 1. For example, the selectivity of polymers prepared with template 2 for 1,3- vs. 1,4-diacetylbenzene $\alpha_{1,3/1,4} = (58/43)/(42/55) = 1.69$.

Table I. Hydrolysis Yield of Polymer Ketal Template^a

| Template | Loading ($\mu\text{mol/g}$) | Matrix | Yield |
|---|----------------------------------|--------|-------|
|  | 60 | DVB | 56 |
| | 60 | DIP | 100 |
|  | 60 | DIP | 100 |
| | 12 | DIP | 100 |
|  | 60 | DVB | 0 |
|  | 60 | DVB | 20 |
| | 60 | DIP | 82 |
| | 12 | DIP | 77 |
|  | 60 | DIP | 86 |
| | 12 | DIP | 67 |

^a See text for conditions.Table II. Rebinding Ratios and Corrected Selectivities (α)^a

| Template | Rebinding Substrates | | | |
|---|--|--|--|--|
| | Ac / 1,3 | 1,3 / 1,4 | 1,4 / fl | 1,3 / fl |
|  | 60 : 40 | 45 : 55 | 65 : 35 | 60 : 40 |
|  | 40 : 60 ($\alpha_{1,3/\text{Ac}} = 2.25$) | 58 : 42 ($\alpha_{1,3/1,4} = 1.69$) | 80 : 20 ($\alpha_{1,4/\text{fl}} = 2.15$) | 85 : 15 ($\alpha_{1,3/\text{fl}} = 3.8$) |
|  | | | 75 : 25 ($\alpha_{1,4/\text{fl}} = 0.62$) | 70 : 30 ($\alpha_{1,3/\text{fl}} = 0.64$) |

^a Ac = acetophenone; 1,3, 1,4 = 1,3- and 1,4-diacetylbenzene; fl = 2,7-diacetylfluorene. Typical rebinding conditions employed equimolar amounts of competing ketones in a fourfold excess over the number of available sites on the polymer in refluxing benzene containing a catalytic amount of TSA.

We are continuing our efforts to establish the relative importance of functional group positioning, hydrophilicity and complementary shape in the molecular recognition process.¹¹

Acknowledgment. We thank the National Institutes of Health and Hughes Aircraft Corporation for financial support of this work.

Registry No. (S)-(DIP)-(3-(4-ethenylphenyl)-1,5-dioxaspira[5.5]undecane) (copolymer), 100047-21-0; (S)-(DIP)-(6-(4-ethenylphenyl)-2-methyl-2-phenyl-*m*-dioxane) (copolymer), 100047-23-2; (S)-(DIP)-(5,5'-bis(4-ethenylphenyl)hexahydrodispiro[*m*-dioxane-2,2'-(1'*H*)-naphthalene-6,6'-(7*H*),2''-*m*-dioxane]) (copolymer), 100047-25-4; (1,4-bis[5-(4-ethenylphenyl)-2-methyl-*m*-dioxan-2-yl]benzene)-(S)-(DIP) (copolymer), 100047-27-6; (S)-(DIP)-(2,7-bis[5-(4-ethenylphenyl)-2-methyl-*m*-dioxan-2-yl]fluorene) (copolymer), 100084-88-6; (DVB)-(3-(4-ethenylphenyl)-1,5-dioxaspira[5.5]undecane) (copolymer), 100047-28-7; (DVB)-(1,4-bis[5-(4-ethenylphenyl)-2-methyl-*m*-dioxan-2-yl]benzene) (copolymer), 100047-30-1; acetophenone, 98-86-2; 1,3-diacetylbenzene, 6781-42-6; 2,7-diacetylbenzene, 961-27-3; 1,4-diacetylbenzene, 1009-61-6.

(11) For related work regarding molecular recognition of template functionalized polymers, see: Wulff, G.; Heide, B.; Helfmeier, G., preceding paper in this issue. We are grateful for Professor Wulff for an exchange of information prior to publication.

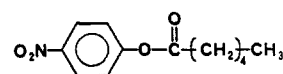
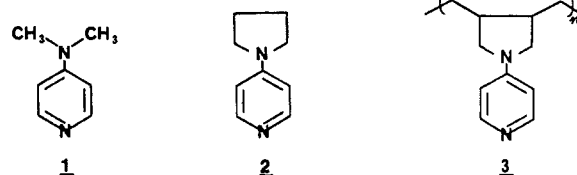
Inverse Phase Transfer Catalysis. First Report of a New Class of Interfacial Reactions

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Phase-transfer catalysis has been used to promote a variety of interfacial reactions involving small molecule reactants,¹ polymer synthesis,² and polymer modification.³ All transfer agents employed to date facilitate transport of a water-soluble or solid reactant into an organic phase. We present evidence here for a new class of reactions involving transport of an organic-soluble reactant into an aqueous phase for reaction.

Our approach is based on 4-aminopyridine supernucleophiles. 4-(Dimethylamino)pyridine (DMAP, 1) and 4-pyrrolidinopyridine



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(PPY, 2) have been used to accelerate a variety of homogeneous reactions.⁴ We recently synthesized a polymer analogue of PPY⁵ that displays *greater* catalytic activity in homogeneous reactions than PPY, the most active of the small molecule supernucleophiles.⁶

The first reaction studied involved the acylation of aqueous racemic alanine with organic-soluble acid chlorides.⁷ Table I summarizes the conversions and product yields for fixed reaction times of DMAP-catalyzed and uncatalyzed interfacial reactions. The decanoyl chloride reaction was carried out for 1 h, although complete disappearance of the starting material occurred in less than 10 min with DMAP present. The rate acceleration with

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(1) Weber, W. P.; Gokel, G. W. "Reactivity and Structure Concepts in Organic Chemistry"; vol. 4; Springer-Verlag: New York, 1977; Vol. 4.

(2) Rassmussen, J. K.; Smith, H. K. *J. Am. Chem. Soc.* **1981**, *103*, 730.

(3) Mathias, L. J., Carraher, C. E., Eds. *Polym. Sci. Technol.* **1984**, *24*. Plenum Press: NY, 1984.

(4) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(5) Mathias, L. J.; Vaidya, R. A.; Bloodworth, R. H. *J. Polym. Sci., Polym. Lett. Ed.* **1985**, *23*, 289.

(6) Vaidya, R. A. Ph.D. Dissertation, University of Southern Mississippi, Hattiesburg, MS, 1985.

(7) General procedure for acid chloride-amino acid IPTC reactions: Aqueous 1 N NaOH, 10 mL, and 0.01 mol of the amino acid were stirred in a jacketed reactor thermostated at 0 °C and allowed to thermally equilibrate for 10 min. Catalyst, 0.001 mol, dissolved in 1 mL of methylene chloride was added to catalyzed reactions and 1 mL of solvent was added to control reactions. After 5 min, 0.011 mol of the acid chloride dissolved in 9 mL of cold methylene chloride were added in one portion. Reaction times were counted from this instant. After the required reaction time had elapsed, the methylene chloride was evaporated from the mixture and the aqueous phase was cooled and acidified with cold 0.5 M KHSO₄ to pH 2. The reaction products precipitated and were filtered and washed extensively with deionized water. The wet cake was dried at 40 °C in a vacuum oven. The percent acid in the product was determined by using FTIR or ¹H NMR. From the total weight of the product, the amount of the amide and the total amount of acid chloride reacted were calculated.