Oxidation of Some Penicillins and Other Sulphides by Use of a Polymer-supported Peroxy-acid

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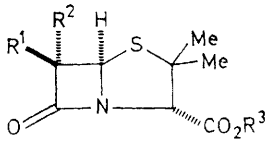
The oxidation of sulphides by a resin containing peroxy-acid residues has been investigated. Tetrahydrothiophen and L-methionine react with 1 equiv. of reagent to give both sulphoxide and sulphone. High yields of sulphone are obtained when more than 2 equiv. of reagent are used. Penicillins and deacetoxycephalosporins react with 1.1—1.3 equiv. of polymeric peroxy-acid to give high yields of sulphoxide, and in several instances removal of the polymer at the end of the reaction period left a solution of just the sulphoxide. Where mixtures of epimeric sulphoxides were formed, the polymeric reagent showed a stereoselectivity similar to that of monomeric reagents. Some success has been achieved in recycling the spent resin reagent. Penicillin G is efficiently oxidised to its *S*-oxide when a solution in acetone is passed down a column of peroxy-acid resin at 40 °C.

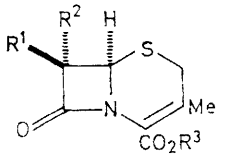
We recently described the preparation of a resin containing aromatic peroxy-acid residues and its use to oxidise olefins to epoxides.[1] We now describe the use of the same resin to oxidise sulphides, mainly penicillins and deacetoxycephalosporins, to sulphoxides or sulphones. The attractive feature of the polymer-supported reagent is that at the end of the reaction period the excess and/or spent peroxy-acid can be separated from the other products simply by filtration or centrifugation. This is especially helpful when the substrate is acidic. Many of the present oxidations proceeded in high yield and in several cases removal of the polymer at the end of the reaction period left a solution containing only the desired sulphoxide or sulphone. An interesting possibility with polymer-supported reagents is that of carrying out reactions by passing a solution of the substrate down a column of the reagent in much the same way that ion-exchange resins are used. We have successfully oxidised a penicillin to its *S*-oxide in this manner.

The peroxy-acid resins used were prepared as before from copolymers of styrene with 1 or 2% *p*-divinylbenzene in the form of 200—400 mesh beads.[1] About 60% of the phenyl residues carried peroxy-acid substituents and the resins had an oxidising capacity of *ca.* 3.9 mmol [O] per g. We first investigated the oxidation of tetrahydrothiophen in tetrahydrofuran and L-methionine in water. Both substrates were oxidised readily and similar results were obtained in each case (see Table 1). The reagent was not very selective when 1 equiv. was used, much sulphone being formed. When more than 2 equiv. of peroxy-acid resin were used high yields of sulphone were obtained. A sample of the L-methionine *SS*-dioxide was isolated and its specific rotation measured. This showed that no racemisation occurred during the oxidation. It is surprising that L-methionine can be oxidised so well in a poor swelling solvent such as water.[1]

We next turned our attention to the oxidation of some penicillins (I) and deacetoxycephalosporins (II). Oxidation of penicillins to *S*-oxides is of interest because the *S*-oxides can be converted into commercially important cephalosporin derivatives.[2] When the penicillins or deacetoxycephalosporins were treated with the polymeric peroxy-acid in dimethylformamide, tetrahydrofuran, or acetone at 20 °C they were oxidised selectively to give the *S*-oxides in high yield. The results (Table 2) show that even quite large molecules like β-lactams can reach a high percentage (>90%) of the reactive groupings on the resin despite the fact that the resin is quite heavily substituted. The oxidations of 6,6-dibromopenicillanic acid (I; $R^1 = R^2 = Br$, $R^3 = H$) and



(I)



(II)

methyl 6α-chloropenicillanate (I; $R^1 = H$, $R^2 = Cl$, $R^3 = Me$) are of particular interest because mixtures of epimeric sulphoxides were produced. The former gave the *R*- and *S*-epimers in the ratio 87 : 13. This ratio should be compared with that (91 : 9) found when

TABLE 1

Oxidations of tetrahydrothiophen and L-methionine

Substrate	Equiv. of peroxy-acid resin	Solvent	Reaction temp (°C)	Yields (%) of oxidation products: Sulphide	Sulphoxide	Sulphone
Tetrahydrothiophen [a]	1.00	THF [c]	4	20	30	23
	2.20	THF	20	0	0	94
L-Methionine [b]	1.00	H_2O	20	32	45	23
	1.33	H_2O	20	0	67	33
	2.50	H_2O	20	0	8	92
	3.30	H_2O	20	0	0	100

[a] Reaction time 16 h; product analysed by g.l.c. [b] Reaction time 140 min; product analysed by ^1H n.m.r. spectroscopy. [c] THF = tetrahydrofuran.

[1] C. R. Harrison and P. Hodge, *J.C.S. Perkin I*, 1976, 605.
[2] R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, 1973, **6**, 32.

m-chloroperbenzoic acid was used under similar reaction conditions.[3] The 6α-chloro-compound gave the *R*- and *S*-epimers in the ratio 5 : 95; *cf.* 12 : 88 with the monomeric peroxy-acid.[4] Hence here, as in the epoxidations carried out with this reagent,[1] the fact that the peroxy-acid residues are attached to the phenyl rings of polystyrene makes little or no difference to the stereoselectivity of the reagent.

Polymeric reagents become more attractive if the spent reagent can be recycled. The spent resin from the oxidations of penicillin V (I; R^1 = PhO·CH_2CO·NH, R^2 = R^3 = H) could be regenerated and re-used to oxidise this substrate twice before the polymer began to show serious signs of physical deterioration. A carboxy-substituted polystyrene resin that can undergo twelve oxidation–reduction cycles without apparent change in physical form has been described recently.[4] It differed from our reagent mainly in the extent of substitution (*ca.* 15% to be compared with our *ca.* 80%). It appears, therefore, that less substituted resins are more suitable than highly substituted resins for recycling, but the method used to introduce the carboxy-substituents and the conditions of oxidation (which differed slightly from ours) and reduction may also influence the stability.

Finally we investigated the possibility of oxidising a penicillin to its *S*-oxide by passing a solution down a column of peroxy-acid resin. For this purpose a polymeric peroxy-acid was prepared from a macroporous polystyrene in the form of 20—50 mesh beads. It was considered that for use in columns this resin would be superior to those used in our other work because macroporous resins swell less when treated with solvents, and also because the coarser beads give better flow rates. By using the column of reagent at 40 °C, penicillin G (I; R^1 = PhCH_2·CO·NH, R^2 = R^3 = H) in acetone was oxidized to its *S*-oxide in 87% yield when the residence time was 10—15 minutes and 91% yield when the residence time was 30 min. This is to be compared with a yield of 85% for a normal batch experiment for 2 h at 20 °C with 1.5 equiv. of the resin. The spent resin in the column could be regenerated *in situ* to 99% of its original activity. Fréchet and Haque have also shown that peroxy-acid resins can be generated from columns of macroporous carboxy-resins.[4] There is little doubt that the operations carried out with the column could be automated.

TABLE 2

Oxidation of penicillins and deacetoxycephalosporins with polymeric peroxy-acid [a] (1.1—1.3 equiv.) at 20 °C

Substrate R^1, R^2	R^3	Reaction solvent [b]	Time (h)	Configuration of sulphoxide	% Product in residue [c]	Yield (%) [d]
(a) Penicillins (I)						
PhO·CH_2·CO·NH, H	H	DMF	0.5	*S*	100	99
PhO·CH_2·CO·NH, H	H	THF	1	*S*	100	100
PhOCH_2CONH, H	Me	THF	2	*S*	81	81
PhCH_2·CO·NH, H	H	An	2	*S*	100	86
PhCH_2·CO·NH, H	Me	An	2	*S*	100	91
Phthalimido, H	H	An	4	*R*	100	96
Phthalimido, H	Me	An	2	*R*	79	78
Br, Br	H	THF [e]	1	*R*, *S*	71	69
H, Cl	Me	THF [e]	1	*R*, *S*	95	90
(b) Deacetoxycephalosporins (II)						
PhCH_2·CO·NH, H	H	DMF	4	*S*	100	100
PhCH_2·CO·NH, H	Ph	DMF	2	*R*, *S*	98	90
PhO·CH_2·CO·NH, H	Me	DMF	2	*S*	High [f]	High

[a] Reagent prepared from 2% crosslinked polystyrene unless indicated otherwise. [b] DMF = dimethylformamide, THF = tetrahydrofuran, An = acetone. [c] Analysed by ^{1}H n.m.r. spectroscopy. Acidic products were esterified with diazomethane prior to measurement of the spectra. [d] This takes into account the recovery of material from the polymer. [e] Reagent prepared from 1% crosslinked polystyrene. [f] Addition of water to the filtrate caused the product to crystallise out in high yield.

EXPERIMENTAL

General methods are as given previously.[1,3]

Preparation of Polymeric Peroxy-acids.—The peroxy-acid resins used for the work summarised in Tables 1 and 2 were prepared from polystyrene beads (200—400 mesh) *via* chloromethylation as described before.[1,5] Unless indicated otherwise the polystyrene was crosslinked with 2% of *p*-divinylbenzene. The peroxy-acid resins generally had an oxidation capacity of *ca.* 3.9 mmol [O] per g.

The peroxy-acid resin used for the column work was prepared from Amberlite XE-305 beads (20—50 mesh).[6] This resin (52 g) in dichloromethane (600 ml) was chloromethylated with chloromethyl methyl ether (42 g) and tin(IV) chloride (23 g), first at 0 °C then at 20 °C for 4 h by the usual procedure.[5] Chlorine analysis showed that 23% of the phenyl residues in the product had a chloromethyl substituent. Conversion of the chloromethyl groups into peroxy-acid groups in the usual way [1,5] gave a resin with an oxidation capacity of 1.92 mmol [O] per g. This indicates that the chloromethyl groups were essentially quantitatively converted into peroxy-acid groups.

Reactions Summarised in Tables 1 *and* 2.—The substrate (1 mmol) in the appropriate solvent (4 ml) was treated with a suspension of the peroxy-acid resin under the conditions shown in the Tables. At the end of the reaction period the resin was filtered or centrifuged off to leave a solution of the product(s).

[3] C. R. Harrison and P. Hodge, *J.C.S. Perkin I*, 1976, 1772.
[4] J. M. J. Fréchet and K. E. Haque, *Macromolecules*, 1975, **8**, 130.
[5] C. R. Harrison, P. Hodge, J. Kemp, and G. M. Perry, *Makromol. Chem.*, 1975, **176**, 267.
[6] S. Sano, R. Tokunaga, and K. A. Kun, *Biochim. Biophys. Acta*, 1971, **244**, 201.

The products from the tetrahydrothiophen oxidations were analysed [1] by g.l.c., with use of authentic samples of the starting material and the derived sulphoxide and sulphone for comparison.

The solutions from the L-methionine oxidations were evaporated to dryness and the residues analysed by ^{1}H n.m.r. spectroscopy (D_2O–Na_2CO_3 as solvent), the proportions of the various products being determined from the relative intensities of the *S*-methyl signals. The residue that consisted entirely of the sulphone had, after recrystallisation from alcohol, $[\alpha]_D^{20}$ +11.9 (*c* 2.0 in H_2O) and +30.0° (*c* 1.0 in dil. HCl) (lit.,[7] +13.5 and +30.3°, respectively).

The penicillin substrates were already available.[3] The deacetoxycephalosporins were kindly donated by Glaxo Laboratories. The solutions of products from the oxidations of the β-lactams were evaporated to dryness and the residues analysed by ^{1}H n.m.r. spectroscopy [solvent $CDCl_3$, $(CD_3)_2CO$, or $(CD_3)_2SO$], acidic products being esterified with diazomethane prior to measurement of the spectra. Spectra of the starting materials and authentic samples of the sulphoxides were measured for comparison and the proportions of the various products were determined from the ratios of the 3- and 5-H signals.

Reactions Carried out with a Column.—The column (15 cm × 12 mm) was fitted with a No. 2 sintered filter at the bottom and a water jacket through which water from a thermostatic bath was passed. The macroporous peroxy-acid resin (2.0 g, 3.8 mmol) in acetone was introduced into the column and the column temperature was raised to 40 °C. The jacket extended above the resin bed so that liquids introduced were heated before they reached the resin. A solution of penicillin G (724 mg, 2.0 mmol) in acetone (5 ml) was passed down the column, the residence time being 10—15 min. The column was then washed with acetone (2 × 5 ml) and the combined acetone solutions were evaporated to dryness. The residue (740 mg) was methylated (CH_2N_2) and analysed by ^{1}H n.m.r. spectroscopy. The yield of sulphoxide was 87% and the recovery of starting material (as its ester) 11%. The resin was washed with tetrahydrofuran at 40 °C. The column temperature was then reduced to 20 °C and a mixture of 85% hydrogen peroxide (4 ml) and methanesulphonic acid (4 ml) introduced. After 12 h the oxidation mixture was drawn off and the column washed repeatedly with tetrahydrofuran until the washings were peroxide-free. A small sample of the resin was removed from the column and dried. By iodimetry [1] its oxidation capacity was 1.90 mmol [O] per g.

In a similar experiment with a residence time of 30 min the yield of sulphoxide was 91%.

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[7] B. Iselin, *Helv. Chim. Acta*, 1961, **44**, 61.