Stereoselectivity, Non-stereospecificity, and the Lifetime of the Thiometaphosphonimidate Intermediate formed in the Reactions of the Diastereoisomers of a Phosphonamidothioic Chloride with t-Butylamine

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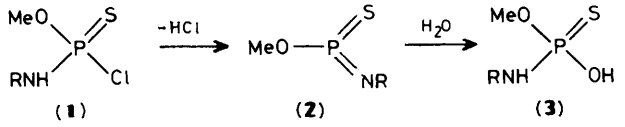
Both diastereoisomers of $Bu^tP(S)(Cl)NHR$ [RNH = (*S*)-PhMeCHNH] react with Bu^tNH_2 (0.25 M) in an aprotic solvent to give the same mixture of the diastereoisomers of $Bu^tP(S)(NHBu^t)NHR$ (no stereospecificity), but the diastereoisomer ratio of the product (stereoselectivity) increases from 57 : 43 (MeCN) to 80 : 20 (cyclohexane) as the polarity (ε_r) of the solvent is reduced.

Interest continues in the role of monomeric metaphosphate and related 3-co-ordinate P^V species as intermediates in nucleophilic substitutions at P=O centres.[1,2] Recent stereochemical studies have concentrated mainly on metaphosphate itself[3] or thiometaphosphate,[4] although the original work of Gerrard and Hamer[5] was concerned with the thiometaphosphorimidate (**2**). In these studies stereochemistry has been used to probe the existence and lifetime[6] of the planar 3-co-ordinate P^V intermediate. The extent to which the transformation of substrate into product is non-stereospecific can be taken as a measure of the extent to which the reactive intermediate becomes free and symmetrically solvated before it is trapped by the nucleophile. Thus, for example, the fact that optically active samples of the phosphoramidothioic chloride (**1**) give racemic product (**3**) on alkaline hydrolysis in aqueous dimethoxyethane[5] implies reaction *via* the free thiometaphosphorimidate (**2**) (Scheme 1). As a measure of lifetime stereospecificity has an inherent limitation: the scale ends at racemisation. It can take us up to the point at which the intermediate exists long enough for substitution to be completely non-stereospecific, but it cannot take us further. We have sought to extend the information available from stereo-



R = cyclo-C_6H_{11}

Scheme 1

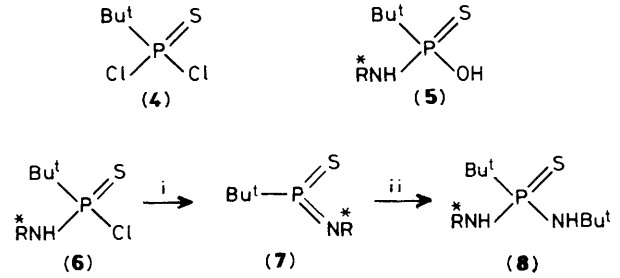
Table 1. Diastereoisomer ratio of the product (**8**) formed in the reactions of the diastereoisomerically enriched samples A and B of the substrate (**6**) with Bu^tNH_2.

Solvent (ε_r)		Diastereoisomer ratio of product (**8**) Sample A	Sample B
MeCN	(35.9)	57 : 43	57 : 43
Me_2CO	(20.6)	58.5 : 41.5	58.5 : 41.5
CH_2Cl_2	(8.9)	63 : 37	63 : 37
$CHCl_3$	(4.8)	78 : 22	78 : 22
cyclo-C_6H_{12}	(2.0)	80 : 20	81 : 19

chemistry by augmenting measurements of stereospecificity (or the lack of it) with measurements of stereoselectivity.

The phosphonamidothioic acid (**5**) [$\delta_P(CDCl_3)$ 93.4 and 95.0 p.p.m.; mixture of diastereoisomers] was prepared from t-butylphosphonothioic dichloride (**4**), by heating in (*S*)-α-methylbenzylamine containing water, and was converted into the phosphonamidothioic chloride (**6**) by treatment with oxalyl chloride.† Although the diastereoisomers of (**6**) were not completely separated by chromatography [silica gel; eluant 1—1.5% ethyl acetate in light petroleum] it was possible to obtain samples of sufficient purity for stereochemical studies: A, 94.5% fast running diastereoisomer, $\delta_H(CCl_4)$ 1.62 (d, J_{HH} 6 Hz, Me) and 1.29 (d, J_{PH} 21 Hz, PBu^t); B, 89% slow running diastereoisomer, $\delta_H(CCl_4)$ 1.51 (d, J_{HH} 6 Hz, Me) and 1.30 (d, J_{PH} 21 Hz, PBu^t).

The two diastereoisomers of the phosphonamidothioic chloride (**6**) were separately added to 0.25 M solutions of t-butylamine (10 mol equiv.) in MeCN at 25 °C (Scheme 2). The reactions were complete inside 5 min. Analysis by g.l.c. (3% OV 225, 192 °C) showed that both diastereoisomers of (**6**) had been converted cleanly into the same 57 : 43 mixture of the diastereoisomers of the phosphonothioic diamide (**8**): R_t 14.3 and 16.7 min; $\delta_H(CDCl_3)$ 1.47 and 1.49 (d, J_{HH} 7 Hz, Me), 1.21 and 1.41 (s, NBu^t), and 1.17 and 0.99 (d, J_{PH} 17 Hz, PBu^t) (values for major diastereoisomer given first). When the reactions were repeated but with interruption (addition of CF_3CO_2H) at *ca.* 50% completion (t = 6 s) the diastereoisomeric purity of the remaining substrate was seen to have changed little (A; 94.5 → 90%) or not at all (B), whereas the product diastereoisomer ratio (57 : 43) was the same in both cases. The fact that the two diastereoisomers of the substrate give stereochemically identical products is therefore not a result of their equilibration but a consequence of their reactions with t-butylamine being completely non-stereospecific.‡ This is consistent with the intermediacy of a thiometaphosphonimidate (**7**) that exists long enough to diffuse away from the chloride leaving group, and attain stereochemical equilibrium with its environment, before it is trapped by the amine nucleophile. The fact that the product diastereoisomer ratio differs somewhat from 50 : 50 shows that there is a small degree of stereoselectivity in the reaction of the free thiometaphosphonimidate with the nucleophile. That this stereoselectivity originates entirely in the product-forming reaction of the thiometaphosphonimidate follows from the complete absence of stereospecificity.



*RNH = (*S*)-PhMeCHNH

Scheme 2. *Reagents:* i, Bu^tNH_2 (-Bu^tNH_3Cl); ii, Bu^tNH_2

Comparable experiments were then carried out using solvents less polar (smaller ε_r) than MeCN. In each case reaction still proceeded with essentially complete non-stereospecificity but the stereoselectivity was not the same as in MeCN (Table 1); it increased as the polarity of the solvent decreased, to the extent that the product diastereoisomer ratio reached 80 : 20 in cyclohexane.

The most reasonable explanation for the increase in stereoselectivity seems to be that a significant proportion of previously-successful collisions between the intermediate and the nucleophile fail, in the less polar solvents, to go on to product. That being so, the lifetime of the thiometaphosphonimidate must be sufficient for it not only to exist as a free intermediate but also to survive several collisions with the nucleophile. By examining both stereospecificity and stereoselectivity it has therefore been possible to obtain information on the lifetime of the 3-co-ordinate P^v intermediate that measurements of stereospecificity alone could not possibly provide.

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† The new compounds (**5**), (**6**), and (**8**) were fully characterised by spectroscopy and elemental analysis. By using a single enantiomer of α-methylbenzylamine each of these compounds was obtained as just two stereoisomers; for the type of work described in this Communication, however, the racemic amine should be equally satisfactory.

‡ Control experiments show that the diastereoisomers of the products (**8**) do not interconvert under the conditions of the reaction.

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