Acid-catalysed Methanolysis of Methylphenylphosphinic Amides: Stereochemistry and Mechanism

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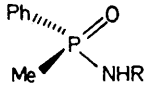
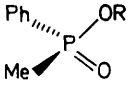
Summary Methylphenylphosphinic amide (**1**) and its *N*-phenyl (**2**) and *N*-*p*-nitrophenyl (**3**) analogues undergo methanolysis with complete inversion of configuration in 0·15 M HCl–MeOH; in 1·5 M HCl–MeOH the extent of inversion decreases in the order (**1**) > (**3**) > (**2**).

STEREOCHEMICAL studies of the acid-catalysed reactions of phosphinic amides with alcohols have hitherto been confined to the methanolysis of *N*-(phenyl)methylphenylphosphinic amide (**2**),[1,2] for which Koizumi *et al.*[2] reported predominant but not exclusive inversion of configuration at phosphorus. This important observation was seen as compelling evidence for the reaction occurring by a dissociative (*A*1; racemisation) mechanism as well as by the normal associative (*A*2; inversion) pathway. Haake and his co-workers[1,3] had previously deduced that hydrolysis of a phosphinic amide such as (**2**), in which the leaving group is aniline, has a merged *A*1–*A*2 mechanism, and that the mechanism changes with the leaving group, being associative (*A*2) when it is the more nucleophilic ammonia (as in **1**) and dissociative (*A*1) when it is the weakly nucleophilic *p*-nitroaniline (as in **3**). Against this background we report the synthesis and methanolysis of the optically active phosphinic amides (**1**) and (**3**).



(**1**); R = H
(**2**); R = Ph
(**3**); R = *p*-$NO_2 \cdot C_6H_4$



(**4**); R = Menthyl
(**5**); R = Me

Optically active methylphenylphosphinic amide,† $[\alpha]_D$ + 8·3° (MeOH), enantiomer ratio *ca.* 20:1 by n.m.r. analysis,‡ was prepared (48%) from (−)-$(S)_P$-menthyl methylphenylphosphinate (**4**)[4] by reaction with KNH_2 in NH_3–tetrahydrofuran. A sample of enantiomerically pure (**1**), $[\alpha]_D$ + 9·2° (*c* 2·8 in MeOH), was obtained by crystallisation from benzene–chloroform (3:1). By analogy with the inversion of configuration that occurs when (**4**) reacts with PhNHLi,[5] the (*S*)configuration may be assigned to (+)-(**1**). Reaction of (+)-(**1**) in dioxan with, successively, potassium and an excess of *p*-nitrofluorobenzene gave after chromatography (alumina) and crystallisation (ethyl acetate) (*S*)-*N*-(*p*-nitrophenyl)methylphenylphosphinic amide (**3**)† (32%), $[\alpha]_D$ + 43·6° (*c* 1·7 in MeOH). (−)-(*S*)-*N*-(Phenyl)methylphenylphosphinic amide (**2**) (> 98% one enantiomer by n.m.r. analysis), $[\alpha]_D$ − 28·5° (*c* 2·1 in MeOH) was obtained from (**4**) by known methods.[5] The (*S*) configuration of (+)-(**3**) was confirmed by reduction of the nitro-group and deamination to give (−)-(*S*)-(**2**).

Methanolysis reactions were carried out by adding the appropriate amide to an excess of methanolic HCl at 28 °C. After neutralisation (NH_3) of the reaction mixture methyl methylphenylphosphinate was isolated by preparative t.l.c. (alumina) and distillation. The purity of the phosphinate was established by g.l.c., its identity confirmed spectroscopically, and its optical rotation measured in benzene (see Table) and in methanol.

The phosphinate obtained from the anilide (**2**) in 0·15 M HCl–MeOH was seen by n.m.r. spectroscopy to be essentially a single enantiomer (⩾ 97%). The specific rotation in benzene agrees well with the recently reported value (−56°, benzene) for pure (−)-(*S*)-methyl methylphenylphosphinate (**5**)[6] and shows that methanolysis under these conditions proceeds with essentially complete inversion. The specific rotation in methanol (−48·5°) differs little from the value (−47·5°, MeOH) recorded by Koizumi *et al.*[2] for the product from (**2**) in dilute HCl–MeOH. Their conclusion that reaction proceeds with substantial (> 20%) racemisation is incorrect because it rests on the assumption of too high a value (−61°) for the specific rotation of pure (**5**) in methanol.

TABLE. $[\alpha]_D$ (*c* 1·5—2·5 in benzene) of methyl methylphenylphosphinate obtained from methanolysis of the phosphinic-amides (**1**)—(**3**) in HCl–MeOH.

Amide	[HCl] = 0·15 M	[HCl] = 1·5 M
(+)-(*S*)-(**1**)	−57·5° (−51·9°)[a]	— (−51·7°)[a]
(−)-(*S*)-(**2**)	−56·5°	−36·9°
(+)-(*S*)-(**3**)	−57·2°	−50·7°

[a] Values in parentheses relate to experiments using 95% optically pure amide.

Under the same conditions the amides (**1**) and (**3**) also react with complete inversion of configuration. Such behaviour is not unexpected for (**1**) since hydrolysis,[3] and presumably methanolysis, is associative (*A*2) for a primary phosphinic amide. For the *p*-nitroanilide (**3**), however, where by analogy to hydrolysis a dissociative (*A*1) mechanism might have been expected,[1] complete stereospecificity is more surprising. Although the intermediate phosphinyl-ium cation ($PhMeP^{+}{=}O$) in an *A*1 process might well react extremely quickly with methanol to give largely the phosphinate with inverted configuration, complete stereospecificity is more reasonably explained by an associative (*A*2) mechanism.

In 1·5 M HCl–MeOH the anilide (**2**) no longer gives optically pure phosphinate. We have established that non-stereospecificity is an integral part of methanolysis by interrupting a reaction at *ca.* 60% completion: the large rotation of the recovered anilide ($[\alpha]_D$ − 27·85° in MeOH) shows that racemisation prior to methanolysis is not of major importance.§ Koizumi *et al.*[2] related the reduced optical purity of the product from methanolysis of anilide (**2**) in more acidic media to a larger proportion of the substrate reacting by a dissociative (*A*1) mechanism. The *p*-nitroanilide (**3**), for which a dissociative reaction is relatively more favourable, should in that case give a product of even lower optical purity. In fact, we find the opposite to be true. We conclude that even at higher acidities the case for a dissociative (*A*1) mechanism is far

† The identities of new optically active compounds were established by comparison with the racemic modifications prepared from methylphenylphosphinic chloride with ammonia (for **1**) and *p*-nitroaniline (for **3**). The racemates gave satisfactory spectroscopic and analytical data.

‡ N.m.r. spectra of optically active compounds were recorded as solutions containing the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III).

§ Methyl methylphenylphosphinate does not racemize significantly under the conditions of the reaction.

from proven, and note that an associative (*A*2) mechanism need not give complete inversion if a five-co-ordinate intermediate (with the possibility of pseudorotation) is formed when methanol attacks the protonated amide. Nucleophilic catalysis by chloride ion might also provide a non-dissociative route to phosphinate with retained configuration.

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[1] D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8066.
[2] T. Koizumi, Y. Kobayashi, and E. Yoshii, *J.C.S. Chem. Comm.*, 1974, 678.
[3] T. Koizumi and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8073.
[4] O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4842.
[5] A. Nudelman and D. J. Cram, *J. Amer. Chem. Soc.*, 1968, **90**, 3869; *J. Org. Chem.*, 1971, **36**, 335.
[6] K. E. DeBruin and D. E. Perrin, *J. Org. Chem.*, 1975, **40**, 1523, observed $[\alpha]_D$ + 56° (benzene) for pure (*R*)-methyl methylphenylphosphinate.