Acid-catalysed Methanolysis of (*N*-Aryl)methylphenylphosphinic Amides: Changes in the Stereochemistry resulting from Nucleophilic Participation by Chloride Ion

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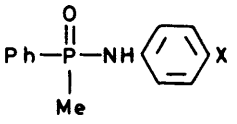
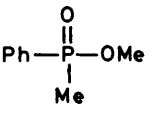
(*S*)-(*N*-Phenyl)methylphenylphosphinic amide (1) and its (*N*-*p*-nitrophenyl) (2) and (*N*-*p*-methoxyphenyl) (3) analogues react stereospecifically in methanolic trifluoromethanesulphonic acid to give methyl methylphenylphosphinate (4) with complete inversion of configuration. The presence of lithium trifluoromethanesulphonate does not disturb the stereochemistry, but the presence of lithium chloride causes some of the phosphinate (4) to be formed with retention of configuration. Chloride ion apparently acts as a nucleophilic catalyst and thereby provides an alternative (retention) to the direct (inversion) methanolysis pathway. The proportion of reaction proceeding with retention depends on the nucleophilicity of the leaving group in the amide, decreasing in the order (3) ≥ (1) > (2).

(*N*-PHENYL)METHYLPHENYLPHOSPHINIC AMIDE (1) is readily converted into the phosphinate (4) in methanol containing acid. The stereospecific inversion of configuration observed at low concentrations of acid is consistent



(1) X = H
(2) X = NO_2
(3) X = OMe



(4)

with an associative (*A*2) mechanism.[1,2] Koizumi and his colleagues [1] attributed the partial loss of stereospecificity at higher acidities to the occurrence of a part of the reaction with racemisation by a dissociative (*A*1) mechanism. That explanation, however, did not seem able to account for the results of subsequent experiments. Using hydrogen chloride as catalyst we found that the *p*-nitroanilide (2) undergoes methanolysis with less deviation than (1) from complete inversion of configuration, although it is more favourably disposed to react by a dissociative (*A*1) mechanism; and that with sufficiently high concentrations of hydrogen chloride both (1) and (2) give predominantly phosphinate of retained configuration.[2] We tentatively suggested that the competing pathway is associative and involves participation by chloride ion as a nucleophile.[2] The experiments now reported have been undertaken to test that hypothesis.

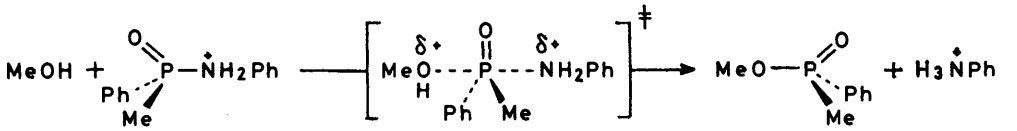
RESULTS AND DISCUSSION

With 0.15M-trifluoromethanesulphonic acid as catalyst, the methanolysis of enantiomerically pure (−)-(*S*)-(*N*-phenyl)methylphenylphosphinic amide (1) gives the phosphinate (4) having $[\alpha]_D$ −57.7° (in PhH). This value is as high as previous estimates of the rotation of pure (*S*)-(4) [2,3] and shows that reaction proceeds with complete inversion of configuration. An associative (*A*2) mechanism is indicated, with methanol displacing aniline from the protonated substrate in an S_N2-like transition state (Scheme 1) or by way of a five-coordinate phosphorane intermediate.[2] In contrast to the situation noted earlier with hydrogen chloride,[2] increasing the concentration of acid to 1.5M now causes no decrease in the enantiomeric purity of the methanolysis product (Table). Since trifluoromethanesulphonic acid is a stronger acid than hydrogen chloride [4] (and trifluoromethanesulphonate a correspondingly weaker nucleophile than chloride ion) the previously observed deviation from inversion cannot reasonably be ascribed simply to the increased acidity of the reaction medium.

Specific rotations of the methyl methylphenylphosphinate obtained from the phosphinic amides PhMeP(O)-NHC_6H_4X-*p* in methanolic CF_3SO_3H at 32.2 °C

$[H^+]$/M	Added salt	X = H (1) $[\alpha]_D^{PhH}$ (°)	X = NO_2 (2) $[\alpha]_D^{PhH}$ (°)	X = OMe (3) $[\alpha]_D^{PhH}$ (°)
0.15	None	−57.7	−57.8	−56.6
1.5	None	−58.3	−57.7	−56.7 [a] (−57.5)
0.15	2.5M-$LiOSO_2CF_3$	−57.7	−58.2	−57.1
0.15	0.5M-LiCl	−54.4	−56.8	−52.4
0.15	1.5M-LiCl	−47.0	−52.9	−45.8
0.15	2.5M-LiCl	−39.4	−46.0	−37.4 [a] (−37.7)
0.15	2.5M-LiBr	−56.2	−56.4	−55.5 [a] (−55.9)

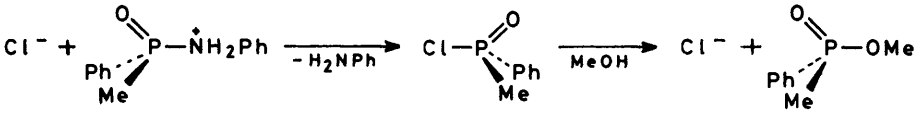
[a] G.l.c. examination showed that the phosphinate was contaminated with a small amount of *p*-methoxyaniline. The estimated value of $[\alpha]_D$ for uncontaminated phosphinate is given in parentheses.



SCHEME 1

Introducing lithium chloride into the 0.15M-trifluoromethanesulphonic acid reaction medium has a marked effect on the stereochemistry of methanolysis (Table).

With 0.5M-lithium chloride *ca.* 3% of the product is formed with retention of configuration, and this proportion increases to 9% with 1.5M-lithium chloride and 16% with 2.5M-lithium chloride. Since lithium trifluoromethanesulphonate exerts no comparable influence on the stereochemical course of reaction it may be inferred that lithium chloride does not merely alter the ionic strength of the reaction medium. Rather, some specific role must be found for chloride ion, and nucleophilic participation (Scheme 2) seems most likely. This



SCHEME 2

would lead by way of the phosphinic chloride to phosphinate of retained configuration.* True, the proportion of reaction proceeding with retention when [LiCl] = 1.5M is not as great as was found [2] using [HCl] = 1.5M. However, if the nucleophilic activity of methanol is reduced less by dissolved lithium ions than by protons, it is reasonable that chloride ion should compete with methanol less effectively in the salt solution. Moreover, it is conceivable that chloride ion is associated more strongly with Li^+ than with H^+.

Accepting that chloride ion does participate as a nucleophile, it should be possible to increase the proportion of the methanolysis product formed with retention of configuration by increasing the ability of chloride to compete for the protonated substrate. To this end the methanolysis of (*S*)-(1) with [CF_3SO_3H] = 0.15M and [LiCl] = 1.5M was repeated but with dioxan replacing some of the methanol solvent. The optical rotation of the phosphinate product decreased from −47.0° (9% retention) in 100% methanol to −37.3° (18% retention) in 80% (v/v) methanol and −24.5° (29% retention) in 60% methanol. Doubtless much of the observed change in stereochemistry is a direct consequence of the increased molar ratio of chloride ion to methanol, but reduced solvation of chloride in the mixed solvent may also contribute to its more effective participation as a nucleophile.

If the methanolysis of anilide (1) is indeed liable to nucleophilic catalysis, anions other than chloride might be expected to influence the stereochemistry. Accordingly, we have examined the effect of added lithium bromide. With both 0.5M and 1.5M-lithium bromide in 0.15M methanolic trifluoromethanesulphonic acid the rotation of the phosphinate product ($[\alpha]_D$ −57.1°) shows no clear evidence for participation by bromide ion, but with 2.5M-lithium bromide it seems (Table) that a very small proportion of reaction does proceed with retention of configuration. It is not difficult to appreciate why lithium bromide has so little effect: hydrogen bromide is a stronger acid than hydrogen chloride [5] so that bromide ion, albeit less heavily solvated, might well be less nucleophilic than chloride ion towards the rather hard phosphoryl centre.[6] Trifluoromethanesulphonate is even less basic than bromide ion and so could not be expected to exert any appreciable effect as a nucleophile.

The *p*-nitroanilide (2) is less reactive than the anilide (1) in acid solution because, being less basic, it exists to a much smaller extent in its reactive protonated form.[7] Once it is protonated, however, the low basicity (pK_b 13.0) [8] and nucleophilicity of *p*-nitroaniline make the P–N bond more labile. Thus (2) should undergo methanolysis with relatively little nucleophilic assistance from the solvent, and in methanol containing added lithium chloride it should show little selectivity for attack by the more nucleophilic but less abundant chloride ion. In other words, we would anticipate that nucleophilic participation by chloride ion will be less evident in the methanolysis of (2) than it is for (1). The Table contains the values of the optical rotation of the phosphinate obtained from (+)-(*S*)-(2) (>99% one enantiomer) in methanolic trifluoromethanesulphonic acid. As with the anilide (1), reaction is stereospecific with inversion in the absence of salt or with added lithium trifluoromethanesulphonate but proceeds with partial retention of configuration in the presence of lithium chloride. Of immediate concern, the relatively small effect of lithium chloride is entirely consistent with the view that it owes its effect to the chloride ion participating as a nucleophile.

In contrast to *p*-nitroaniline, *p*-methoxyaniline (pK_b 8.7) is more basic than aniline (pK_b 9.4), albeit only slightly so.[8] We would therefore predict that the *p*-methoxyanilide (3) will be more sensitive than the anilide (1) to nucleophilic catalysis, although we would expect the difference to be small. An optically active sample of (3), $[\alpha]_D$ −2.8° (in MeOH) (≥99% one enantiomer by n.m.r. examination) was obtained from the reaction of $(S)_P$-menthyl methylphenylphosphinate with the potassium salt of *p*-methoxyaniline. In the analogous preparation of (1), reaction proceeds with inversion of configuration at phosphorus; assuming the same to be true for (3), the (−)-enantiomer can be assigned the *S*-configuration. The results in the Table show that the behaviour of the *p*-methoxyanilide (3) on methanolysis is very similar to that of the anilide (1) although chloride ion does appear to have a marginally greater effect on the stereochemistry. Admittedly the observed differences could be largely accommodated by possible experimental error, but the fact that they always have the same sense adds to their credibility. Certainly such

* As shown in Scheme 2, nucleophilic catalysis by chloride ion leads to phosphinate of retained configuration. In fact it is possible that the intermediate phosphinic chloride racemises to a small extent by exchange with chloride ion before it reacts with methanol. The proportion of reaction proceeding by the catalytic mechanism would then be somewhat greater than the proportion of product having retained configuration.

differences as there are agree with the prediction of greater sensitivity to nucleophilic catalysis in the case of the *p*-methoxyanilide.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded on a Perkin-Elmer 237 instrument and n.m.r. spectra (tetramethylsilane internal standard) with a JEOL JNM-PS-100 instrument. Optical rotations were measured at 589 nm and 20 ± 2 °C with a cell of path length 100 mm (capacity *ca.* 0.9 ml) using a Perkin-Elmer 141 polarimeter. G.l.c. analyses were performed on a Pye 104 flame ionisation chromatograph with a 1.5 m × 4 mm i.d. glass column packed with 3% silicone OV 17 on silanised 100—120 mesh Diatomite C 'Q'. Trifluoromethanesulphonic acid (Aldrich) and lithium trifluoromethanesulphonate (Alfa Division of Ventron) were used as supplied; other lithium salts were dried at 120 °C and 0.1 mmHg.

Methylphenylphosphinic chloride and (−)-(*S*)$_P$-menthyl methylphenylphosphinate, m.p. 77—78° (lit.,[9] 79—80°), $[\alpha]_D$ −92.0° (*c* 1.7 in PhH) (lit.,[9] −94°), diastereoisomerically pure by n.m.r. examination, were prepared by published procedures.[9]

(N-p-*Methoxyphenyl*)*methylphenylphosphinic Amide* (3).—Methylphenylphosphinic chloride (0.52 g, 3.0 mmol) in benzene (8 ml) was added dropwise to an ice-cold solution of *p*-methoxyaniline (0.74 g, 6.0 mmol) in a mixture of benzene (10 ml) and chloroform (10 ml). After 30 min at room temperature the bulk of the solvent was removed under reduced pressure and water (15 ml) was added. The mixture was extracted with chloroform (40 ml; 2 × 10 ml) and the combined extracts were washed with aqueous potassium carbonate and water and then evaporated. The residue was chromatographed on alumina (50 g). The material eluted with ether–methanol (19 : 1) eventually crystallised from acetone–ether (1 : 1) when cooled to −20° and scratched. Recrystallisation afforded (N-p-*methoxyphenyl*)-*methylphenylphosphinic amide* (3) (0.49 g, 1.9 mmol, 63%), m.p. 128.5—129°, $\nu_{max.}$ (Nujol) 3 130 (NH) and 1 180 cm^{-1} (P=O), δ($CDCl_3$) 8.05—7.35 (5 H, m, PPh), 6.84 (4 H, AA'BB', NAr), 6.52br (1 H, d, J_{PH} 10 Hz, NH), 3.68 (3 H, s, OMe), and 1.72 (3 H, d, J_{PH} 15 Hz, PMe) (Found: C, 64.2; H, 6.1; H, 5.3. $C_{14}H_{16}NO_2P$ requires C, 64.4; H, 6.2; N, 5.4%).

(−)-(S)-(N-p-*Methoxyphenyl*)*methylphenylphosphinic Amide* (*S*)-(3).—A suspension of potassium hydride (0.78 g, 20 mmol) in tetrahydrofuran (20 ml) was stirred at 0 °C and *p*-methoxyaniline (2.85 g, 23 mmol) in tetrahydrofuran (10 ml) was added. After 10 min a solution of (*S*)$_P$-menthyl methylphenylphosphinate (2.65 g, 9.0 mmol) in tetrahydrofuran (15 ml) was added dropwise over 10 min. After a further 5 min, g.l.c. (3% OV 17; 250 °C) showed the absence of starting phosphinate (t_R 3.2 min) and the presence of a single important product (t_R 12.8 min) having the same retention time as racemic (3). The reaction was quenched by stirring with ammonium chloride (1.33 g, 25 mmol) for 5 min and then cautiously adding water (1 ml) in tetrahydrofuran. Most of the solvent was removed on a rotary evaporator, water (10 ml) was added, and the mixture was extracted with chloroform (40 ml; 2 × 10 ml). The combined extracts were washed with water, dried (Na_2SO_4), concentrated, and chromatographed on alumina (90 g). Elution with ether followed by ether–methanol (19 : 1) gave a dark oil which precipitated a brown solid (1.68 g) on addition of ether. The n.m.r. spectrum showed this material to be the required amide (3) (6.4 mmol, 71%) but only after a second chromatography and repeated crystallisation from dichoromethane–ether (1 : 2) and acetone–ether (1 : 1) was colourless (−)-(*N*-*p*-methoxyphenyl)-methylphenylphosphinic amide (1.03 g) obtained. It had m.p. 131.5—132.5°, $[\alpha]_D$ −2.80° (*c* 2.4 in MeOH), $\nu_{max.}$ (Nujol) 3 170 (NH) and 1 180 cm^{-1} (P=O), δ($CDCl_3$) 8.05—7.30 (5 H, m, PPh), 6.81 (4 H, AA'BB', NAr), 5.76br (1 H, d, J_{PH} 10 Hz), 3.68 (3 H, s, OMe), and 1.75 (3 H, d, J_{PH} 14 Hz). When a small amount of racemic (3) was added to the n.m.r. sample a signal (caused by the other enantiomer [10]) appeared at δ 1.66 (d, J_{PH} 14 Hz). No signal had previously been visible at this position, showing that the (−)-(3) was ⩾99% a single enantiomer. It was assigned the *S*-configuration because the related preparation of (*N*-phenyl)methylphenylphosphinic amide (1) (see below) gave the known (*S*)-enantiomer.

(−)-(*S*)-(*N*-Phenyl)methylphenylphosphinic amide (*S*)-(1) was prepared as above using aniline in place of *p*-methoxyaniline. After chromatography on alumina (eluant ether–methanol, 19 : 1) and crystallisation from 1 : 1 dichloromethane–ether the product (43%) had m.p. 161—164° (lit.,[7] 163.5—165.5°), $[\alpha]_D$ −28.6° (*c* 2.8 in MeOH) (lit.,[7] −28°), and was a single enantiomer (>99.5%) by n.m.r. examination.[10]

(+)-(*S*)-(*N*-*p*-Nitrophenyl)methylphenylphosphinic amide (*S*)-(2), m.p. 190.5—191.5°, $[\alpha]_D$ +43.0° (*c* 2.1 in MeOH), >99% one enantiomer by n.m.r. examination,[10] was prepared by the method previously described.[2]

Methanolysis of Phosphinic Amides.—In general the required reaction medium was prepared by dissolving the appropriate amount of a lithium salt in dry methanol (*ca.* 6 ml), adding 2.0 ml of a 0.77M methanolic solution of trifluoromethanesulphonic acid, and making up to 10.0 ml with methanol. The appropriate optically active phosphinic amide (0.24 mmol) dissolved in methanol (0.5 ml) was added and the reaction was allowed to proceed at 32.2 °C for 30 min using (*S*)-(3), 60 min using (*S*)-(1), or 200 min using (*S*)-(2). In some experiments the lithium salt was omitted, and in some a higher concentration of acid (see Table) was used with the reaction time reduced to 6, 12, or 40 min. Reaction was quenched by neutralising the acid with 4.5M methanolic ammonia, and most of the solvent was then carefully removed under reduced pressure. The residue was mixed with water (8 ml) and extracted with dichloromethane (10 ml; 2 × 6 ml), and the combined extracts were dried (Na_2SO_4) and concentrated. Methyl methylphenylphosphinate was isolated by preparative t.l.c. on alumina [developing solvent 3% methanol in ether for experiments involving amides (1) and (3) (phosphinate R_F 0.35, aniline and *p*-methoxyaniline R_F 0.7) and 6% methanol in ether for experiments involving (2) (phosphinate R_F 0.6, *p*-nitroaniline R_F 0.85)] and purified by Kugelrohr distillation, b.p. 120° (oven temp.) at 6 mmHg. The purity of the phosphinate was established by n.m.r. spectroscopy and by g.l.c. on 3% OV 17 at 175° (phosphinate t_R 5.5 min, aniline t_R 1.2 min, *p*-methoxyaniline t_R 2.7 min) or 210° (phosphinate t_R 2.6 min, *p*-nitroaniline t_R 6.5 min) and the identity confirmed by comparison of the i.r. spectrum with that of an authentic sample. The optical rotation was measured in benzene (concentration *ca.* 2.5). The phosphinate was then redistilled and the rotation measured again. Each value of $[\alpha]_D$ shown in the Table is the average of two determinations differing usually by <0.6° and never by >1.0°.

A control experiment established that the optical purity of a sample of (−)-methyl methylphenylphosphinate in methanolic 0.15M-trifluoromethanesulphonic acid containing 2.5M-lithium chloride did not change during 4 h at 32 °C.

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