A stereochemical approach to the Kabachnik–Fields reaction mechanism

Mudaris N. Dimukhametov,* Evgenia V. Bayandina, Elena Yu. Davydova, Aidar T. Gubaidullin, Igor A. Litvinov and Vladimir A. Alfonsov

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 75 5322; e-mail: mudaris@iopc.knc.ru

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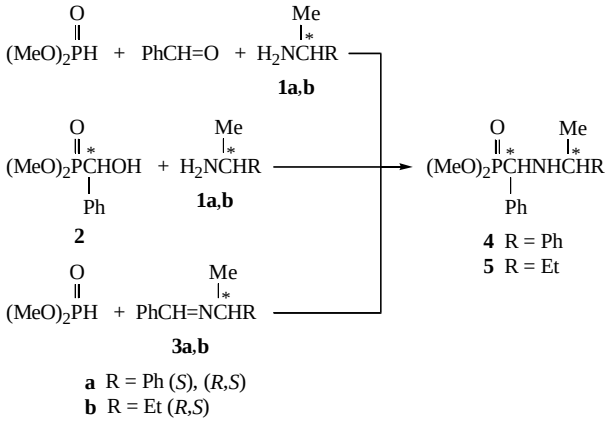
A comparison of the diastereomeric composition of Kabachnik–Fields reaction products with those of two reactions simulating its stereo-controlling steps showed that only the 'imine' mechanism works in the $(MeO)_2P(O)H$–PhCHO-[(*S*),(*R*,*S*)-$H_2NCH(Ph)Me$] system, like in the phosphite–imine system; in a similar system containing (*R*,*S*)-*sec*-butylamine, additional 'nucleophilic amination' of the initially formed α-hydroxybenzyl phosphonate occurs.

The Kabachnik–Fields reaction (KFR) is important for the synthesis of α-aminoalkyl phosphonates, which possess useful properties.[1] Although the synthetic potential of the KFR is employed successfully, its mechanism is poorly known. We performed the first comparative study of the stereochemical result (*de*) of the KFR in the $(MeO)_2P(O)H$–PhCHO–chiral amines **1a**,**b** system and of two-component reactions simulating separate stereo-controlling steps in a three-component system, *viz.*, the 'nucleophilic amination' of α-hydroxybenzyl dimethyl phosphonate **2** with amines **1a**,**b** and the addition of $(MeO)_2P(O)H$ to chiral imines **3a**,**b** (the Pudovik reaction) (Scheme 1). The expected products of all the three directions are α-aminobenzyl phosphonates **4** and **5**, each being a mixture of two diastereomers **A** and **B**. To ensure the correct comparison of the results, all the reactions were carried out under identical conditions.



Scheme 1

According to $^{31}P\{^1H\}$ NMR spectra of the reaction mixtures, the KFR in both systems (reagent ratio of 1:1:1; boiling benzene; 2 h; water removal by azeotropic distillation) results in three phosphorus-containing products [amine **1a**: δ_P 23.5 (**2**), 25.4 (**4A**), 25.8 (**4B**) in the ratio 2.70:1:3.75 (*S*-amine), 2.34:1:3.21 (*R*,*S*-amine), respectively; amine **1b**: δ_P 23.50 (**2**), 25.15 (**5A**), 25.19 (**5B**) in the ratio 1 (**2**) : 2.17 (**5A** + **5B**)]. In the case of amine **1a**, the subsequent refluxing of the reaction mixture does not change the number of phosphorus-containing products or the intensity ratio of their signals in the ^{31}P NMR spectra. However, in the case of amine **1b**, the intensity of the signal with δ_P 23.5 in the $^{31}P\{^1H\}$ NMR spectrum under similar conditions decreased gradually and almost disappeared after 4 h.

Column chromatography in the C_6H_6–MeOH (5:1) (amine **1a**) and C_6H_6–diethyl ether (1:1) (amine **1b**) systems gave pure products of both KFRs. The structures of compounds **2**, **4A**, **4B**, **5A** and **5B** were established by ^1H NMR.† The absolute configuration (*R*) of the carbon atom at the α-position with respect to the phosphorus atom in **4B** (from optically pure **1a**) was determined by X-ray diffraction analysis‡ in coordinates of the second chiral centre at the C(5) atom, which is known to have (*S*) configuration.

The ^1H NMR spectra allowed us to determine the diastereomer ratio **5A**/**5B** based on a comparison of the integral intensities of two doublets of the HCP proton. This ratio is 1.19:1 for the completed KFR with amine **1b**.

Pudovik reactions in the $(MeO)_2P(O)H$–chiral imines **3a**,**b** system carried out under the same conditions as the KFR give compounds **4A** and **4B** in the ratios 1:4.12 (**3a** from enantiopure **1a**) and 1:3.93 (**3a** from racemic **1a**) (^{31}P NMR) and also **5A** and **5B** in the ratio 1.52:1 (^1H NMR). Furthermore, according to ^{31}P NMR data, prolonged refluxing (longer than 4 h) of a mixture of compound **2** with amine **1a** in benzene under KFR conditions does not yield compound **4** in amounts that can be detected spectroscopically. On the contrary, the model reaction of compound **2** with amine **1b** under KFR conditions took place: the signal of compound **2** in the ^{31}P NMR spectrum almost disappeared after 8 h. The region around δ 25 displays

† **2**: mp 101 °C (lit.,[2] 102 °C). ^1H NMR [Bruker WM-250, 250 MHz, $(CD_3)_2CO$, TMS] δ: 3.66 (d, 3H, MeO, $^3J_{HP}$ 10.6 Hz), 3.71 (d, 3H, Me′O, $^3J_{HP}$ 10.6 Hz), 5.13 (d, 1H, CHP, $^2J_{HP}$ 12.9 Hz), 7.32–7.58 (m, 5H, Ph).

4A (from a **4A**:**4B** mixture, 3:1): ^1H NMR, δ: 1.36 (d, 3H, MeC, $^3J_{HH}$ 6.4 Hz), 2.54 (s, 1H, NH), 3.47 (d, 3H, MeOP, $^3J_{HP}$ 10.4 Hz), 3.77 (q, 1H, HCPh, $^3J_{HH}$ 6.4 Hz), 3.81 (d, 1H, HCP, $^2J_{HP}$ 20.0 Hz), 3.83 (d, 3H, Me′OP, $^3J_{HP}$ 10.4 Hz), 7.25–7.42 (m, 5H, Ph).

4B: mp 96.5–97.5 °C, {$[\alpha]_D^{20}$ –15.5° (*c* 3.4, C_6H_6)}. ^1H NMR (Bruker WM-250, 250 MHz, CD_3CN, TMS) δ: 1.35 (d, 3H, MeC, $^3J_{HH}$ 6.4 Hz), 2.52 (s, 1H, NH), 3.55 (d, 3H, MeOP, $^3J_{HP}$ 10.4 Hz), 3.79 (d, 3H, Me′OP, $^3J_{HP}$ 10.4 Hz), 3.86 (q, 1H, HCPh, $^3J_{HH}$ 6.4 Hz), 4.21 (d, 1H, HCP, $^2J_{HP}$ 20.2 Hz), 7.27–7.39 (m, 5H, Ph).

Mixture **5A** and **5B** (1.5:1): n_D^{20} 1.7138. ^1H NMR (Bruker WM-250, 250 MHz, CCl_4, TMS) δ: 0.85 (t, 3H, MeCCN, $^3J_{HH}$ 7.2 Hz), 0.88 (t, 3H, Me′CCN, $^3J_{HH}$ 7.2 Hz), 0.98 (d, 3H, MeCN, $^3J_{HH}$ 5.8 Hz), 1.36 (m, 2H, CH_2CN), 2.07 (m, 1H, NH), 2.38 (m, 1H, CCHN), 2.51 (m, 1H, CCH′N), 3.41 (d, 3H, MeO, $^3J_{HP}$ 10.7 Hz), 3.75 (d, 3H, Me′OP, $^3J_{HP}$ 10.7 Hz), 4.06 (d, 1H, HCP, $^2J_{HP}$ 22.5 Hz), 4.12 (d, 1H, H′CP, $^2J_{HP}$ 22.3 Hz), 7.25–7.41 (m, 5H, Ph).

‡ *X-Ray diffraction study of compound* **4B**. Crystal of **4B**, $C_{17}H_{22}NO_3P$, monoclinic, space group $P2_1$. At 20 °C a = 10.362(2) Å, b = 5.9637(4) Å, c = 13.860(5) Å, β = 95.08(2)°, V = 853.1(4) Å^3, Z = 2, M = 319.34, d_{calc} = 1.24 g cm^{-3}, μ(Cu) = 15.16 cm^{-1}, F(000) = 340. The intensities of 1993 reflections were measured on an Enraf-Nonius CAD-4 diffractometer at 20 °C [λ(CuKα irradiation, $\omega/2\theta$-scanning, $2\theta_{max}$ = 148°]; of these, 1650 reflections with $I \geq 3\sigma$ were observed. The structure was solved by the direct method using the SIR program[3] from the MolEN software package.[4] The structure was refined by a full-matrix least-squares method in an anisotropic approximation; all hydrogen atoms were located by different synthesis and refined isotropically in final least-squares iterations. The absolute crystal structure and absolute molecule configuration were determined by the Hamilton test[5] with 95% probability. The final divergence factors are R = 0.049, R_w = 0.075 based on 1608 reflections with $F^2 \geq 3\sigma$.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 213979. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

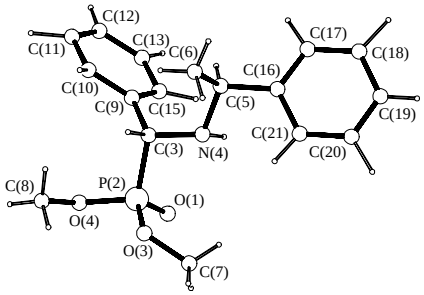
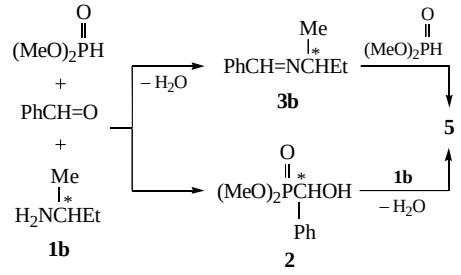


Figure 1 Molecular geometry of **4B** in a crystal. Selected bond lengths (Å): P(2)–O(1) 1.470(4), P(2)–O(3) 1.574(3), P(2)–O(4) 1.558(3), P(2)–C(3) 1.805(5), O(3)–C(7) 1.444(9), O(4)–C(8) 1.438(9), N(4)–C(3) 1.486(6), N(4)–C(5) 1.466(7), C(3)–C(9) 1.519(6), C(5)–C(6) 1.513(9), C(5)–C(16) 1.518(7); selected bond angles (°): O(1)–P(2)–O(3) 114.3(2), O(1)–P(2)–O(4) 113.2(2), O(1)–P(2)–C(3) 112.5(2), O(3)–P(2)–O(4) 103.3(2), O(3)–P(2)–C(3) 106.4(2), O(4)–P(2)–C(3) 106.3(2), P(2)–O(3)–C(7) 119.9(4), P(2)–O(4)–C(8) 123.3(4), C(3)–N(4)–C(5) 115.3(4), P(2)–C(3)–N(4) 105.2(3), P(2)–C(3)–C(9) 111.3(3), N(4)–C(3)–C(9) 116.9(4), N(4)–C(5)–C(6) 111.2(4), N(4)–C(5)–C(16) 108.8(4), C(6)–C(5)–C(16) 110.7(4).

signals corresponding to compounds **5A** and **5B** in the ratio 1:1.59. Note that, first, this reaction results in some prevalence of diastereomer **5B**, and second, the stereoselectivity of the Pudovik reaction is noticeably higher than that of the KFR.

A comparison of the stereochemical results of the three reactions in each of the two reaction series allowed us to make the conclusions given below. The KFR with amine **1a** in boiling benzene occurs *via* the addition of $(MeO)_2P(O)H$ to imine **3a**, which is initially formed from PhCHO and amine **1a** ('imine' mechanism). The basicity of the amine is sufficient to catalyse the addition of $(MeO)_2P(O)H$ to PhCHO to give compound **2**; however, the thermodynamic stability of **2** under the reaction conditions and its low reactivity in the 'nucleophilic amination' step make compound **2** a by-product. The KFR with amine **1b** mainly occurs through the initial formation of imine **3b** from PhCHO and amine **1b**, which then enters the Pudovik reaction with $(MeO)_2P(O)H$ ('imine' mechanism) (Scheme 2). On the other hand, the overall result of the KFR is noticeably affected



Scheme 2

by the initial formation of compound **2** from PhCHO and $(MeO)_2P(O)H$. Its subsequent amination with amine **1b** results in the KFR product **5**.

Thus, depending on the nature of reagents, the KFR can involve either one of the known mechanisms exclusively or two alternative mechanisms simultaneously.

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