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A Study on the Kabachnik–Fields Reaction of Benzaldehyde, Cyclohexylamine, and Dialkyl Phosphites

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ABSTRACT: *The Kabachnik–Fields reaction of benzaldehyde, cyclohexylamine, and dimethyl phosphite carried out at 80°C in acetonitrile takes place via an imine (PhC=N—^{c}Hex) intermediate, as the monitoring by in situ Fourier transform IR spectroscopy suggested. The corresponding α-hydroxyphosphonate was also formed in a quantity of 13% that was not converted to α-aminophosphonate under the conditions applied. The outcome was similar to the Kabachnik–Fields reaction with diethyl phosphite as the P-component. Molecular modeling and subsequent DFT calculations carried out under solventless conditions supported the experimental results and indicated the formation of a high number of ideally positioned H bonds as the key determinant for the conformation of the starting, intermediate, and product states. The relative energies of the possible intermediates were in accord with the observation that the formation of the α-hydroxyphosphonate is a "dead-end" route.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 23:171–178, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20767

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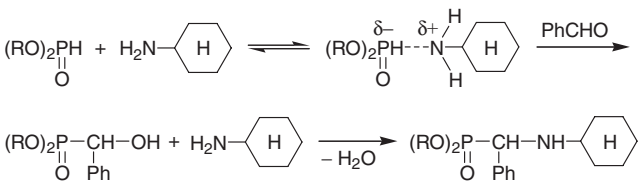
INTRODUCTION

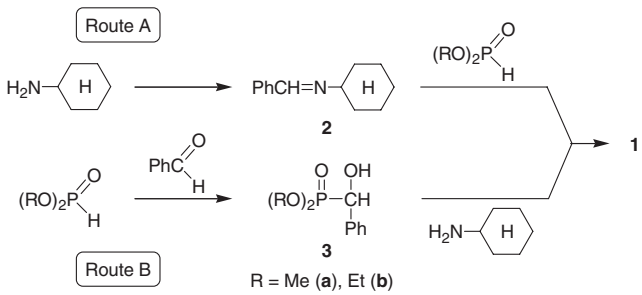
α-Aminophosphonic acids may be considered as phosphorus analogues of α-amino acids [1]. They can act as antimetabolites, for which they are important targets for drug research because of their low mammalian toxicity [2]. Diaryl α-aminophosphonate derivatives are, for example, selective and highly potent inhibitors of serine proteases and thus can mediate the pathophysical processes of cancer growth, metastasis, osteoarthritis, or heart failure [3]. Dialkylglycine decarboxylase [4] and leucine aminopeptidase [5] are also effectively inhibited by α-aminophosphonates. Cyanoacrylate [6] and amide derivatives [7] of α-aminophosphonates are antivirally active compounds and inactivators of tobacco mosaic virus. Furthermore, certain α-aminophosphonates proved to be suitable for the design of continuous drug-release devices due to their ability to increase the membrane permeability of a hydrophilic probe molecule [8].

The solvent-free, catalyst-free, Kabachnik–Fields reaction provides a green procedure for the synthesis of such compounds [9]. Although the reaction itself has been known for more than 50 years [10,11], an up-to-date and comprehensive knowledge of its mechanism is still missing.

Cherkasov et al. studied the mechanism of the Kabachnik–Fields reaction in detail. One possibility



SCHEME 1 From Refs. [12,15].



SCHEME 3

is that an imine is formed from the carbonyl compound and the (primary) amine, and then the dialkyl phosphite is added onto the C=N moiety of the imine. The other route that they considered involves the formation of an α-hydroxyphosphonate by the addition of the dialkyl phosphite to the carbonyl group of the oxo component. Then the hydroxyphosphonate undergoes substitution by the amine to afford α-aminophosphonate. Mainly on the basis of kinetic studies, it was thought that the mechanism is dependent on the nature of the reactants. For example, the condensation of aniline, benzaldehyde, and a dialkyl phosphite was shown to follow the "imine" mechanism [12,13]. A similar route was experienced for the reaction of benzaldehyde, propylamine, and diethyl phosphite [14].

In another example, Cherkasov et al. suggested that the reaction of the more nucleophilic cyclohexylamine, benzaldehyde, and a dialkyl phosphite takes place via the "hydroxyphosphonate" route. Here, an interaction was shown to precede the addition of the dialkyl phosphite on the C=O group of the oxo compound. According to this, an H bond is formed between the P(O)H moiety of the phosphite and the nitrogen atom of the amine (Scheme 1) [12,15].

Later, however, Matveeva and Zefirov proved that the condensation of cyclohexylamine, benzaldehyde, and dialkyl phosphite follows the "imine route" and concluded that there is no experimental evidence for the hydroxyphosphonate route being involved [16].

It should be noted that the reaction of cyclohexylamine, benzaldehyde, and dibutylphosphine oxide, which can be regarded to be as an extended Kabachnik–Fields condensation, was shown to proceed according to the "imine" mechanism [12,17]. It seems to be probable that the actual mechanism is dependent on the components of the reaction, but the "imine" route is more general than the pathway involving an "α-hydroxyphosphonate" intermediate [1]. Gancarz and Gancarz suggested that a reversible formation of the α-hydroxyphosphonate may also occur; at the same time, if it is rearranged to the corresponding phosphate, this is a "dead-end" route [18]. It can be said that in the Kabachnik–Fields reaction, a soft nucleophile, that is the dialkyl phosphite, and a hard nucleophile, that is the amine, compete for the electrophilic carbonyl compound. The softer the carbonyl compound is, the faster it reacts with the softer P nucleophile and the slower it reacts with the harder amine nucleophile [19].

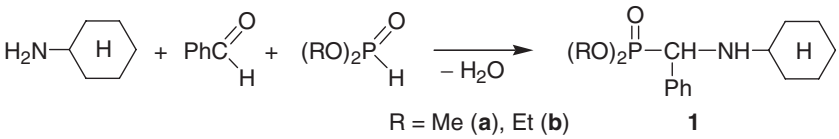
On the basis of the contradicting literature data, it was a challenge for us to study the Kabachnik–Fields reaction of cyclohexylamine, benzaldehyde, and dialkyl phosphites in detail. We wished to clarify which mechanism is effective.

RESULTS AND DISCUSSION

The model reaction studied was the condensation of cyclohexylamine, benzaldehyde, and dialkyl phosphites affording dialkyl α-cyclohexylamino-α-phenyl-methylphosphonate (**1**) (Scheme 2).

In principle, the Kabachnik–Fields reaction under discussion may take place either via imine (Schiff base) **2** or α-hydroxyphosphonate **3** (Scheme 3).

At first, the condensation with dimethyl phosphite was studied. The possible components of the reaction, Schiff base **2**, α-hydroxyphosphonate **3a**,



SCHEME 2

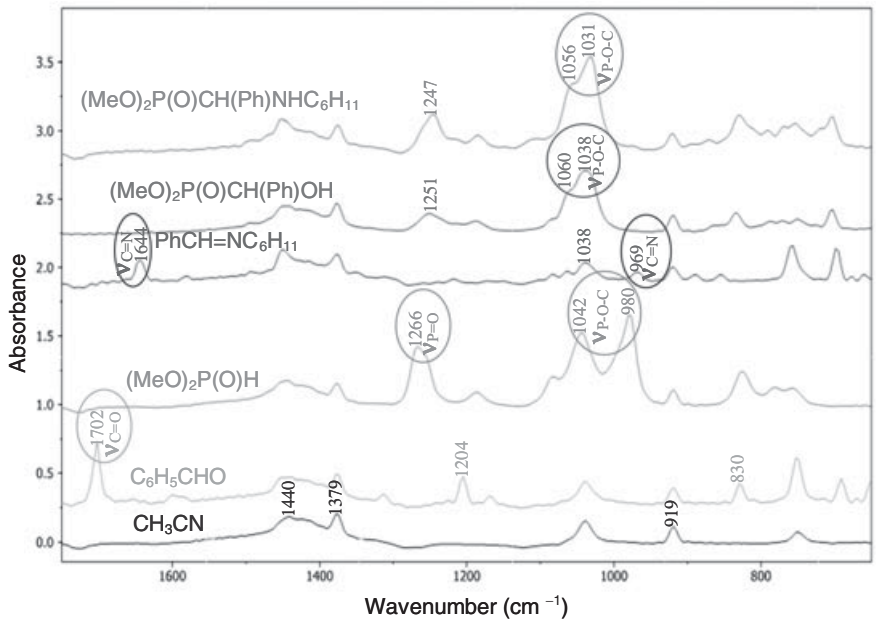


FIGURE 1 IR spectra of the reaction components measured in acetonitrile solution.

and α-aminophosphonate **1a**, were prepared in separate experiments (see the Experimental section), and the infrared (IR) spectra of benzaldehyde, dimethyl phosphite, imine **2**, hydroxyphosphonate **3a**, and aminophosphonate **1a** were recorded in acetonitrile solution. The spectra are shown in Fig. 1; the characteristic absorptions are summarized in Table 1. Because of its lack of IR absorption in the region of 800–1700 cm^{-1}, the spectrum of cyclohexylamine was not included.

The reagents benzaldehyde and dimethyl phosphite revealed intense absorptions at 1702 or 980, 1042 and 1266 cm^{-1}, respectively. The peaks at 1702, 980/1042, and 1266 cm^{-1} are due to $\nu_{C=O}$, ν_{P-O-C}, and $\nu_{P=O}$ stretching vibrations, respectively. The imine (**2**) showed intense signals at 969 and 1644 cm^{-1}. As the first one overlaps with the peak of $(MeO)_2P(O)H$ at 980 cm^{-1}, the absorption at 1644 cm^{-1} that is due to the $\nu_{C=N}$ vibration may help in the identification. The hydroxyphosphonate **3a** and aminophosphonate **1a** can be recognized from the series of signals at 1038, 1060, and 1251 or 1031, 1056, and 1247 cm^{-1}. The absorptions at around 1035 and 1058 cm^{-1} are due to the ν_{P-O-C} stretching vibration, whereas those at around 1249 cm^{-1} are the consequence of the $\nu_{P=O}$ vibration.

The Kabachnik–Fields reaction monitored by in situ Fourier Transform (FT) IR spectroscopy was carried out by heating an acetonitrile solution of dimethyl phosphite and cyclohexylamine to 80°C, and benzaldehyde was then added. Collection of the spectra was started when all the three components were in the flask. The benzaldehyde was converted instantly to Schiff base **2**, which was transformed to aminophosphonate **1a** by a reaction with dimethyl phosphite. The intermediate (**2**) appeared at 1644 cm^{-1} and could be seen for ca. 2 h with the maximum concentration at 10 min. With the disappearance of the imine (**2**), the aminophosphonate (**1a**) appeared, as it was suggested by the

TABLE 1 Characteristic IR Absorptions of the Reaction Components Measured in Acetonitrile Solution[a]

CH_3CN	C_6H_5CHO	$(MeO)_2P(O)H$	$PhCH{=}NC_6H_{11}$	$(MeO)_2P(O)CH(Ph)OH$	$(MeO)_2P(O)CH(Ph)NHC_6H_{11}$
	1702		1644		
1440					
1379	1204	1266		1251	1247
		1042		1060	1056
919		980	969	1038	1031

[a]The molar ratio of the corresponding component and acetonitrile is 1:10.

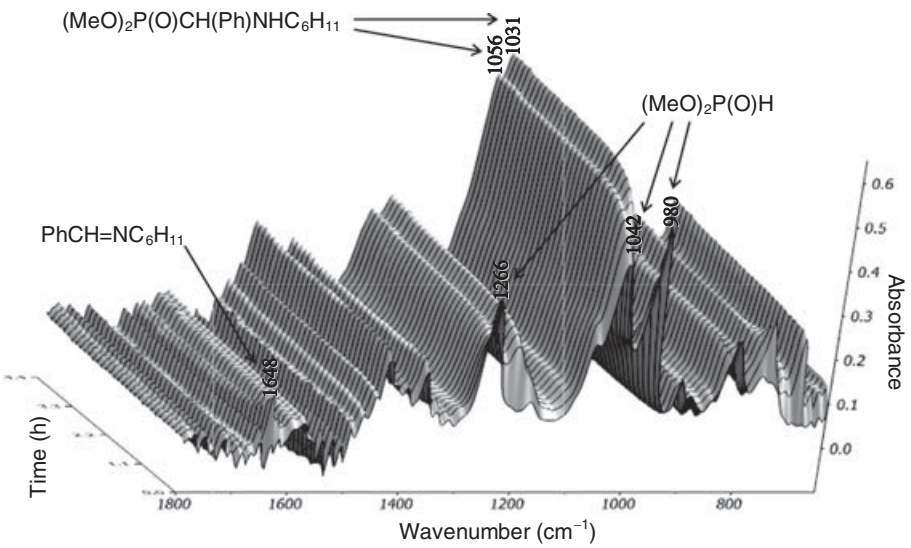


FIGURE 2 A segment of the time-dependent IR spectrum for the Kabachnik–Fields reaction of dimethyl phosphite, cyclohexylamine, and benzaldehyde at 80°C in acetonitrile.

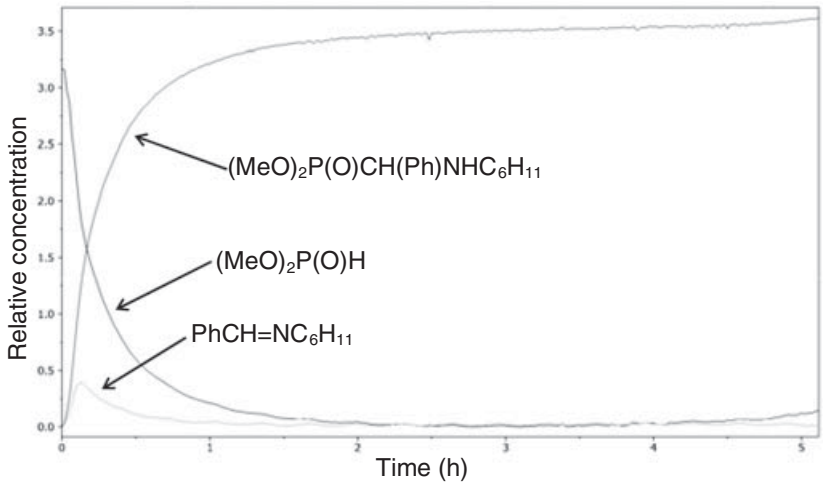


FIGURE 3 Concentration profile for the Kabachnik–Fields reaction studied at 80°C in acetonitrile.

signals at 1031 and 1056 cm^{-1}. The three-dimensional (3D) diagram for the Kabachnik–Fields reaction under discussion can be seen in Fig. 2. The reaction mixture was analyzed by means of ^{31}P and ^{13}C NMR, as well as mass spectrometry of the oil obtained after evaporation and flash column chromatography. The major component (87%) of the oil was α-aminophosphonate (**1a**) as expected, but α-hydroxyphosphonate (**3a**) was also present as a minor (13%) product. For the details, see the Experimental section.

The above experiment serves as direct evidence for the pathway via Schiff base **2** ("route A" in Scheme 3) in the case of the three-component condensation under discussion. It is also seen that the α-hydroxyphosphonate (**3a**) is also formed to a smaller extent, and that this species (**3a**) does not undergo further reaction with the cyclohexylamine present in the mixture under the conditions of the reaction (at 80°C). Hence, the formation of hydroxyphosphonate **3a** is a "dead-end" route from the point of view of formation of the α-aminophosphonate **1a**.

The relative concentration–time diagram obtained after deconvolution is shown in Fig. 3. The intermediacy of imine **2** can be well seen, and the reaction time is approximately 3.5 h.

It was also possible to reproduce the IR spectra of the reaction components such as dimethyl phosphite, Schiff base **2**, and aminophosphonate **1a** (Fig. 4). It can be seen that the real IR spectra are

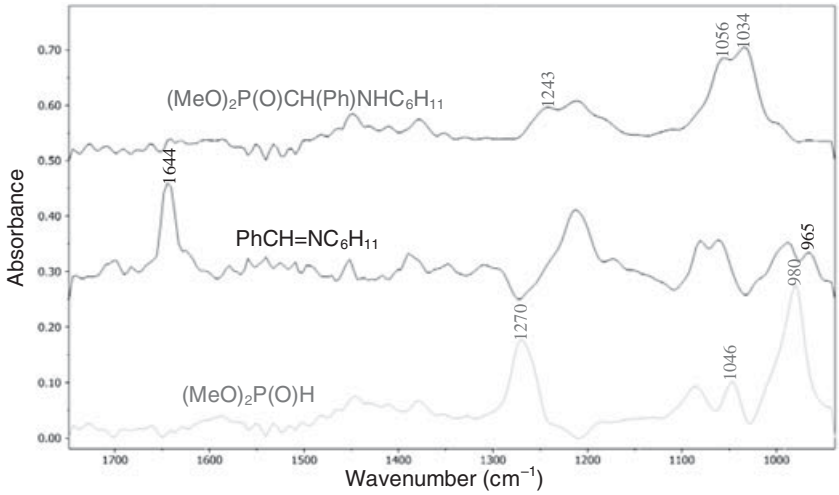


FIGURE 4 IR spectra for the reaction components obtained from the 3D diagram after deconvolution.

almost identical to those obtained by deconvolution (Fig. 1 vs. Fig. 4).

The Kabachnik–Fields reaction of benzaldehyde, diethyl phosphite, and cyclohexylamine was also carried out in acetonitrile solution at 80°C. After a 4-h reaction time, ^{31}P NMR analysis of the concentrated reaction mixture suggested the presence of 85% α-aminophosphonate **1b** and 15% of α-hydroxyphosphonate **3b**.

Theoretical Calculations of the Solventless Kabachnik–Fields Reaction

The reactant, intermediate, and product state models were studied by molecular modeling methods and density functional calculations. For the details, see the Experimental section. Both possible routes, the one through an imine and the other through an α-hydroxyphosphonate intermediate, were considered under one-pot, solvent-free, and catalyst-free conditions. The solvent- and catalyst-free accomplishments were found to be especially efficient under microwave irradiation [9,20–22]. Stereostructures of the assemblies in the different states and relative energies are presented in Figs. 5 and 6 and Table 2, respectively.

In the reactant state (**A**), the dimethyl phosphite and the amine molecules are bound by an H bond, with an H bond distance of 3.11 Å (measured between donor and acceptor), whereas the aldehyde carbonyl oxygen is positioned halfway between the methoxy groups of the phosphite, with an average O···C$_{methyl}$ distance of 3.49 Å. It should be noted that the P=O segment proved to be a more powerful H bond attractant than the C=O moiety of aldehyde.

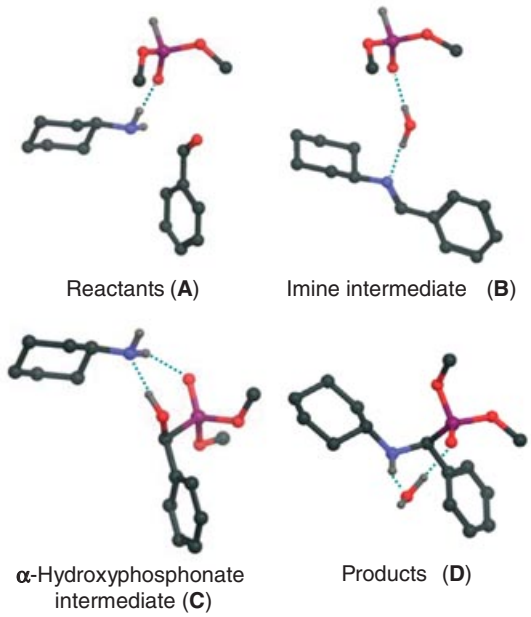


FIGURE 5 Stereostructure of the reactant (benzaldehyde, cyclohexylamine, and dimethyl phosphite (**A**)), imine (**B**), hydroxyphosphonate (**C**), and product (**D**) assemblies calculated.

TABLE 2 Relative Energies for the Four States Calculated

	Relative Energy (kJ mol^{-1})
Reactant (benzaldehyde, cyclohexylamine, and dimethyl phosphite (**A**))	0.0
Imine intermediate (**B**)	−18.6
Hydroxyphosphonate intermediate (**C**)	−40.5
Product (**D**)	−42.9

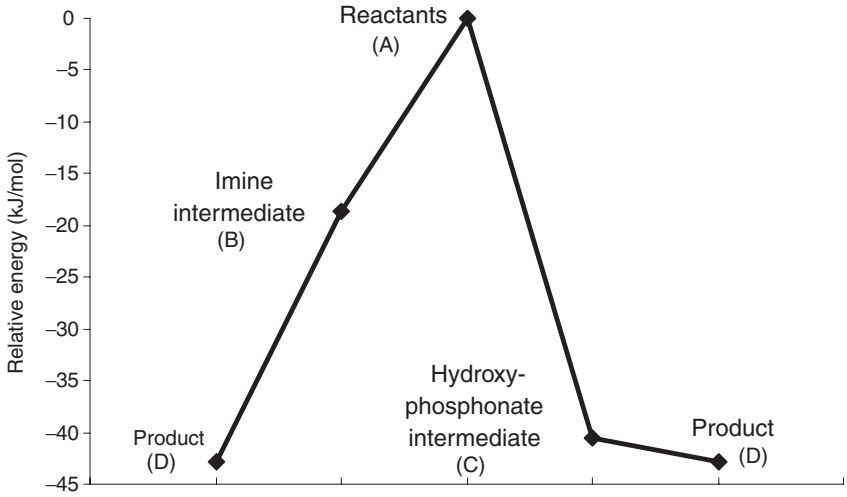


FIGURE 6 Relative energies for the reactant (benzaldehyde, cyclohexylamine, and dimethyl phosphite (**A**)), imine (**B**), hydroxyphosphonate (**C**), and product (**D**) states calculated.

The "imine intermediate" and the phosphite are held together by two H bonds with the participation of the water molecule released in the condensation of the amine and the aldehyde. In this associate (**B**), the N···O and the O···O distances are 2.93 and 2.84 Å, respectively.

In the structure of the complex formed between the α-hydroxyphosphonate intermediate and the unreacted amine (**C**), the amine participates in two H bond interactions, one with the double-bonded oxygen of the P=O group and one with the α-hydroxyl substituent of the hydroxyphosphonate.

In the product state (**D**), the water molecule formed as the side product is fixed to the α-aminophosphonate by two H bonds. The first one involves an interaction between the oxygen of the P=O group and one of the hydrogen atoms of water, whereas the other one is based between the oxygen atom of water and the proton of the amino group. The former is a considerably stronger association with a donor–acceptor O—O distance of 2.73 Å, whereas the length of the latter H bond measured at the O—N atoms is 3.19 Å.

The relative stability of the aforementioned four states (**A**–**D**) can be regarded as a good indicator to show how the reaction may take place (Fig. 6 and Table 2). It can be seen that the formation of the α-hydroxyphosphonate associate **C** (or intermediate (**3a**)) is not unfavorable at all. However, it represents a "dead-end" route, as species **3a** does not undergo substitution reaction with cyclohexylamine under the conditions of the reaction applied to afford the corresponding α-aminophosphonate (**1a**). This may be due to the marginal energy gain (2.4 kJ mol^{-1}) of the final substitution step. The possibility of the substitution of α-hydroxyphosphonates, which are quite hindered model compounds, by amines is studied separately, and our results will be published in due course. On the other hand, the reaction proceeds quite easily through the imine intermediate. The results of the calculations are in full agreement with our preparative experiments and with our observations by in situ FT IR measurements. It can also be seen that the Kabachnik–Fields reaction under discussion proceeds similarly under solventless conditions and in acetonitrile solution. The energetic ordering of the conformations was found highly dependent on the number of ideally positioned H bonds of the arrangements, which was, therefore, concluded to be the driving force of the assembly of the studied states.

In conclusion, our study combining monitoring by in situ FT IR spectroscopy and preparation suggests that the Kabachnik–Fields reaction of cyclohexylamine, benzaldehyde, and dialkyl phosphite takes place via the imine intermediate at 80°C in acetonitrile used as the solvent; however, some α-hydroxyphosphonate is also formed that does not take part in a subsequent substitution under the conditions of the reaction applied. The theoretical results obtained by calculations indicate that the situation may be similar under solvent-free conditions. This means that in our case, the course suggested by Cherkasov and coworkers [12,15] does not work and the α-hydroxyphosphonate may not be a real intermediate. At the same time, the conclusion of Matveeva and Zefirov that the Kabachnik–Fields condensation under discussion takes place via the imine route [16] is confirmed. However, the course of the Kabachnik–Fields reactions may, in

general, depend on the nature of the starting materials [12,13,15,16] and the conditions applied.

EXPERIMENTAL

Equipment

The ^{31}P and ^{13}C NMR spectra were taken on a Bruker DRX-500 spectrometer (Bruker BioSpin GmbH, Karlsruhe, Germany) operating at 202.4 and 125.7 MHz, respectively. The couplings are given in Hertz.

The synthesis of aminophosphonate was carried out in a CEM Discover microwave reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a pressure controller using 20–30 W irradiation.

In situ FT IR measurements were conducted using a ReactIR 1000 equipment (Mettler-Toledo Inc., Columbus, OH). An attenuated total reflectance (ATR) diamond measuring head was placed in a 100-mL four-necked flask equipped with a dropping funnel, a condenser, a thermometer, and a magnetic stirrer. The temperature was maintained by using an appropriately adjusted oil bath.

Synthesis of Imine **2**

A mixture of 3.3 mL (32.5 mmol) of benzaldehyde and 3.7 mL (32.5 mmol) of cyclohexylamine in 20 mL of acetonitrile was stirred at 26°C for 3 h. The solvent and volatile components were then removed in vacuum to afford 5.9 g (97%) of Schiff base **1**. IR (neat) 694, 753, 965, 1449, 1644, 2856, 2916 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 24.6 (C_3), 25.6 (C_4), 34.3 (C_2), 69.7 (C_1), 127.9 ($C^*_{3'}$), 128.3 ($C^*_{2'}$), 130.1 ($C_{4'}$), 136.6 ($C_{1'}$), 158.1 (C=N) *may be reversed. (The numbers 1–4 refer to the cyclohexyl group, whereas numbers 1′–4′ refer to the phenyl ring.)

Synthesis of Dimethyl α-Hydroxybenzylphosphonate **3a**

5.7 mL (56.6 mmol) of benzaldehyde was added to a suspension of 21.0 g (0.21 mol) of Brockmann II Al_2O_3 in 40 mL of CH_2Cl_2. Then the mixture was stirred for 2 h. The dichloromethane was evaporated, and the mixture was kept at 26°C for 1 week. After completion, the mixture was extracted with 3 × 50 mL of CH_2Cl_2. The solvent of the combined extracts was evaporated, and the solid residue so obtained was washed with 2 × 5 mL of diethyl ether to give 9.8 g (80%) of α-hydroxyphosphonate **3a** as white crystals in a pure form. Mp 101–102°C, mp [23] 102°C; ^{31}P NMR ($CDCl_3$) δ 24.3, δ_P [23] 24.3; IR (KBr) 700, 776, 1027, 1054, 1153, 1238, 1452, 2957, 3266 cm^{-1}.

Synthesis of Dimethyl α-Cyclohexylaminobenzylphosphonate (**1a**)

A mixture of 0.16 mL (1.7 mmol) of dimethyl phosphite, 0.17 mL (1.7 mmol) of benzaldehyde, and 0.2 mL (1.7 mmol) of cyclohexylamine was measured in a sealed tube and irradiated (20–30 W) in a CEM microwave reactor equipped with a pressure controller at 100°C for 30 min. Chromatography (silica gel as the absorbent and 3% methanol in dichloromethane as the eluant) of the crude mixture furnished 0.22 g (45%) of aminophosphonate **1a**. ^{31}P NMR ($CDCl_3$) δ 26.5; ^{13}C NMR ($CDCl_3$) δ 24.2 and 24.7 (C_3), 25.9 (C_4), 31.7 and 34.2 (C_2), 53.1 (J = 6.5) and 53.3 (J = 2.2) (OCH_3), 53.8 (J = 7.1, C_1), 57.1 (J = 154.3, *C*HN), 127.6 (d, J = 3.1, $C_{4'}$), 128.2 (J = 13.3, $C^*_{3'}$), 128.3 (J = 9.5, $C^*_{2'}$), 136.2 (J = 2.7, $C_{1'}$) *may be reversed. (The numbers 1–4 refer to the carbon atoms of the cyclohexyl group, whereas numbers 1′–4′ refer to the carbon atoms of the phenyl ring.) δ_C [24] ($CDCl_3$) 24.8, 25.3, 26.4, 32.2, 34.7, 53.6, 53.8, 54.4, 57.5 (J = 153.6), 128.3, 128.7, 128.9, 136.6; IR (neat) 700, 830, 1032, 1185, 1245, 1452, 2853, 2928 cm^{-1}.

Monitoring the Kabachnik–Fields Reaction Carried out at 80°C

A solution of 5.5 mL (60.0 mmol) of dimethyl phosphite and 7.6 mL (66.0 mmol) cyclohexylamine in 30 mL of acetonitrile was heated to 80°C, and 6.1 mL (60.0 mmol) of benzaldehyde was added dropwise in 5 min. The mixture was stirred for 4 h. The resulting 3D diagram is shown in Fig. 2.

After evaporating the acetonitrile, according to ^{31}P NMR, the crude mixture consisted of 87% of aminophosphonate **1a** (^{31}P NMR ($CDCl_3$) δ 26.5) and 13% of hydroxyphosphonate **3a** (^{31}P NMR (CDCl3) δ 24.1). Chromatography of the crude product furnished 13.1 g (76%) of aminophosphonate **1a**.

An analogous reaction, but applying 7.7 mL (60.0 mmol) of diethyl phosphite instead of dimethyl phosphite, was also carried out. A similar workup afforded a mixture consisting of 85% of aminophosphonate **1b** (^{31}P NMR ($CDCl_3$) δ 24.2, δ_P [16] 24.3) and 15% hydroxyphosphonate **3b** (^{31}P NMR (CDCl3) δ 21.5, δ_P [25] 21.5).

Molecular Modeling

Molecular modeling and subsequent Density Functional Theory (DFT) calculations were carried out. Monte Carlo multiple minimum (MCMM)

search [26]—as implemented in MacroModel [27]—involved the random variation (within the range of 0–180°) of a randomly selected subset of all torsional angles (a minimum of 2° and a maximum of 12°), combined with the variable molecules selection (MOLS) method for translations and rotations of the complexing partners with respect to each other. The combined MCMM/MOLS procedure allowed random translation (0–5 Å) and rotation (0–180°) during a Monte Carlo step. Calculations consisted of 50,000 steps. The perturbed structures were minimized using a truncated Newton algorithm [28]. Calculations were carried out using the optimized potential for liquid simulations 2005 force field [29]. Atomic charges were calculated by using the electrostatic potential method [30] from B3LYP/6-31G** wave functions of the geometry-optimized noninteracting partners of each discussed state, using Jaguar [31].

The applied MCMM procedure results in a collection of conformers that span the energy range specified in the calculation (50 kJ mol^{-1}, in our case). The low-energy conformers of this set describe an ensemble that can be expected to shape the macroscopic descriptors of the given state. Therefore, in each case, conclusions were drawn based on trends that were general within the low-energy conformations of the given state, which were considered as such if their conformational energy did not exceed the global minimum (lowest) energy by more than 8.2 kJ mol^{-1} (approximately 2 kcal mol^{-1}).

Final conformation and energy ordering of the different states were obtained by DFT gas-phase optimization (B3LYP/6-31G**) of characteristic, low-energy conformers of the force-field calculations (typically 3–6 low-energy conformers), followed by further B3LYP/6-311G**++ optimization of the two best conformers.

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