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## Nucleophilic Addition to Carbonyl Compounds. Competition Between Hard (Amine) and Soft (Phosphite) Nucleophile.

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**Abstract:** In the Kabachnik Fields reaction mixture, two nucleophiles: dialkyl phosphite and the amine compete for the electrophilic carbonyl compound. Reaction mixture composition studies, kinetic studies as well as theoretical calculations, indicate that the softer the carbonyl compound is, the faster it reacts with the softer phosphorus nucleophile and the slower it reacts with the harder amine nucleophile. It in turn results in the different ratio of products namely formation of aminophosphonates vs. hydroxyphosphonates.

### INTRODUCTION

The key step in the Kabachnik Fields synthesis of aminophosphonates<sup>1-6</sup> is the nucleophilic addition of a nucleophilic amine to a carbonyl compound followed by the addition of dialkyl or diaryl phosphite to the resulting imine. The formation of aminophosphonate is frequently accompanied by the formation of a hydroxyphosphonate or a product of its rearrangement.<sup>7</sup> This is due to the presence of one electrophile (carbonyl compound) and two nucleophiles (amine and phosphite) in the reaction mixture, which may compete for the electrophilic center. Thus there are at least two possible reactions. The first starts with the amine catalysed nucleophilic addition of phosphite and hydroxyphosphonate formation (scheme 1 path A). The second begins with nucleophilic attack of amine and formation of imine. In the last case the addition of phosphite to the imine leads to the formation of the aminophosphonate as final product (scheme 1 path B).

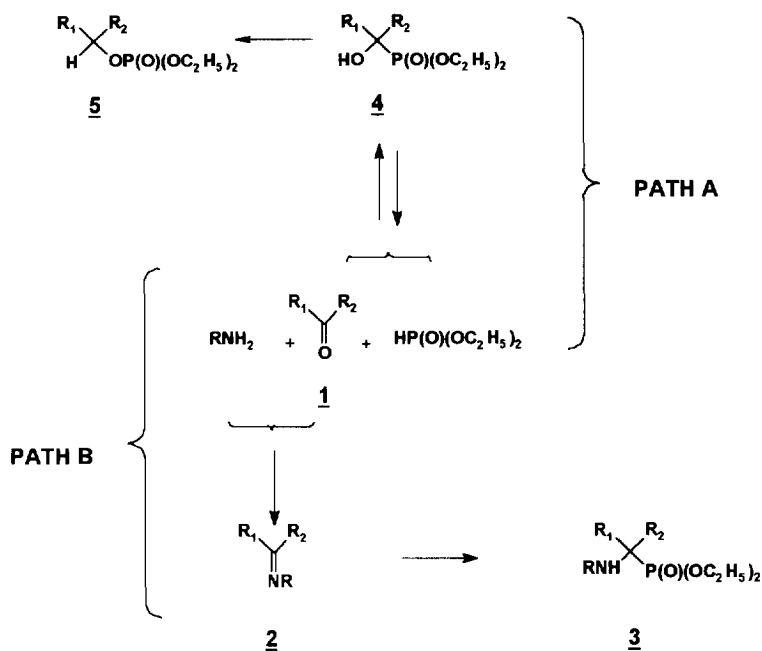
We have observed the different ratio of an aminophosphonate (path B product) and hydroxyphosphonate (path A product) in the reaction mixture, for various carbonyl compounds, depending on the structure of the used carbonyl substrate. In this paper we would like to present arguments that the direction of the reaction (path A vs. B) could be explained in terms of the interaction of hard and soft nucleophiles with hard and soft electrophiles.

### RESULTS AND DISCUSSION

#### *Reaction mixture studies.*

To study the products which are formed in the reaction, equimolar amounts of carbonyl compound, butylamine and diethyl phosphite were kept at room temperature and in a separate experiment at 60°C. The reaction was controlled by taking the <sup>1</sup>H and <sup>31</sup>P NMR after certain periods of time. Two aldehydes (aromatic - benzaldehyde and aliphatic - valeric aldehyde) and five ketones (aliphatic - acetone and cyclohexanone,

aliphatic aromatic - acetophenone and aromatic - benzophenone and fluorenone) were used as carbonyl compounds. The results obtained at room temperature and at 60°C are similar. The only substantial difference between the reactions at room and elevated temperatures was the greater reaction rate of the latter reaction. Data obtained for studies at the room temperature are collected in Table 1.



Scheme 1

Table 1. NMR studies of the product composition of the reaction of carbonyl compound (1-valeric aldehyde, 2-benzaldehyde, 3-acetone, 4-cyklohexanone, 5-acetophenone, 6-benzophenone, 7-fluorenone) butylamine and diethyl phosphite. The data in Table are given as the percentage of the carbonyl or the product obtained from carbonyl compound. For details see text.

path	product	carbonyl compound													
		1		2		3		4		5		6		7	
		a	b	a	b	a	b	a	b	a	b	a	b	a	b
	1	5	0	17	7	12	2	14	13	78	10	90	18	82	6
B	2	9	1	54	15	2	1	0	1	3	18	0	1	0	0
	3	86	99	5	48	83	91	80	80	0	4	0	1.5	0	0
A	4	0	0	24	30	3	6	8	7	19	68	10	2	18	2
	5	0	0	0	0	0	0	0	0	0	0	0	77	0	92

column a- after 20 min, column b - after 24hrs

Analysing the data from Table 1 one should notice that in the case of valeric aldehyde, acetone and cyclohexanone the nucleophilic addition of amine and formation of imine leading to aminophosphonate (path B) is much faster than the nucleophilic attack of diethyl phosphite (path A). The reverse is true for benzophenone and fluorenone. In the case of benzaldehyde and acetophenone both reactions are more or less

of the same order. This is manifested in the formation of imine and its addition product with diethyl phosphite i.e. aminophosphonate (according to path B) or hydroxyphosphonate or accompanied by the product of its rearrangement i.e. phosphate (via path A) in more or less equal amount.

#### *Kinetic studies.*

Data obtained for the formation of the products studied by means of the NMR at certain time intervals suggest that aliphatic carbonyl compounds prefer the reaction with amine rather than phosphite. The opposite is true for the aromatic carbonyl compounds. The studies of the product composition do not prove, however that the imine or hydroxyphosphonate are formed because of the kinetic preference of the reaction of one carbonyl compound with amine or phosphite. It could also be true that they are thermodynamically more stable products in a series of subsequent reactions. To check which case takes place we set up kinetic experiments. In the first one we have measured the formation of imine by observation of the changes in UV spectra of the mixture of carbonyl compound with 100 fold excess of butylamine in absolute ethyl alcohol. <sup>8</sup> Pseudo first order kinetic parameters of the imine formation are given in the Table 2.

Table 2. The observed pseudo first order reaction rates for the reaction of carbonyl compounds with butylamine (upper row) or diethyl phosphite (lower row). The reaction rates were measured in absolute ethanol at 25°C and are given in  $\text{sec}^{-1} \times 10^4$

	propionic aldehyde	benzaldehyde	acetone	acetophenone	fluorenone
Carbonyl compound + BuNH <sub>2</sub>	>500 <sup>a</sup>	85.3	15.3	2.0	<0.1 <sup>b</sup>
Carbonyl compound + Et <sub>3</sub> N + HP(O)(OEt) <sub>2</sub>	172.0	1.8	3.3	5.5	1.6

<sup>a</sup> -reaction too fast for accurate determination

<sup>b</sup> -reaction too slow for accurate determination

In another kinetic experiment the reaction rate between phosphite and carbonyl compound was measured by observing the changes in UV spectra of the solutions of the carbonyl compounds with 100 fold excess of diethyl phosphite in absolute ethyl alcohol. The 100 fold excess of triethylamine was used as a catalyst in this reaction. The presence of a catalyst is necessary since the reaction is running only when being catalysed by amine or another base. Tertiary amine must be used in order to avoid the competing imine formation. The  $k_{\text{obs}}$  values of this reaction are collected in Table 2. The formation of imine from acetone is one order faster than the reaction with diethyl phosphite. On the other hand the reaction of fluorenone with diethyl phosphite is more than one order faster than its reaction with amine. In the case of acetophenone those reactions are of the same order. Data for benzophenone are not available since the change in the UV spectra were too small to follow the reaction. Kinetic studies data collected in the Table 2 are in full agreement with the data from the reaction mixture composition studies done by means of NMR.

#### *Theoretical calculations.*

Analysing the NMR as well as kinetic studies one should notice that the preference of path B over path A

becomes stronger once we move from aromatic to aliphatic aldehydes or ketones. This cannot be due to the changes of electrophilicity of the carbonyl center, since it should affect both nucleophiles in the same direction. In this case it is clear, especially when one compares acetone and fluorenone (two extremely different behaving ketones), that the aliphatic ketones react with the amine faster than with phosphite, whereas in the case of fluorenone and benzophenone the rate ratio is completely reverted. It cannot be explained by the steric reasons also. A systematic altering of steric and electronic factors might explain the situation, however it is hard to achieve the changes in one without altering the others. Data in Table 1, however, show that the bulkier phosphite nucleophile prefers the reaction with more sterically crowded aromatic ketones and aldehydes. It is completely opposite one would expect if steric factors were important. Additionally we have also studied the reaction with sterically crowded ketones, i.e. diisopropylketone and diisobutylketone. Though in these cases the reactions were much slower when compared with acetone and cyclohexanone but gave similar product composition. After 10 hrs at 60°C still 60-70% of unreacted ketone were detected. The other 30-40% of ketone were found to be converted mostly to products via path B (more than 95%). Only a trace of hydroxyphosphonate was detected by means of the  $^1\text{H-NMR}$  and  $^{31}\text{P-NMR}$ . These experiments clearly indicate that steric contribution is neglectable in the observed ratios of the reaction mixture products, but is significant in the reaction rates reported in Table 2.

There should be another parameter in addition to steric factors, positive charge or nucleophilicity of the carbonyl group which governs the direction of the reactions. It could be Pearson's hardness and softness which was introduced in 1960s<sup>9</sup> and developed later.<sup>10-12</sup> Hard and soft bases and acids were originally defined only in general terms.<sup>9</sup>

*Soft base* - donor atom is of high polarizability, low electronegativity, easily oxidised and associated with empty, low-lying orbitals;

*Hard base* - donor atom is of low polarizability, high electronegativity, hard to reduce, and associated with empty orbitals of high energy and hence inaccessible;

*Soft acid* - the acceptor atom is of low positive charge, large size, and has several easily excited outer electrons. Polarizable.

*Hard acid* - acceptor atom is of high positive charge, small size, and does not have easily excited outer electrons. Not polarizable.

According to this definition the aliphatic aldehydes and aliphatic ketones are hard acids, whereas aromatic aldehydes and ketones are soft ones. On the other hand amines are hard bases and phosphites are soft ones. Now the explanation of the studied reactions seems to be straightforward. Hard amine reacts faster with hard carbonyl compounds and soft phosphite prefers the soft aromatic carbonyl compounds. Those considerations are however qualitative.

Density-functional theory offers the theoretical framework to explicitly calculate the electronegativity ( $\chi$ ) as the first derivative of the energy with respect to the number of electrons and the hardness ( $\eta$ ) of the chemical species as the second derivative of the energy with respect to the number of electrons.<sup>13</sup> The electrophilicity is

thus calculated as  $\chi = \frac{dQ}{dN}$  and hardness as  $\eta = \frac{d^2Q}{dN^2}$ . In order to study the discussed reaction in a quantitative way we calculated the necessary parameters i.e. the charge on the carbonyl carbon, the electrophilicity of the carbonyl group and its softness for all the studied aldehydes, ketones and amines as well as for phosphite. The

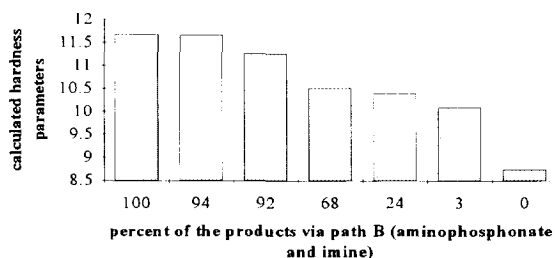
electrophilicity was calculated as  $\frac{dQ}{dN}$  and hardness as  $\frac{d^2Q}{dN^2}$  using a GRINDOL program.<sup>14</sup> For the detailed description of the program and theoretical background see References<sup>15-16</sup> Results of the calculations i.e. the charge on carbonyl carbon as well as the softness parameters for the carbonyl compound amine and diethyl phosphite are collected in Table 3 and illustrated in Figure 1.

Table 3. Results of theoretical calculations. Data in Table compare the observed percentage amounts of the products of the reaction between carbonyl compound (1-valeric aldehyde, 2-acetone, 3-cyclohexanone, 4-benzaldehyde, 5-acetophenone, 6-benzophenone, 7-fluorenone), butylamine and diethyl phosphite by path A vs B as well as calculated charge on the carbonyl carbon and hardness of the carbonyl compounds.

	1	2	3	4	5	6	7
path B : path A	100:0	94:6	92:8	68:32	24:76	3:97	0:100
charge on the carbonyl carbon	0.556	0.670	0.598	0.525	0.599	0.540	0.521
hardness	11.684	11.663	11.264	10.526	10.398	10.093	8.738

The corresponding hardness parameters for diethyl phosphite, diethyl phosphite anion and amine are 11.937, 8.413, 12.945 respectively.

Fig 1. The correlation between the calculated hardness parameter of the carbonyl compound and the percentage of the products according to path B



From Table 3 and Figure 1 one can see that the charge calculated on the carbonyl carbon does not correlate with the ratio of the products via path A or B. Earlier it was postulated that steric parameters are not responsible for the observed composition of the reaction mixture. It was suggested that hardness of the nucleophile and electrophile might be important. The qualitative predictions are totally proven by the calculations, see Table 3. Comparing the softness parameters for the carbonyl compounds and that for amine and phosphite one should notice that relatively softer aromatic carbonyl compounds prefer softer phosphorus nucleophile and that relatively harder aliphatic carbonyl compounds prefer harder nitrogen nucleophile. The aromatic - aliphatic carbonyl ketone (acetophenone) and benzaldehyde have intermediate hardness parameters and they react with both nucleophiles (hard amine and soft phosphorus) with more or less the same reaction rate.

## EXPERIMENTAL PART

NMR spectra were recorded on AMX 300 MHz Bruker instrument, operating at 300.13 MHz (<sup>1</sup>H) and 121.499 (<sup>31</sup>P). Measurements were made in CDCl<sub>3</sub>. All compounds analysed in the reaction mixture were additionally synthesized in pure forms and were fully characterised by NMR, IR, and elemental analyses. The

details of their synthesis and spectral characteristics are given in the literature.<sup>17</sup> IR spectra and elemental analysis were performed at the Institute of Organic Chemistry, Biochemistry and Biotechnology.

The kinetic experiments were performed on Biochrome Bio-4060 spectrometer in a absolute ethanol solution. The concentration of the carbonyl compounds were  $2 \cdot 10^{-3}$  mole/dcm<sup>3</sup>. To get the pseudo first order kinetics the 100 fold excess of butylamine was added in the measurement of imine formation or 100 fold excess of triethylamine and 100 fold excess of diethyl phosphite in the experiments of hydroxyphosphonate formation. The use of absolute ethyl alcohol is necessary to avoid the hydrolysis of diethyl phosphite and transesterification reactions.<sup>18</sup>

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