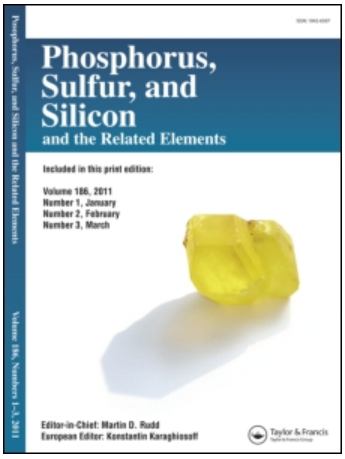


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# STUDIES ON ORGANOPHOSPHORUS COMPOUNDS XL VIII STRUCTURAL EFFECT ON THE INDUCED ASYMMETRIC ADDITION OF DIALKYL PHOSPHITE TO CHIRAL ALDIMINE DERIVATIVES

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# STUDIES ON ORGANOPHOSPHORUS COMPOUNDS XLVIII STRUCTURAL EFFECT ON THE INDUCED ASYMMETRIC ADDITION OF DIALKYL PHOSPHITE TO CHIRAL ALDIMINE DERIVATIVES

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For the evaluation of the predominating factors controlling the stereochemical process of the addition of dialkylphosphite to a chiral Schiffs base resulting from condensation of substituted benzaldehyde and 1-phenylethylamine, various structural effect of the substrates and phosphorus reagents were investigated. The influence of catalyst and solvent is discussed on the basis of the conformational requirements of the complex formed.

*Key words:* Induced asymmetric addition; structural effects; dialkyl phosphite addition.



## INTRODUCTION

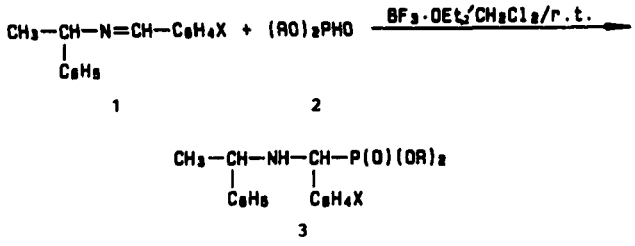
Among numerous methods for the preparation of 1-aminoalkylphosphonic acids the most convenient route is the addition of dialkylphosphite to a Schiff's base.[1-3] The stereochemical behaviour of the addition of dialkylphosphite to the condensation product of benzaldehyde and (R) or (S) 1-phenylethylamine was briefly communicated by Gilmore et al.[4] Since the induced asymmetric addition is too delicate to survive the harsh reaction conditions involved, it seems interesting to examine the potential usefulness of this method as a reliable synthetic route to optically active aminoalkylphosphonic acids. In this paper we wish to report the influence of reaction conditions including structural variation of substrates and reagents, as well as reaction temperature, nature of catalyst and solvent, on the degree of the asymmetric induction during the addition in terms of d.e. value of the reaction.

## RESULTS AND DISCUSSIONS

### *1. Electronic effect of the nuclear substituents of the aldimine derivatives*

Condensation of p-substituted benzaldehyde with 1-phenylethylamine affords aldimine derivatives (**1**) which are then reacted with diethylphosphite (**2b**) in dichloromethane using boron trifluoride ether complex as catalyst. The d.e. value of the product (**3**) was evaluated by $^{31}$P-NMR spectroscopy.

The results in Table I indicate that the electronic effect of the nuclear substitutes of aldimine derivatives on the d.e. value of the addition product with **2b** is not significant. Nevertheless, the reactivity of **1** is determined chiefly by the structural



| 1,3 | X | 2,3 | R |
|---|---|---|---|
| a | H | a | $CH_3$ |
| b | $CH_3$ | b | $C_2H_5$ |
| c | $CH_3O$ | c | i-$C_3H_7$ |
| d | Cl | d | n-$C_4H_9$ |
| e | Br | e | i-$C_4H_9$ |
| f | F | f | $C_6H_5$ |

TABLE I

Electronic effect of the nuclear substituents

| X | H | $CH_3$ | $OCH_3$ | Cl | Br | F |
|---|---|---|---|---|---|---|
| Yield(%) | 80 | 84 | 72 | 79 | 77 | 80 |
| d.e.(%) | 61 | 54 | 60 | 56 | 54 | 56 |



effect of the substituents but the variation in $\Delta\Delta G^{\neq}$ of the transition state is negligible. It can be rationalized by the fact that the substituted benzene ring and C=N bond are located on the same plane. These results encouraged us to investigate the influence of the steric effect of dialkyl phosphites.

## 2. *Steric effect of dialkylphosphites*

Dialkyl phosphites with various bulky degree of alkyl groups were studied. Addition reaction of **2** to **1** was monitored by TLC until all **1** was consumed. The results are tabulated in Table II.

Experimental results demonstrated that the chemical yield of the addition reaction decreases with increase of the steric hindrance of the alkyl group in the order: $CH_3>C_2H_5>n—C_4H_9>i—C_4H_9>i—C_3H_7$. Di-(t-butyl) phosphite gave no adducts with **1** under similar conditions. The low reactivity of **2** with bulky alkyl groups is presumably attributable to the steric effect of the substituent which hinder its addition reaction to compounds with C=N bonds. However, the increase of the steric effect of **2** tends to improve the selectivity of this induced asymmetric addition as shown by the fact that the d.e. value of the reaction increases in the following order: $CH_3<C_2H_5<n—C_4H_9<i—C_4Hg<i—C_3H_7$.

It is coincident with the general concept for the reactivity selectivity principle proposed by Pross.[5] The characteristic behaviour of diphenyl phosphite (**2f**) in this reaction is most promising. It provides excellent d.e. value together with a satisfactory chemical yield. In addition the phenyl group is easy to remove, so the

TABLE II
Steric effect of dialkyl phosphites

| R | $CH_3$ | $C_2H_5$ | i-$C_3H_7$ | n-$C_4H_9$ | i-$C_4H_9$ | $C_6H_5$ |
|---|---|---|---|---|---|---|
| Yield(%) | 85 | 85 | 61 | 74 | 72 | 78 |
| d.e.(%) | 43 | 61 | 83 | 66 | 71 | 80 |

TABLE III
Influence of catalysts

| catalyst | $AlCl_3$ | $BF_3{\cdot}OEt_2$ | $ZnCl_2$ | TsOH | no cat. |
|---|---|---|---|---|---|
| Yield(%) | 77 | 80 | 75 | 72 | 65 |
| d.e.(%) | 70 | 61 | −30* | −50 | −16 |

* Negative values indicate the opposite direction of the induced effect.

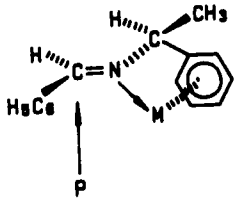


application of **2f** in this addition reaction will open up a broad prospect for the asymmetric synthesis of 1-aminoalkyl-phosphonic acid.

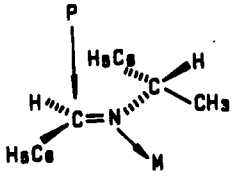
### 3. *Influence of catalysts*

Addition of dialkyl phosphite to Schiffs base proceeds at 140°C without catalyst.[1-3] It is quite obvious that a high reaction temperature is not favourable for our propose. In order to facilitate the reaction at ambient temperature, various types of catalyst were studied at room temperature.

Data on Table III show that the presence of acidic catalysts including Lewis acids and protonic acids (p-toluene sulfonic acid) favours the reaction. With the aid of such catalysts the addition takes place smoothly at room temperature in higher chemical yield and d.e. value. It is necessary to point out that the induced effect of zinc chloride or p-toluenesulfonic acid was in opposite direction as did aluminum trichloride or boron trifluoride. This is probable due to the fact that being a Lewis acid with empty d-orbital of the central atom, $AlCl_3$ or $BF_3$ form a complex with the benzen ring of the Schiff base providing coordination compound with conformation A in dichloromethane, while for $ZnCl_2$ or TsOH formation of complex with conformation B is predominating.




Conformation A




Conformation B

The direction of the asymmetric induction during the present addition reaction is presumably determined by the conformation of the complex formed from catalyst and substrate.

### 4. *Influence of the amount of catalyst and nature of solvent on the asymmetric induction*

In order to confirm the contribution of the conformation of the complex resulting from Schiff base and catalyst to the asymmetric induction during the addition reaction, the effect of various amounts of $BF_3 \cdot OEt_2$ in dichloromethane and toluene on the d.e. value of the reaction was investigated.

As shown by the experimental data, this reaction provides a similar asymmetric induction effect without catalyst in both solvents. With the increase of the amount of $BF_3 \cdot OEt_2$, the d.e. value of the reaction increased markedly in dichloromethane. While in toluene, the negative d.e. value enhanced graduately. A linar relationship was obtained in plotting the amount of catalyst versus d.e. value of the reaction either in $CH_2Cl_2$ or in toluene. (Fig. 1).

This phenomenon may be rationalized by the contribution of conformation A



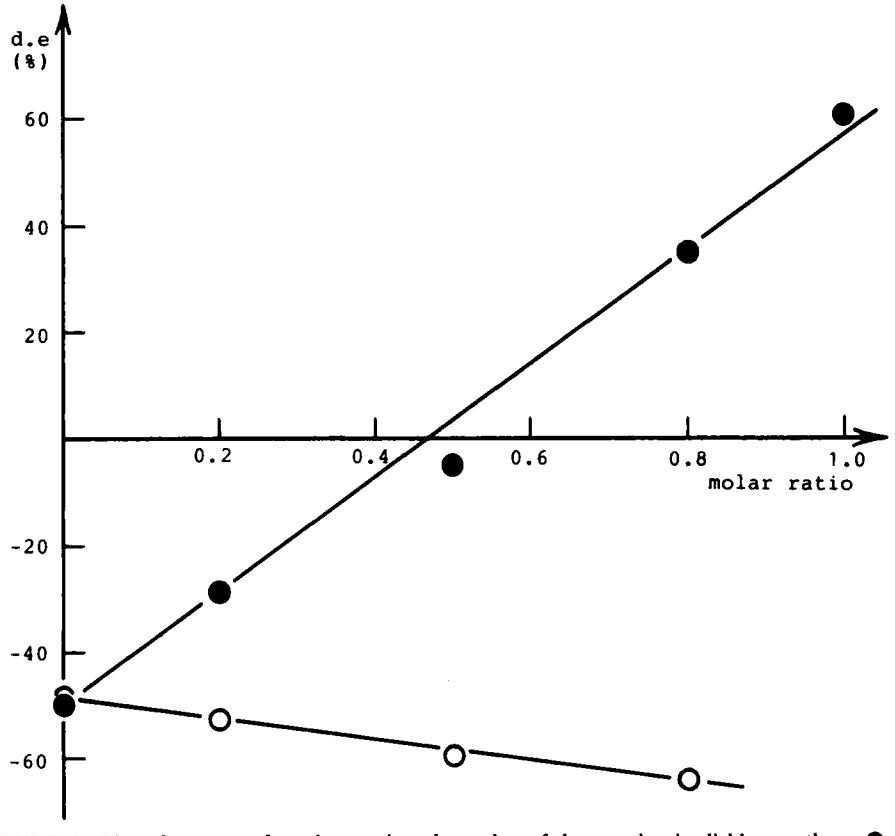



FIGURE 1 Plot of amount of catalyst against d.e. value of the reaction in dichloromethane ● and toluene ○.

and B resulting from different amounts of catalyst in various solvents. In aprotic polar solvents the $\pi$-bonding of $BF_3$ to the benzene ring is significant. It leads to complex formation with conformation A. While in non-polar solvents formation of complex with conformation B is predominating. Various degree of d.e. value of the reaction is therefore attributed to the different ratio of conformation A and B of the complex existing in the reaction system.

## EXPERIMENTAL

$^1$HNMR spectra were recorded on a Varian EM-60A Spectrometer. $^{31}$PNMR spectra were taken from a FX-90Q spectrometer using $CDCl_3$ or $D_2O$ as solvent and 85% $H_3PO_4$ as external standard. MS were recorded on a Finnigan-4021 mass spectrometer.

The d.e. value of the addition product **3** was estimated from the integral value of $^{31}$P-NMR.

*(S)-(−)-1-phenyl-N-p-substituted benzylideneethylamine* (**1**) were prepared by condensation of 1-phenylethylamine with p-substituted benzaldehyde as described.[6,7] The optical rotation of **1** in various solvent were also reported.[6,7] The $^1$HNMR data of **1** are as follow:

$^1$HNMR, $\delta$, ppm

1a: 1.52 (d, 3H, J=6Hz), 4.4 (q, 1H, J=6Hz), 7.28 (m, 8H), 7.64 (m, 2H), 8.13 (s, 1H)
1b: 1.55 (d, 3H, J=6Hz), 2.33 (s, 3H, $CH_3$), 4.4 (m, 1H), 6.9–7.25 (m, 9H, Ar), 8.13 (s, 1H)
1c: 1.48 (d, 3H, J=6Hz), 3.64 (s, 3H), 4.33 (q, 1H), 6.7 (d, 2H, Ar), 7.21 (m, 5H, Ar), 7.38 (d, 2H, Ar), 8.13 (s, 1H)
1d: 1.50 (d, 3H, J=6Hz), 4.40 (q, 1H), 7–7.9 (m, 9H), 8.17 (s, 1H)
1e: 1.51 (d, 3H, J=6Hz), 4.43 (q, 1H), 7.25 (5H, Ph), 7.38 (m, 4H, Ar), 8.23 (s, 1H)
1f: 1.50 (d, 3H, J=6Hz), 4.4 (q, 1H), 6.8–7.4 (m, 7H, Ar), 7.7 (m, 2H, Ar), 8.08 (s, 1H)

*Dialkyl N-[(S)-methylbenzyl]amino-p-substituted benzylphosphonates (3) (General Procedure).* Preparation of **3a**. To a solution of 1.04 g (5 mmole) of **1a** in 10 ml dichloromethane, 0.62 ml (5 mmole) of $BF_3 \cdot OEt_2$ was added and then stirred for 15 min. After addition of 0.69 g (5 mmole) of diethylphosphite, the mixture was stirred for 10 hours at ambient temperature. The resultant product was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure. The d.e. value of the product thus obtained was evaluated by $^{31}$PNMR and recorded in Table I.

For the investigation of the d.e. value of the addition product, various (S)-1-phenyl-N-p-substituted benzylidene ethylamine (**1b–1f**) were used instead of **1a** as for the preparation of **3a** described above. Experimental data are recorded in Table I.

For the investigation of the steric effect of ester alkyl group of **2** on the d.e. value of the addition product, various dialkylphosphites (**2a–2f**) were used. Experimental data are recorded in Table II.

For the investigation of the influence of various catalysts on the d.e. value of the adducts of **1** and **2**, either Lewis acid ($AlCl_3$, $ZnCl_2$) or protonic acid (TsOH) catalysts were used instead of $BF_3 \cdot OEt_2$ as described for the preparation of **3a** (General procedure). Experimental data are tabulated in Table III.

For the investigation of the influence of amount of catalyst in different solvents, various amounts of $BF_3 \cdot OEt_2$ either in $CH_2Cl_2$ or in toluene were used instead of equivalent amounts of $BF_3 \cdot OEt_2$ in $CH_2Cl_2$ as described for the preparation of **3a** (General procedure). Experimental results are represented in Table IV and Figure 1.

*N-[(s)-1-methylbenzyl]aminobenzylphosphonic acid.* A mixture of **3a** (2 mmole) and 5 ml of concentrated HCl was heated with stirring. The completion of the hydrolytic reaction was monitored by Silicon-

TABLE IV

Influence of amount of catalyst in various solvents at room temperature

| | d.e. value with different amounts of $BF_3 \cdot OEt_2$ | | | | |
|---|---|---|---|---|---|
| Solvent | TsOH* | 0.2 | 0.5 | 0.8 | 1.0 |
| $CH_2Cl_2$ | −50 | −29 | −5 | 35.5 | 61 |
| $CH_3C_5H_6$ | −49 | −53 | −60 | −64 | — |

coated paper chromatography using i-PrOH:$CH_2Cl_2$:$NH_4OH$=5:4.4:0.5 as mobile phase.[8] It required usually 5 hours. After the removal of solvent, the residue was dissolved in minimum amount of ethanol and then treated with propylene oxide until pH=5–6. The precipitated solid was filtered, dried and recrystallized from aqueous ethanol. An acidic product was obtained with mp. 223–225°C, yield 79%. Anal. $C_{15}H_{15}NO_3PH_2O$(309.33).

| | | | | | | |
|---|---|---|---|---|---|---|
| Calc. | C, | 58.23; | H, | 6.53; | N, | 4.53; P, 10.01% |
| Found. | C, | 58.06; | H, | 6.40; | N, | 4.46; P, 9.65% |

$^1$HNMR ($D_2O$) ppm, 1.51 (m, 3H, CH3), 4.10 (m, 1H), 7.3 (m, 5H, Ph); $^{31}$PNMR ($D_2O$) 9.12 ppm; MS (m/e), 210 [(M—P(OH)$_3$)+, 21.05%], 194 [(M-210-$CH_3$)$^+$, 21.05%], 105 (PhCH=NH, 100%), 91 (PhCh2+).

N-[(1S)-(−)-1-methylbenzyl]aminobenzylphosphonic acid is obtained analogously from its dialkylesters in satisfactory yield. (From diethylester, 73%; diisopropylester, 53%; di-n-butylester, 70%; diisobutylester, 61; diphenylester, 83%).

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