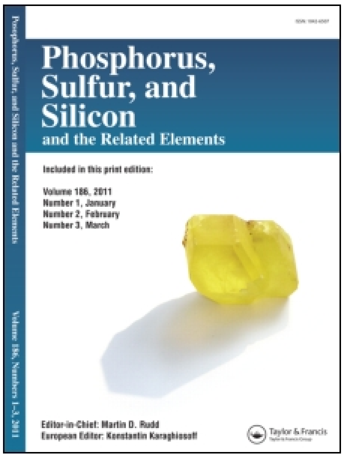

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SOLVENT AND COUNTERION EFFECT ON THE REACTION OF ARYLMETHANEPHOSPHONATE CARBANION METAL COMPLEXES WITH SCHIFF BASES

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SOLVENT AND COUNTERION EFFECT ON THE REACTION OF ARYLMETHANEPHOSPHONATE CARBANION METAL COMPLEXES WITH SCHIFF BASES

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The influence of solvent and metal ion on the reaction of diethyl esters of phenyl-, 4-methylphenyl- and 4-chlorophenylmethanephosphonic acid **1a–c** and N-benzylidene aniline in the presence of alkaline amides or butyllithium is studied. A strong effect of the counterion on the stereochemistry of the aldol stage of the reaction is established. Complete stereochemical control of the reaction is observed with esters **1a–c** using $LiNH_2$ as metallating agent in ether at 10°C, 1 RS2 RS (erythro) adducts being formed as the only or main products. In the presence of $NaNH_2$ or KNH_2 the reaction is considerably or completely shifted to the more stable 1 RS2 SR (threo) isomers.

In better coordinating solvents (THF, DMF, HMPT), however, the stereoselectivity of the reaction even in the presence of $LiNH_2$ decreases (THF, DMF) or threo adduct predominates (HMPT). The 4-chloro-phenylmethanephosphonic ester gives a constant ratio diastereomeric mixture with KNH_2 and $NaNH_2$ in all mentioned solvents. The stereoselectivity of the reaction also decreases in the presence of dibenzo-18-crown-6 using $LiNH_2$ or BuLi as metallating agents.

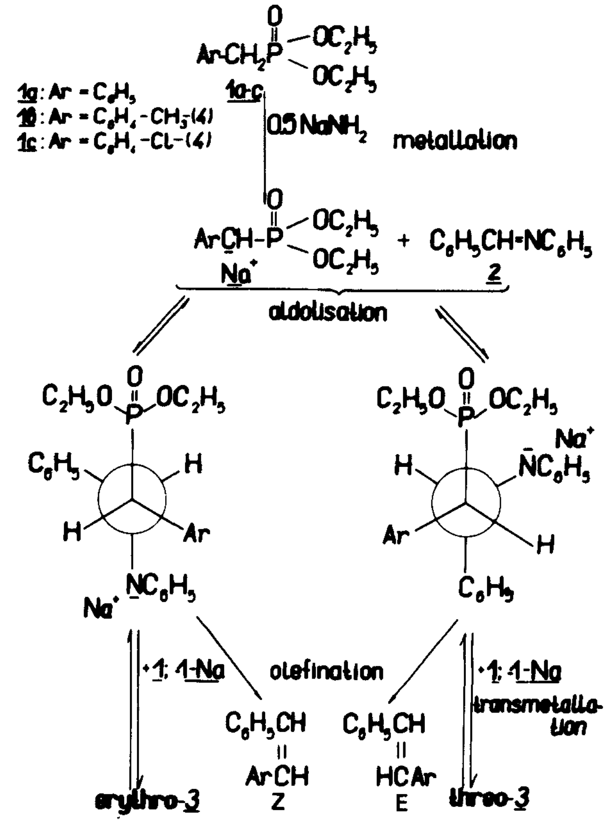
INTRODUCTION

Hitherto the influence of reaction conditions (solvent, metallating agent, temperature) in nucleophilic reactions of phosphonate carbanions (their metal complexes) has been mainly studied on the reaction of carbonylolefination[1–4] (reaction of Horner–Emmons).

In previous papers[5–8] we showed that, depending on the conditions, the reaction of PO-activated CH-acids **1a–c** with benzylideneaniline **2** in the presence of an 0.5 mole of $NaNH_2$ leads to diastereomeric mixtures of addcuts **3** (in different ratios) and (or) olefines **4** according to Scheme 1.

The most important distinction of this reaction from the Horner's PO-activated olefination of carbonyl compounds and Schiff bases[9] is (1) the use of "catalytic amounts" of the metallating agent ($NaNH_2$), and (2) the existence of a new, transmetallation stage. This is due to the higher basicity of the intermediate N-anion of **3** in comparison with the analogous O-anion in Horner's reaction. For this reason in many cases *N*-adducts **3** are obtained in high yields, especially at low temperature.

Recently[10] we investigated the effect of the solvent on the aldol stage of the reaction of the



SCHEME 1

4-methylphenylmethanephosphonate ester **1b** with benzylideneaniline **2**. We found that the first product of the reaction in ether is the 1RS2RS (erythro) adduct, while on increasing the reaction temperature or on prolonging the reaction time it transfers to the more stable threo isomer.

RESULTS AND DISCUSSION

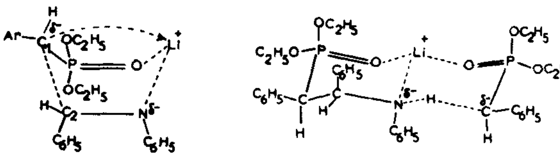
Now we report our results on the solvent and counterion effect on the reaction of diethyl esters of phenylmethanephosphonic acid **1a**, 4-methylphenylmethanephosphonic acid **1b** and 4-chlorophenylmethanephosphonic acid **1c** with benzylideneaniline **2** using 0.5 mole of alkaline amides ($LiNH_2$, $NaNH_2$, KNH_2) or 1 mole of BuLi.

The obtained results are shown on the Tables I–IV, where, for comparison, data from our previous experiments with $NaNH_2$,[10] are also included. In some experiments the quantity of benzaldehyde, obtained after hydrolosis of the unreacted **2**, was determined.

a) Experiments in the Presence of $LiNH_2$ or BuLi

As shown in Table I in ether both at −33°C and 10°C arylmethanephosphonic esters **1a–c** react with **2** in a high degree of stereoselectivity forming as the result of kinetic control almost only the 1RS2RS (erythro) isomers **3**. This indicates that in the mentioned conditions the aldol stage of the reaction is practically irreversible. This high degree of stereoselectivity, as well as the high degree of conversion of the reactants to products can be explained by formation of six-membered Li-chelates, **3–Li**. They are strongly stabilized by coordination of Li^+ with the PO-group after rotation about the $C_1—C_2$ bond of the primarily formed antiperiplanar conformation of the erythro-N-anion.

This high stability of the erythro-Li^+-chelate is obviously due to the high coordinating ability of both PO-group and Li-ion, which prevails over the gauche interaction of the bulky aryl substituents at C_1 and C_2 (see Scheme 2). The erythro-threo isomerisation through the starting reactants, therefore, proceeds much more slowly than the transmetallation of the starting CH-acid by the erythro-Li^+-chelate.



RETROALDOL DECOMPOSITION of the ERYTHRO-$\overset{+}{Li}$-CHELATE (possible transition state)

TRANSMETALLATION (possible transition state)

SCHEME 2

TABLE I

Reaction of **1a–c** with **2** (conc. 5 M) in the presence of $LiNH_2$ (2.5 M)

N	1	T°C	Time min.	Solvent	Adducts 3 Yield %	 Configuration	 Er:Thr
1.	**1a**	10	15	ether	79		88:12
2.	**1a**	10	75	ether	95		90:10
3.	**1a**	10	15	THF	54		50:50
4.	**1a**	10	75	THF	70		64:36
5.	**1a**	10	75	THF + c.e.a			67:33
6.	**1a**	10	240	HMPT	43	100 Thr	
7.	**1a**	−10	15	DMF	87		29:71
8.	**1a**	10	75	DMF	87		14:86
9.	**1b**	10	15	ether	78	100 Er	
10.	**1b**	10	75	ether	96		90:10
11.	**1b**	−33	360	ether	99	Er ≫ Thr	
12.	**1b**	−10	150	ether	97	Er ≫ Thr	
13.	**1c**	10	15	ether	83		80:20
14.	**1c**	10	75	ether	96		84:16
15.	**1c**	10	15	THF	70		76:21
16.	**1c**	10	75	THF	77		75:25
17.	**1c**	10	75	THF + c.e.			67:33
18.	**1c**	10	75	HMPT	76		27:73

TABLE II

Reaction of **1a** and **1c** with **2** (conc. 0.2 M) in the presence of BuLi (0.2 M)

N	1	T°C	Time min.	Solvent	Adducts 3 Yield %	Configuration	Er:Thr
1.	**1a**	−33	60	THF	77		48:52
2.	**1a**	−60	120	THF	74		51:49
3.	**1a**	−70	120	THF	87		88:12
4.	**1a**	−70	120	THF + c.e.[a]			85:15
5.	**1c**	−70	120	THF	86		81:19
6.	**1c**	−70	120	THF + c.e.			67:33

[a] c.e. dibenzo-18-crown-6.

It is worth noting that the high stereoselectivity of the reaction of benzylmethylsulphoxide anions has been explained by similar strong Li-oxygen chelation.[11]

The lower stereoselectivity of the reaction in THF with respect to the erythro adducts indicates a greater reversibility of the aldol stage in this solvent. This is probably due to the better Li^+ solvating ability of THF than that of diethyl ether.[12]

The experiments with BuLi (Table II) show that high stereoselectivity, also with respect to the erythro adducts, is achieved not before a considerable decrease of the temperature (−70°C). This observation is due to an increase of the reversibility of the reaction in dilution (0.2 M) and cooling, because of an increase in the quantity of the solvent-separated ion pairs in the solution (compare with Ref. 13).

The retroaldol decomposition of the erythro adducts **3–Li** and their conversion into the threo isomers via the starting reactants increases in HMPT, whose PO-group competes with the PO-group of the Li-chelates for coordination with Li^+.

In the presence of a strong complexing agent as dibenzo-18-crown-6 the stereoselectivity of the reaction in THF at −70°C decreases considerably only in the case of phosphonate **1c** the ratio Er/Thr changes from 81:19 to 67:33, Table II). This indicates that the equilibrium: erythro-Li-chelate + crown ether $\rightleftharpoons$ N-anion of **3** + Li-crown ether shifts to the right slowly.

b) Experiments in the Presence of $NaNH_2$

The data on the Table III show, that in ether at 10°C in the presence of $NaNH_2$ the reaction of

TABLE III

Reaction of **1a–c** with **2** (conc. 5 M) in the presence of $NaNH_2$ (2.5 M)

N	1	T°C	Time min.	Solvent	Adducts 3 Yield %	Configuration	Er:Thr
1.	**1a**	10	15	ether	70	Thr ≫ Er	
2.	**1a**	10	75	ether	77	100 Thr	
3.	**1a**	10	75	THF	75	100 Thr	
4.	**1a**	10	75	HMPT	83	100 Thr	
5.	**1b**	−33	240	ether	75	100 Er	
6.	**1b**	10	15	ether	37		46:54
7.	**1b**	10	75	ether	72	100 Thr	
8.	**1b**	10	75	HMPT	76	100 Thr	
9.	**1b**	10	75	DMF	32		55:44
10.	**1c**	−33	75	ether	75		48:52
11.	**1c**	10	15	ether	75		47:53
12.	**1c**	10	75	ether	79		50:50
13.	**1c**	10	75	HMPT	80		52:48

TABLE IV

Reaction of **1a–c** with **2** (conc. 5 M) in the presence of KNH_2 (2.5 M)

N	1	T°C	Time min.	Solvent	Adducts 3		
					Yield %	Configuration	Er:Thr
1.	**1a**	10	15	ether	20	Thr ≫ Er	
2.	**1a**	10	75	ether	18	100 Thr	
3.	**1a**	10	75	THF	12[a]	100 Thr	
4.	**1a**	10	15	HMPT	49		52:48
5.	**1a**	10	75	ether	75	100 Thr	
6.	**1b**	−33	150	ether	95	Er ≫ Thr	
7.	**1b**	10	15	ether	21	Thr ≫ Er	
8.	**1b**	10	75	ether	oil	Thr ≫ Er	
9.	**1b**	10	75	THF	oil		49:51
10.	**1b**	10	75	HMPT	70	Thr ≫ Er	
11.	**1c**	10	15	ether	70		52:48
12.	**1c**	10	75	ether	71		47:53
13.	**1c**	10	15	THF	20[b]		49:51
14.	**1c**	10	75	THF	22[c]		48:52
15.	**1c**	10	15	HMPT	70		49:51
16.	**1c**	10	75	HMPT	97		56:44
17.	**1c**	10	75	DMF	7[d]		49:51

[a] The quantity of benzaldehyde is 77 %.
[b] The quantity of benzaldehyde is 56 %.
[c] The quantity of benzaldehyde is 54 %.
[d] The quantity of benzaldehyde is 70 %.

1a–c with **2** is reversible and fast. As a result only thermodynamically preferred threo adduct (from **1a** and **1b**) or diastereoisomeric mixture (from **1c**) are formed (Table III). In HMPT **1a** and **1b** react with **2** highly stereoselectively with respect to threo adducts. In DMF both the stereoselectivity of the reaction and the yield of adducts are reduced. Obviously in ether and HMPT at 10°C the equilibrium is quickly shifted towards the threo-chelates, while in the more polar and with high solvating ability DMF it is appreciably shifted towards the starting reactants.

At low temperature (−33°C) **1b** reacts with **2** stereoselectively to form the erythro adduct, while **1c** gives the diastereoisomeric mixture. **1a** does not react at this temperature (−33°C), probably because of a strong retardation of the metallation (preliminary metallated at 10°C ester **1a** and then cooled to −33°C reacts with **2**).

c) *Experiments in the Presence of KNH_2*

In the presence of KNH_2 at 10°C in all (similar to that with $NaNH_2$) being examined solvents (see Table IV) the reaction of **1a** and **1b** with **2** is reversible and fast, 1RS2SR (threo) adducts being the main products.

At low temperature (−33°C) in both cases (KNH_2 and $NaNH_2$) erythro adducts are formed exclusively or predominantly.

On the base of these results it might be supposed, that at low temperature Na- and K-erhthro chelates possess a sufficient stability, that transmetallation is faster than their retroaldol decomposition and isomerisation. Conversely, at 10°C the same erythro chelates are insufficiently stable (because of the weak coordination and chelation of Na^+ and K^+ with PO-group), so the retroaldol decomposition and the isomerisation Er → Thr is faster than transmetallation of the erythro chelates.

The diethyl ester of 4-chloro-phenylmethanephosphonic acid **1c** in the presence of KNH_2 or $NaNH_2$ reacts with **2** giving a diastereomeric mixture of adducts in almost constant ratio (Er/Thr 1:1), independent of the nature of the solvent and temperature. This ratio does not change in the presence of dibenzo-18-crown-6 (Table IV). The reason could be: (a) fast retroaldol decomposition of the erythro N-anion and fast achievement of the equilibrium Er $\rightleftharpoons$ Thr or (b) mutual conversion of erythro N-anion into threo-N-anion without return to the starting reactants, e.g. by epimerisation. J. Seyden-Penne *et al.*[2,3] explained the constant ratio of the isomeric cinnamonitriles by similar partial epimerisation of an intermediate oxyanions in the reaction of benzaldehyde and strong CH-acid with cyanomethanephosphonic ester (as a carbanion). In our case this process is also probable because of the increased CH-acidity at C_2-position, caused by the *p*-chlorophenyl group, attached at the same carbon atom.

EXPERIMENTAL

The configuration of the diastereoisomers **3** was determined preliminary by IR spectroscopy and TLC.[5,6,8]

The crude products **3** were studied by TLC on silica gel 60 F_{254} (aluminium sheets "Merk"), the ratio Er/Thr being measured densitometrically ("Vitatron" TLD 100).

The quantity of benzaldehyde, obtained after hydrolysis of the unreacted **2** was determined as 2,4-dinitrophenylhydrazone.[14]

Diethyl Esters of 2-phenylamino-2-phenyl-1-arylethane-phosphonic acids 3

An alkaline amide ($LiNH_2$, $NaNH_2$ or KNH_2, 2.5 mmole) was added to a mixture of diethyl ester of arylmethane phosphonic acid **1** (5 mmole) and benzylidene aniline **2** (5 mmole) in 1 ml anhydrous solvent (ether, THF, HMPT or DMF), cooled to the corresponding temperature (see the tables). After stirring for 15–240 min the mixture was hydrolyzed with 10 ml 7% hydrochloric acid and the crude product was washed with water until neutral. When the residue is a mixture of cristalline and oily product the aqueous solution is extracted with ether and the quantity of benzaldehyde is determined as 2,4-dinitrophenyl hydrazone according to Ref.[14]

The crude product was dissolved in $CHCl_3$, the spots on a silica gel are developed 3–4 times with ether/hexane 2:1 and the ratio Er/Thr—measured densitometrically.

Experiments in the Presence of BuLi

To a solution of **1** (5 mmole) in 8 ml anhydrous THF, cooled to −60°C or −70°C, butyllithium (5 mmole, 15% in hexane), diluted with 8 ml THF, was added under argon. After stirring for 1 hr benzylidene aniline **2** (5 mmole) in 5 ml THF was added and the stirring continued for 1 or 2 hrs at this temperature. The mixture was hydrolyzed by 10 ml water, followed by addition of 10 ml 7% hydrochloric acid, then extracted with chloroform (2 × 30 ml) and studied as described above.

In some experiments dibenzo-18-crown-6 (5 mmole) was added before the addition of **2**.

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