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Diastereoselectivity in Nucleophilic Displacement Reactions at Phosphorus; Isolation and Characterization of a Pentacoordinated Intermediate

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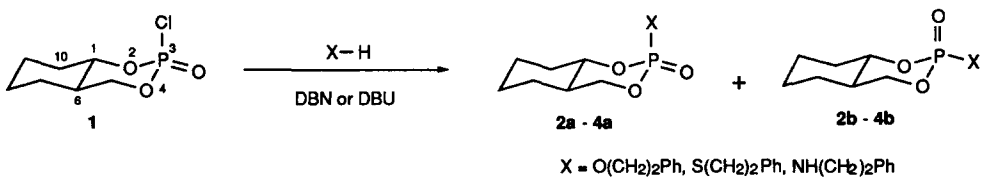
Abstract: Reaction of the axially substituted *trans*-3-chloro-2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decan-3-one ((±)-**1**) with O- and S-nucleophiles in the presence of DBN preferentially proceeds with retention at P, whereas the epimeric ratio is reversed with DBU as the auxiliary base. N-nucleophiles exclusively react with inversion; in the presence of DBN, a pentacoordinated compound (**5**), which is considered to be a reaction intermediate, was isolated as the main product.

In the course of our current investigations concerning the inhibition of serine hydrolases with organophosphates, we have prepared several novel 2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decan-3-ones as inhibitors and model compounds.[1] Being configurationally and conformationally locked, these *trans*-decaline congeners are good probes for the investigation of stereochemical implications by ^{31}P NMR spectroscopy. Several years ago, such compounds were studied intensively, and a set of arguments for the unequivocal assignment of their structures has been established.[2,3] Hence, the ^{31}P NMR resonance of the axial epimer is shifted upfield with respect to the equatorial one and the splitting pattern in the ^{1}H-coupled ^{31}P NMR is indicative of the conformation of the heterocyclic ring. According to stereoelectronic considerations, axially substituted phosphates and thiophosphates preferentially adopt a chair and its equatorial counterparts a twist-boat conformation; the situation is reversed in the amidates. Experimentally, the axial isomer mostly elutes faster in a chromatographic system.

The axially substituted chloridate (±)-**1**,[2b] as a highly reactive starting material, was treated with a series of O-, N-, and S-nucleophiles under various conditions with the aim to isolate both P-epimers for further investigation. In order to enhance the reactivity of several reluctant S-nucleophiles,[1b] 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added as an auxiliary base. Unexpectedly, we observed inversion of the epimeric ratio when changing from DBN to DBU. An even more pronounced effect was also found for analogous reactions with O-nucleophiles, whereas N-nucleophiles exhibited a different behaviour. In this note we report directly comparable results obtained with similar nucleophilic reagents under identical reaction conditions, the only difference being the nature of the auxiliary base (Scheme 1). Representative results are summarized in the Table.[4]

Scheme 1



Reaction of (±)-**1** with 2-phenylethylamine in the presence of either DBU or DBN only yielded the equatorially substituted product **4b**; the axial epimer **4a** could not be detected[5] (see Table). Thus, the earlier statement that amines attack solely by inversion at phosphorus[6] is confirmed under our reaction conditions.

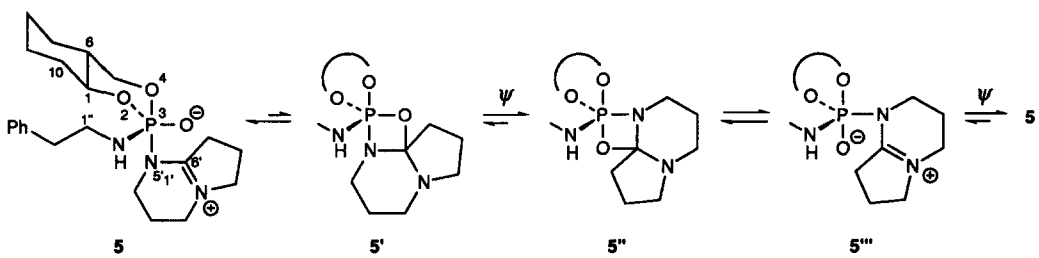
Table. Diastereoselectivities of nucleophilic displacement reactions of (±)-**1**.

Nucleophile	Auxiliary Base	Products	Epimeric Ratio (%)[a] **a** (ax) RET	**b** (eq) INV
$Ph(CH_2)_2$-OH	DBU	**2a,2b**	11	89
	DBN		75	25
$Ph(CH_2)_2$-SH	DBU	**3a,3b**	20	80
	DBN		80	20
$Ph(CH_2)_2$-NH_2	DBU	**4b**	-	100
	DBN	**4b,5**	**5** (80%)	**4b** (20%)

[a] Determined from the ^{31}P NMR spectra of the reaction mixture before chromatography.

Surprisingly, an unexpected compound was the main product when using DBN as the auxiliary base in the reaction of (±)-**1** with 2-phenylethylamine[7]. Based on the CIMS (m/z 420.4, $[M+H]^+$), its molecular formula can be assigned as $C_{22}H_{34}N_3O_3P$ (M_r 419.48). The presence of both the 2-phenylethylamine and the DBN substituents is revealed by the ^1H and ^{13}C NMR spectra (δ_H 7.18, s, Ar-H; δ_C 163.6 ppm, amidinium C(6')[8]). Moreover, the characteristic splitting ($^2J_{C,P}$ and $^3J_{C,P}$) of the corresponding ^{13}C signals clearly show an intact 2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decane moiety in a double chair conformation ($^2J_{P,H\text{-}eq(5)}$ = 22 Hz). As a consequence, the phosphorus is pentacoordinated. This finding is corroborated by the ^{31}P chemical shift (δ 8.2 ppm) which is indicative of a PO_3N_2 species in a trigonal bipyramid (TBP)[9]. These spectroscopic arguments, combined with stereoelectronic considerations, lead to the assignment of the betaine constitution **5** as depicted in Scheme 2. The attachment of the 2,4-dioxa[4.4.0]decane moiety is chosen in an arbitrary manner.

Scheme 2



The relative positions of the equilibria between the theoretically possible isomers **5**, **5'**, **5"**, and **5'''** are estimated according to stereoelectronic (relative apicophilicities) and steric effects (ring strain in a TBP). Hence, as inferred by ^{13}C NMR[8] and from the above mentioned criteria, the betaine **5** represents the most stable sructure. All attempts to crystallize the labile compound for an X-ray crystallographic analysis were unsuccessful.

The mechanism of nucleophilic displacement reactions between phosphate esters and related compounds has been the subject of significant investigations from which conflicting results have emerged.[10] In particular, exocyclic displacements occur with a bewildering variety of stereochemistries, dependent upon the nature and conformation of the substrate, leaving group, attacking nucleophile, solvent, and added salts.[10a]

The two auxiliary bases of the present study have been roughly considered to have only minor differences; nevertheless they unexpectedly display largely disparate effects. As can be seen in the Table, the reactions of O- and S- nucleophiles follow a partly mixed pathway, with predominant retention (DBN) and inversion (DBU) at phosphorus. Unfortunately, we found the vast literature[10] devoid of unambiguous arguments which could convincingly explain our experimental facts. Taking account of all relevant aspects, we assume the bulkiness of the two bases to be the essential feature. Hence, the bulkier DBU is considered to act as a general base catalyst and the entering nucleophile to react *via* direct 'in-line' $S_N2(P)$ displacement under inversion, whereas the smaller DBN participates as a nucleophilic activation agent and leads *via* two consecutive 'in-line' inversions to overall retention[11]. The isolation of the TBP **5** strongly supports these hypotheses. Although experiments to use **5** as starting material for subsequent nucleophilic displacements were unsuccessful, probably due to its instability, we consider the pentacoordinated compound **5** to be a true intermediate. The reaction with the N-nucleophile proceeds exclusively *via* an 'in-line' substitution process, which yields the stereoelectronically favoured[2,3] equatorial epimer (**4b**).

Several explanations may account for the respective side-products. The DBU-retention products (**2a**, **3a**) might be formed (a) through 'adjacent' attack of the nucleophile, pseudorotation and apical departure of the leaving group, (b) by epimerization of the stereoelectronically less favoured equatorial primary products (**2b**, **3b**), or (c) by a double inversion process where DBU may also act as a nucleophilic activator, as described above. The DBN-inversion products (**2b**, **3b**) could be the result of (a) DBN acting as a general base catalyst, or (b) epimerization of the intermediary equatorial DBN^+-adducts to the axial ones (a process which seems to be favoured as the cationic substituent is supposed to have high relative apicophility) and subsequent inversion by the aromatic nucleophile. However, the transitory occurrence of a hypervalent P(6) intermediate[10-12] in terms of the sequence P(4) $\rightleftharpoons$ P(5) $\rightleftharpoons$ P(6) $\rightleftharpoons$ P(5)' or P(5)" $\rightleftharpoons$ P(4)' cannot be precluded either.

To the best of our knowledge this is the first report on $S_N2(P)$ reactions where the structure of two otherwise very similar catalysts is crucial for the mechanism and it presents a further example of how the overall stereochemical outcome is extremely dependent on the reaction conditions.

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4. All compounds **2-4** gave accurate elemental analyses and were unambiguously characterized by IR, ^1H, ^{13}C, ^{31}P NMR, and CIMS. In a representative experiment the phosphorochloridate (±)-**1** (2 mM) in dry toluene

(2.5 ml) was added to the nucleophile (2 mM) and the auxiliary base (2 equiv.) in dry toluene (10 ml) at 0°. After stirring for 2 h under argon at 0°, the precipitate was filtered off and the residue chromatographed on SiO_2 with dry Et_2O. **Selected Data:**[13] *Trans-3-(2-phenylethoxy)-2,4-dioxa-3λ⁵-phosphabicyclo[4.4.0]decan-3-ones* (**2a/2b**, 45%). **2a** (axial epimer): colourless crystals, mp. 85.5-89.5°; R_f 0.18; ^{31}P NMR: δ -6.9 (dt, $^3J_{P,H\text{-}eq(5)}$ = 23.1, $^3J_{P,H2(1')}$ = 6.4). **2b** (equatorial epimer): colourless, viscous oil; R_f 0.11; ^{31}P NMR: δ -4.0 (m, $w_{1/2} \approx 35$). *Trans-3-(2-phenylethylthioxy)-2,4-dioxa-3λ⁵-phosphabicyclo[4.4.0]decan-3-ones* (**3a/3b**, 30%). **3a** (axial epimer): colourless crystals, mp. 36-37.5°; R_f 0.40; ^{31}P NMR: δ 20.9 (dt, $^3J_{P,H\text{-}eq(5)}$ = 26.4, $^3J_{P,H2(1')}$ = 13.6). **3b** (equatorial epimer): colourless, viscous oil; R_f 0.25; ^{31}P NMR: δ 27.9 (m, $w_{1/2} \approx 32$). *Trans-3-(2-phenylethylamino)-2,4-dioxa-3λ⁵-phosphabicyclo[4.4.0]decan-3-one* (**4b**, equatorial epimer, 57%): slightly yellow viscous oil; R_f 0.17; ^{31}P NMR: δ 6.9 (ddt, $^3J_{P,H\text{-}eq(5)}$ = 22.0, $^3J_{P,H2(1')} \approx {}^2J_{P,NH} \approx 11$).

5. As the axial isomer **4a** was not formed under the applied displacement conditions, it was prepared for comparison from (2-phenylethylamino)phosphoryl dichloride (obtained from $POCl_3$ and 2-phenylethylamine, amorphous powder (74%), ^{31}P NMR: δ 15.6) and (±)-*trans*-2-hydroxymethyl-1-cyclohexanol[2d] yielding **4a/4b** (*ca.* 1:1, 65%) and chromatographic separation.[1b] **4a**: colourless crystals, mp. 155-158°; R_f 0.29; ^{31}P NMR: δ 3.3 (m, $w_{1/2} \approx 37$).

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7. 2-Phenylethylamine (4.4 mM) and DBN (2 equiv.) in dry toluene (20 ml) were treated with (±)-**1** (4.5 mM) in dry toluene (5 ml) under argon at 0° for 2 h. The organic phase was filtered, carefully neutralized and extracted with 2N HCl. The toluene layer contained the P-equatorial substitution product **4b** (6%). The H_2O phase was treated with 2N NaOH and re-extracted with toluene. After the usual work-up the adduct **5** was obtained as a slightly yellow viscous oil (25%). **Selected Spectroscopic Data:**[13] IR ($CHCl_3$): 3000, 2940, 2880, 1645, 1455, 1245, 1070, 1030, 945 cm^{-1}. ^1H NMR: δ 7.18 (s, 5H, Ar-H). ^{13}C NMR: δ 19.3, 19.4 (C(3'),C(8')); 23.6 (d, $^4J_{9,P}$ = 1.9, C(9)); 24.2 (C(8)); 25.1 (C(7)); 28.4 (d, $^3J_{7',P}$ = 4.3, C(7')); 32.4 (d, $^3J_{10,P}$ = 8.9, C(10)); 37.0 (C(2")); 38.2 (C(1")); 39.9 (C(4')); 40.9 (d, $^3J_{6,P}$ = 4.6, C(6)); 48.3 (C(2')); 52.4 s, C(9')); 70.2 (d, $^2J_{5,P}$ = 5.7, C(5)); 79.3 (d, $^2J_{1,P}$ = 5.2, C(1)); 125.2, 127.6 (2C), 128.6 (2C), 140.8 (Ar-C); 163.6 (C(6')). ^{31}P NMR: δ 8.2 (br. 'dtt', $^2J_{P,H\text{-}eq(5)}$ = 22, $^3J_{P,NH} \approx {}^3J_{P,H(4')} \approx {}^3J_{P,H2(1")} \approx 11$). CIMS (m/z, rel. int.): 420 (100, $[M+H]^+$, M = 419.48 ($C_{22}H_{34}N_3O_3P$)), 296 (5, $[M\text{-DBN}]^+$).

8. C(6) of $DBNH^+$ resonates at 163.9 ppm ($CDCl_3$). As a derivative of an ortho-ester, an oxazaphosphetane isomer (**5'**, **5"**) would resonate at significantly higher field; see *e.g.* Kalinowski, H.O.; Berger, S.; Braun, S. *^{13}C-NMR-Spektroskopie*, G. Thieme Verlag: Stuttgart, New York; 1984, pp. 162-170.

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13. The NMR spectra were recorded in $CDCl_3$ (298K) on a VARIAN XL-200 instrument (δ in ppm, J in Hz) at 81 MHz ($^{31}P\{^1H\}$ and ^1H-coupled ^{31}P, ext. 85% H_3PO_4 = 0), at 100 MHz ($^{13}C\{^1H\}$, DEPT), and at 200 MHz (^1H, TMS = 0).

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