Tetrahedron Letters No. 34, pp 2927 - 2930, 1977. Pergamon Press. Printed in Great Britain.

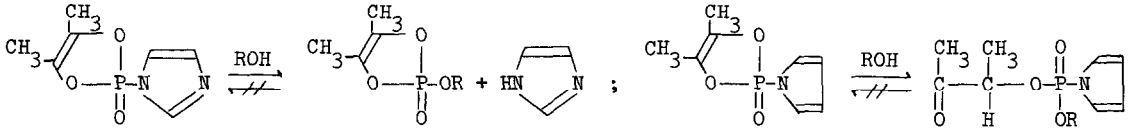
A CYCLIC ENEDIOL N-PHOSPHORYLPYRROLE, AND ITS CONTRASTING BEHAVIOR vs THE ANALOGOUS N-PHOSPHORYLIMIDAZOLE

Fausto Ramirez*, Hiroshi Okazaki and James F. Marecek
Department of Chemistry, State University of New York at Stony Brook
Stony Brook, N.Y. 11794

(Received in USA 26 May 1977; received in UK for publication 27 June 1977)

The high energy cyclic enediol N-phosphorylimidazole, CEP-IM[1] (1), undergoes rapid and quantitative displacements at P(4)[1] with ring-retention to yield, in the case of alcohols, the cyclic triesters, CEP-OR (2; Scheme 1)[2]. This reaction constitutes the basis for a new method of synthesis of unsymmetrical dialkyl phosphates. This Communication describes the preparation of the crystalline cyclic enediol N-phosphorylpyrrole, CEP-PY (3), and summarizes the striking differences in behavior of the two analogous types of heterocyclic phosphoramides.

Scheme 1:



1 2 3 4a and 4b

The reaction: CEP-Cl[3,4] + C_4H_4NK[5] ⟶ CEP-PY (3) + KCl is carried out for 1 hr at 25° in diethyl ether, under N_2. The product[6], 3, separates from the cold filtrate as colorless crystals, m.p. 69-70°, in ca. 50% yield; $\delta^{31}P$ = -8.8 ppm[7] to low field of H_3PO_4 = 0; γ^1H = 8.00 (singlet) 3.58 and 2.85 (mult.) ppm vs TMS = 10; $\delta^{13}C$ = 11.2 (J = 10.3 Hz), 135.8 (J = 1.2 Hz) ppm for CH_3 and C=C, respectively, and 113.9 (J = 12.4 Hz), 122.7 (J = 7.0 Hz) ppm for the ring (vs TMS = 0; proton-decoupled; all spectra in $CDCl_3$). The crystals of 3 become pink-brown when exposed to air.

CEP-PY, 3, undergoes a rapid displacement at phosphorus with ring-opening when treated with one mol equiv of an alcohol in aprotic solvents. No cyclic ester 2 is formed; the products are the two diastereomers, 4a and 4b of the alkyl(1-methylacetonyl) N-phosphorylpyrrole, which are produced in ca. 60:40 proportion, with t 1/2 = 6 min, 1 hr, and 15 hr for R = CH_3, c-C_5H_9, and $(CH_3CH_2)_2CH$, respectively[8], at 25° in 0.2 M $CDCl_3$ solutions (Scheme 1); 4a,b are isolated in ca. 85% yield. Under comparable conditions, the corresponding reactions of CEP-IM (1) with alcohols are too fast for measurements by the present technique.

Imidazole is an effective catalyst for the reaction of CEP-PY (3) with the alcohols; methanol and cyclopentanol react too rapidly for measurements by the present technique, but t 1/2 = 3 min for 3-pentanol (at 25°, 0.2 M $CDCl_3$, with one mol equiv of reagents and imidazole). The two diastereomers, 4a and 4b are now formed in 50:50 proportion.

Phenol reacts rapidly with CEP-IM, 1, to give 2 (R = C_6H_5)[9]. However, phenol does not react with CEP-PY, 3, unless a base, e.g., triethylamine, is present; the product is 4a,b (R = C_6H_5). This suggests that CEP-PY is less electrophilic than CEP-IM and, hence, requires a stronger nucleophile, $C_6H_5O^-$ for reaction. "Lower electrophilicity" in this context is taken to mean a lower degree of reactivity due to a lower energy content of the P(4) compound relative to another P(4) compound.

The diastereomers, 4a,b, formed in the uncatalyzed reaction undergo a subsequent and relatively slower reaction (one diastereomer faster than the other), which involves the pyrrole ring and the acetyl group, and which appears to be promoted by traces of acid. The structure of this product will be discussed in the full paper. The secondary reaction does not take place in the presence of imidazole. The structures[6] of 4a,b are based on: (a) ^1H nmr spectra, which show two singlets for the acetyl groups (e.g., τ = 7.93 and 7.73 ppm, when R = CH_3), two doublets for the $\underline{CH_3}CH$- groups (τ = 8.52 and 8.70 ppm, J = 6.2 Hz), two nearly superimposed doublets for the $\underline{CH_3}OP$- groups (τ = 6.24 ppm, J = 12 Hz), and multiplets for the methine (τ = 5.22 ppm), and the ring (τ = 3.70, 3.00 ppm) protons; (b) ^{31}P nmr spectra, which show two nearly superimposed multiplets (ca. + 2.0 ppm). (c) ^{13}C nmr spectra, which show the expected nuclei.

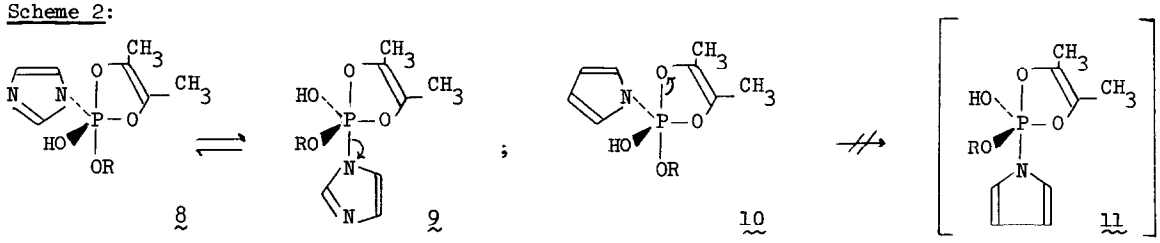
CEP-PY (3) resembles CEP-OR (2), rather than CEP-IM (1) in its reactions with alcohols and phenols, although the reactions of 3 are faster than those of 2; e.g., t 1/2 = 25 min and 28 hr for the uncatalyzed reaction: CEP-OR (2) + ROH $\longrightarrow$ $(RO)_2P(O)OAcn$ (6), when R = CH_3 and c-C_5H_9, respectively (25°, 0.2 M $CDCl_3$). Imidazole is also an effective catalyst for the latter reaction (too fast to measure for R = CH_3; t 1/2 = 15 min for R = c-C_5H_9). Phenol fails to react with CEP-OR unless a base (e.g., triethylamine) is present, in which case the product is $(C_6H_5O)(RO)P(O)OAcn$.

Several factors must be considered in an interpretation of these differences: (i) the relative electrophilicities of the phosphorus atoms in 1 and 3, the nucleophilicity of the reagent, e.g., ROH or $C_6H_5O^-$, and the relative energies of the possible intermediates involved[10] (and of the corresponding transition states leading to those intermediates); and (ii) the relative energies of reactants vs the possible products, i.e., 1 vs 2 or $(RO)(C_3H_3N_2)P(O)OAcn$ (7), and 3 vs 4 or 2, as well as differences associated with the leaving groups, imidazole vs pyrrole[11-13]. A unifying hypothesis to explain the differences in behavior between CEP-IM (1) and CEP-PY (3) assumes that pyrrole is "apicophobic" relative to imidazole, when these heterocycles are bonded to P(5) (Scheme 2). The term apicophobic describes the reluctance of the N-pyrrolyl ligand to move from the equatorial to the apical skeletal position in a TBP[1] oxyphosphorane. This reluctance may reflect a relatively stronger tendency for p-d π-bonding between equatorial N-pyrrolyl and P(5), than between equatorial N-imidazolyl and P(5)[14]. There seems to be more back-donation of electrons to P(5) from the equatorial than from the apical positions, and the converse term "apicophilic" has been applied[14] to certain ligands, e.g.,

fluorine, which tend to become apical presumably because they are able to support the higher degree of electronic charge that is associated with a ligand in that position, relative to the equatorial position[14,15].

The more electrophilic (more energetic) CEP-IM (1) reacts faster to give intermediate 8, which undergoes permutational isomerization to 9 and decomposition to 2, faster than it undergoes ring-opening to 7. The less electrophilic CEP-PY (3) reacts slower to give intermediate 10, which undergoes ring-opening to 4 before it has an opportunity to isomerize to 11. In the CEP-IM reaction, the observed product 2 has lower energy than the reactant 1, and that of alternate product 7, which would result from ring-opening of 8. It is unlikely that the failure of CEP-PY (3) to undergo displacement with ring-retention to give 2 is due to thermodynamic considerations, since the cyclic product 2 probably has lower (or comparable) energy than the cyclic reactant 3.

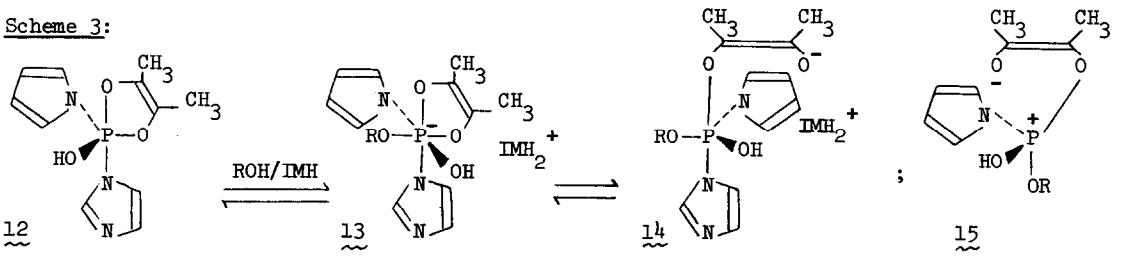
Scheme 2:



An excess of alcohol does not displace pyrrole from the acyclic phosphoramide, 4a,b. This observation is in agreement with the postulated apicophobicity of the N-pyrrolyl ligand, if pyrrole displacement requires its apical placement in a TBP[1] P(5) intermediate[10].

The fact that diastereomers 4a and 4b are obtained in equal amounts in the imidazole-catalyzed reaction, but in unequal amounts in the uncatalyzed reaction, while the addition of imidazole to the products of the uncatalyzed reaction does not affect the proportion of diastereomers, is consistent with the hypothesis that the keto-tautomers, 4a and 4b, are generated via different mechanisms in the presence and in the absence of imidazole. One possible interpretation is that proton-transfer in the P(5) intermediate of the catalyzed reaction, 14, permits the formation of isomers 4a and 4b in their thermodynamically controlled amounts, while the proton-transfer following (or accompanying) the decomposition of the P(5) intermediate of the uncatalyzed reaction, 11 (cf. 15), is too fast to allow for near-equal formation of 4a and 4b.

Scheme 3:



Pyrrole does not react with CEP-IM, 1, or CEP-PY, 3, at 35° in 1 M $CDCl_3$, at least within 4 days, which may simply reflect the poor nucleophilicity of this heterocycle, since the reaction CEP-IM (1) + C_4H_4NH ⇸ CEP-PY (3) + $C_3H_3N_2H$ is thermodynamically allowed because 3 has

a lower energy content than 1. Even a relatively good nucleophile, imidazole, fails to open the CEP-ring of 1 and 3, and a logical explanation is that the acyclic phosphorodiamides 16 and 17, which would be the products of these reactions, are thermodynamically disfavored relative to the cyclic phosphoromonoamides 1 and 3, respectively:

$$\text{CEP-IM } (1) + C_3H_3N_2H \not\longrightarrow (C_3H_3N_2)_2P(O)OAcn \ (16)$$

$$\text{CEP-PY } (3) + C_3H_3N_2H \not\longrightarrow (C_4H_4N)(C_3N_3H_2)P(O)OAcn \ (17)$$

The significant point is that there is no evidence of any exchange in the reaction of imidazole with CEP-PY (3), which is consistent with the conclusion that 3 has lower energy content than CEP-IM (1), or that the pyrrole ligand is apicophobic, or both:

$$\text{CEP-PY } (3) + C_3H_3N_2H \not\longrightarrow \text{CEP-IM } (1) + C_4H_4NH$$

CEP-PY (3) cannot be made from pyrrole and the pyrophosphate, CEPOCEP[2,3] (18), even in the presence of diisopropylethylamine (B). This confirms the low nucleophilicity of the heterocycle since CEP-IM (1) is readily made from imidazole and 18, in spite of the higher energy content of 1 vs 3. Part of the driving force for this synthesis of 1 is provided by salt formation:

$$\text{CEPOCEP } (18) + C_4H_4NH \ (B) \not\longrightarrow \text{CEP-PY } (3) + \text{CEPOH } (B)$$

$$\text{CEPOCEP } (18) + 2C_3H_3NH \longrightarrow \text{CEP-IM } (1) + CEPO^-C_3H_3N_2H_2^+$$

Acknowledgment. This work was supported by Grant GM 20672 from the National Institute of Health, and by Grant CHE76-16785 from the National Science Foundation.

REFERENCES AND NOTES

1. CEP = 1,2-dimethylethenylenedioxyphosphoryl. P(4), P(5) and P(6) = four-, five-, and six-coordinate phosphorus. Acn = 1-methylacetonyl, $CH_3COCH(CH_3)$-. TBP = trigonal bipyramid(al).
2. F. Ramirez, J.F. Marecek and H. Okazaki, J. Am. Chem. Soc., 98, 5310 (1976).
3. F. Ramirez, H. Okazaki, J.F. Marecek and H. Tsuboi, Synthesis, 819 (1976).
4. I.P. Gozman, Izv. Akad. Nauk., SSSR, 2362 (1968).
5. L.A. Carpino and D.E. Barr, J. Org. Chem., 31, 764 (1966).
6. The new compounds gave satisfactory elemental analyses.
7. $\delta^{31}P$ = -6.0 ppm for CEP-IM (1); Ref. 2.
8. The figures are the times at which [Reactant] = [Product], as given by ^1H nmr spectrometry. Results confirmed by ^{31}P nmr spectrometry at 40.5 M Hz.
9. A subsequent, much slower reaction is: $\text{CEP-O}C_6H_5 + C_6H_5O^-C_3H_3N_2H_2^+ \longrightarrow (C_6H_5O)_2P(O)OAcn + C_3H_3N_2H$.
10. "Organophosphorus Stereochemistry", I, II, W.E. McEwen and K.D. Berlin, Ed., Dowden, Hutchinson and Ross, Stroudsburg, Pa., 1975.
11. Although pyrrole is an even weaker acid than imidazole (pK's for $\rangle NH \rightarrow \rangle N^- + H^+$ are 17.51 and 14.17, respectively; Ref. 12), this difference does not correlate well with rate of displacement at P(4) in these systems, since CEP-IM (1) is more reactive than $\text{CEPO-}C_6H_4.NO_2$-p although imidazole is a much weaker acid than p-nitrophenol (pK = 7.15). For the reaction: CEP-OAr + ROH $\longrightarrow$ CEP-OR + ArOH, see Ref. 13.
12. G. Yagil, Tetrahedron, 23, 2855 (1967).
13. F. Ramirez, J.F. Marecek, H. Tsuboi and H. Okazaki, J. Org. Chem., 42, 771 (1977).
14. (a) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E.A. Tsolis and I. Ugi, Angew. Chem. Int. Ed., Engl., 10, 687 (1971); cf. p. 694; (b) F. Ramirez and I. Ugi, Bull. Soc. Chim. France, 453 (1974).
15. See also: (a) S. Trippett, Phosphorus and Sulfur, 1, 89 (1976); (b) K.E. DeBruin and D.M. Johnson, J.C.S. Chem. Comm., 753 (1975); (c) J.A. Boudreau, C. Brown and R.F. Hudson, J.C.S. Chem. Comm., 679 (1975).