yields an active phosphorylating agent and that this agent can be identified as monomeric methyl metaphosphate.[8] The ^{31}P NMR spectrum of the crude reaction mixture in methanol–CD_3CN was observed, and the methyl ester of the diansylphenyl phosphate that resulted from rearrangement was identified by addition of synthetic material;[10] it was formed in 45% yield. In addition to the signals from the phenol phosphate, signals from polyphosphates ($\delta \approx 12$) and from dimethyl phosphate (δ −6.94) were observed.[11] The product was then isolated as the lithium salt (V), and its ^1H NMR spectrum was compared with that of synthetic material. The identifications were unambiguous; see Figure 1.

4,4-Dianisylcyclohexadienone was prepared by a modification of the method for the corresponding diphenyl compound;[13] analyses for 4,4-dianisylcyclohexadienone, 3,4-dianisylphenol, and lithium methyl 3,4-dianisylphenyl phosphate for carbon, hydrogen, phosphorus (where appropriate) and (in some cases) oxygen all fell within acceptable limits. Infrared and NMR spectra correspond to those expected. The ^{31}P signals were solvent-sensitive; in 1:5 CH_3OH/D_2O, the signal from lithium methyl dianisylphenyl phosphate occurred at δ +3.4 relative to 85% phosphoric acid as standard.

Although it was inherently unlikely that the reaction we observed in the presence of a large excess of the strongly basic amine IV consisted in reality of acid-catalyzed rearrangement to dianisylphenol, followed by phosphorylation of the phenol by monomeric methyl metaphosphate, two types of control experiments were conducted. First, a mixture of compound III plus base IV was decomposed in chloroform for 24 h. Then 4,4-dianisylcyclohexadienone was added and the solution heated for an additional 12 h at 72 °C. The reaction mixture was then analyzed for phenol by a coupling reaction with *p*-nitrophenyldiazonium chloride. Prior experiments had demonstrated that this coupling, in a methanol–diisopropylamine solution, produced a dye with maximum wavelength at 370 nm, with intensity proportional to the phenol concentration, down to the levels of 0.3 μmol. A small background from decomposition of the diazonium salt and/or color from the cyclohexadienone set the lower limit of usefulness of the assay. In the control experiment, cited above, the color obtained was approximately equal to that of the blank, indicating that no phenol at all had been formed. Even assuming that the color was due to the presence of phenol, the phenol could then have accounted for only 15% of the lithium methyl dianisylphenyl phosphate produced in the rearrangement.

In a second type of control experiment, an amount of phenol equal to half the yield of product was added to the cyclohexadienone prior to generation of product V from the generating system, III plus IV. Note that, although the phenol was added at a concentration comparable to that of product formed in the absence of added phenol, the concentration was small (~4%) compared to that of the dienone. The yield of lithium methyl dianisylphenyl phosphate was not appreciably increased by the addition (<5% increase). These two control experiments exclude the possibility that the reaction proceeds by way of a prior rearrangement of the dienone and leaves little alternative to reaction through the intermediate, I.

Similar chemistry has been carried out with 4,4-diphenylcyclohexadienone, which yielded lithium methyl 3,4-diphenylphenyl phosphate, albeit in only 3.5% yield.[14] No rearrangement has yet been observed with monomeric metaphosphate ion, instead of methyl metaphosphate. Presumably, the latter, which is much more electrophilic, induces more positive charge in the ring and so better promotes rearrangement.

(7) Conant, J. B.; Cook, A. A. *J. Am. Chem. Soc.* **1920**, *42*, 830. Conant, J. B.; Pollack, S. M. *J. Am. Chem. Soc.* **1921**, *43*, 1665. Conant, J. B.; Coyne, B. B. *J. Am. Chem. Soc.* **1922**, *44*, 2530. Conant, J. B.; Jackson, E. L. *J. Am. Chem. Soc.* **1924**, *46*, 1003. Maynard, J. A.; Swan, J. M. *Proc. Chem. Soc.* **1963**, 61. Maynard, J. A.; Swan, J. M. *Aust. J. Chem.* **1963**, *16*, 596.

(8) The question of whether metaphosphates are ever entirely free, or whether they are transferred in all cases (as with protons) from one nucleophilic site to another, is still under debate. Recently, Jencks[9] and Williams[9] have presented evidence that, in phosphorylation by *N*-pyridinium and *N*-isoquinolinium phosphonates, free PO_3^- is not formed.

(9) M. T. Skoog and W. P. Jencks, private communication; N. Bourne and A. Williams, private communication.

(10) The phenol, obtained by acid-catalyzed rearrangement of the dienone, was phosphorylated with dimethyl phosphorochloridate and the product selectively demethylated by reaction with lithium bromide.

(11) Polyphosphates formed from metaphosphates always appear as mixtures,[12] with the details of the NMR signals varying from case to case.

(12) VanWazer, J. R.; Callis, C. F.; Shoolery, J. N.; Jones, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 5715. Clapp, C.; Westheimer, F. H. *Ibid.* **1974**, *96*, 6710.

(13) Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1962**, *84*, 4527.

(14) The higher yield for the anisyl derivative is consistent with the 500-fold greater migration aptitude of anisyl relative to phenyl groups in the pinacol rearrangement.[15]

(15) Bachmann, W. E.; Ferguson, J. W. *J. Am. Chem. Soc.* **1934**, *56*, 2081.

Intramolecular General Base–Acid Catalysis in Transaminations Catalyzed by Pyridoxamine Enzyme Analogues

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Pyridoxamine phosphate (**1**) and pyridoxal phosphate (**2**) are coenzymes for enzymatic transaminations (Scheme I).[2,3] The enzyme has a catalytic amino group[4] which removes the *pro-S* hydrogen from the 4′-methylene of the ketimine **4**. The resulting ammonium cation reprotonates intermediate **5** on the *si* face, generating chiral **6**. The L amino acid is then released. We describe pyridoxamine enzyme models that imitate this base–acid catalytic sequence.

Catalysts **9–16** (see Chart I) were synthesized from 5-(bromomethyl)pyridoxamine (**8**)[3] with the appropriate nucleophiles and isolated as hydrobromides.[5] The reactions of **9–16** with pyruvic acid in methanol solution were followed in a fashion[6] similar to that described by Martell.[7]

(1) NIH Postdoctoral Fellow, 1981–1983.

(2) Cf.: Bruice, T. C.; Benkovic, S. "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1966; Vol. 2, Chapter 8. Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman: San Francisco, CA, 1979; Chapter 24.

(3) Breslow, R.; Hammond, M.; Lauer, M. *J. Am. Chem. Soc.* **1980**, *102*, 421–422 (for enzyme model **3**).

(4) Morino, Y.; Tanase, S. *J. Biol. Chem.* **1978**, *253*, 252–256.

(5) Structures of all new compounds were consistent with ^1HMR and CI MS data.

(6) Methanol solutions 0.16 mM in catalyst, 0.16 mM in zinc acetate, and 1.6 mM in pyruvic acid or sodium pyruvate were brought to the appropriate "pH" (read with a glass electrode calibrated against *aqueous* pH 7.00 buffer), with 10 mM NaOH in methanol at 30.1 ± 0.1 °C, and scanned repetitively from 460 to 220 nm. At "pH" 5.00 the pyridoxamine peak at 291 nm disappeared in less than 5 min, with simultaneous appearance of a new peak at 324 nm, which we assign to the zinc complex of the ketimine (e.g., **17**). In the slow step this species was quantitatively converted to the zinc chelate of the aldimine (e.g., **19**), with a UV maximum at 383 nm. Clean isosbestic points were observed at 288 and 342 nm in all kinetic runs. At pH 4.00 the ketimine **17** was in rapid equilibrium with a second species with λ_{max} 290 nm, which we believe is the O-protonated phenol related to **17**. Rates of the conversion of ketimine (e.g., **17**) to aldimine (e.g., **19**) were followed at 383 nm. Good first-order plots were linear from 10% to 98% completion, with repeated runs in agreement within 10%. The observed first-order rate constants for compounds **9–16** at pH 4.00 appear in Table I. The reaction of **12** actually showed an optimum[8] near pH 8, but the analogue **9** without a side-chain catalytic group showed an even faster rate increase with increasing pH up to pH 8, so the catalytic rate advantage of **12** was highest at pH 4.00. Above pH 8, formation of the ketimine by dehydration of the carbinolamine becomes rate limiting.

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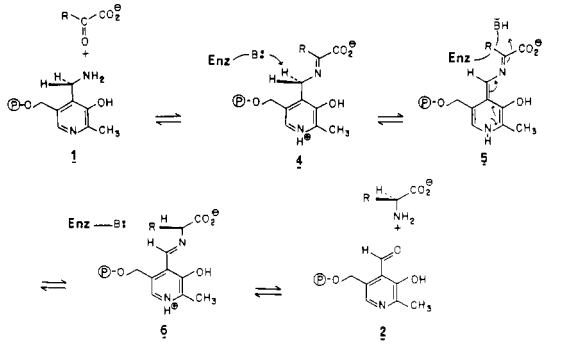
Scheme I



Scheme II

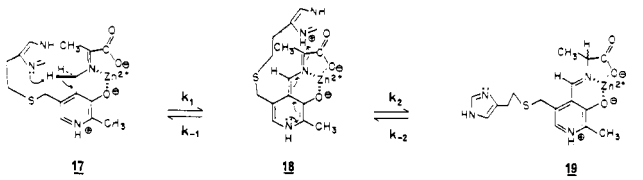


Table I. Rates of Conversion of Ketimines (e.g., **17**) to Aldimines (e.g., **19**) at pH 4.00[a] in Methanol (30.0 °C)

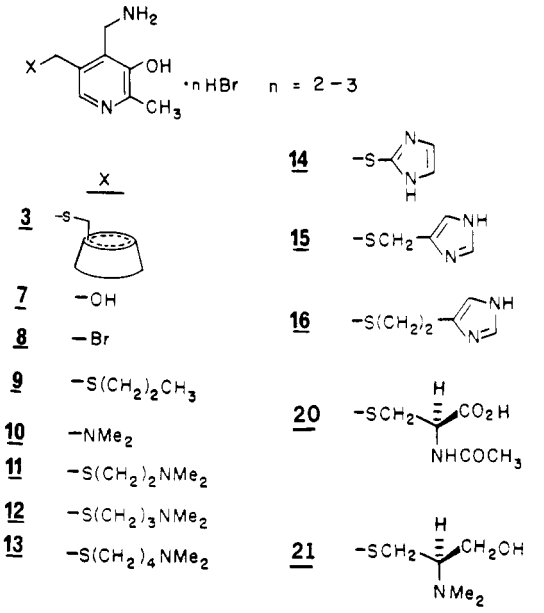
compd	side chain	k_{obsd}, s^{-1} [b]	rel rate
9	SPr	8.7×10^{-6}	1.0
7	OH	1.2×10^{-5}	1.4
10	NMe_2	1.3×10^{-4}	15.0
11	$S(CH_2)_2NMe_2$	2.3×10^{-4}	26.0
12	$S(CH_2)_3NMe_2$	3.3×10^{-4}	38.0
13	$S(CH_2)_4NMe_2$	1.1×10^{-4}	13.0
14	S(Im)	5.4×10^{-5}	6.0
15	SCH_2Im	1.1×10^{-4}	13.0
16	SCH_2CH_2Im	6.8×10^{-4}	78.0
20	*N*-acetylcysteine	9.6×10^{-5}	11.0
21	*N,N*-dimethylcysteinol	2.3×10^{-4}	26.0[c]

[a] "pH" as read with a glass electrode. The pHs were unchanged at the end of the reaction. [b] Standard deviation within each run less than 1%; duplicate runs usually within 1%, with a few within 10%. [c] With α-oxovaleric acid as substrate, which is ca. 20% slower than pyruvic acid.

As Table I shows, all the pyridoxamines with basic side chains (**10–16**) show significant accelerations relative to pyridoxamine itself (**7**) or **9**. However, the optimum catalysis occurs with side-chain groups long enough to reach the remote carbon of **18** to deliver a proton, forming **19** (Scheme II). Models show that the advantage of **12** over **11** is inexplicable if the basic group acts only in the step **17** → **18** but that the greater length of **12** is ideal for the protonation of **18** to form **19**. In **13** the entropy disadvantage of greater length is finally seen. The advantage of imidazole catalysts in **15** and **16** could reflect their rigidity or their lower basicity, and the consequent more favorable equilibrium of the principal protonated state with less favorable but required **17**.

We have also prepared the chiral derivatives **20** and **21**. With α-oxovaleric acid both catalyzed formation of the aldimine; hydrolysis formed norvaline, analyzed by dansylation[9] and chiral HPLC.[10] Compound **21** produced a 39% enantiomeric excess of D-norvaline after 2 h (65% conversion), but **20** showed negligible enantiomeric preference. The dimethylammonium group of **21** can reach the prochiral carbon of the intermediate related to **18**,

Chart I



but the carboxyl group of **20** in its normal conformation[11] cannot. This helps confirm[12] our conclusion that the best catalytic groups act as both bases and acids. With better chiral definition higher optical yields can be expected.

Acknowledgment. This work was supported by the National Institutes of Health.

(7) Matsushima, Y.; Martell, A. E. *J. Am. Chem. Soc.* **1967**, *89*, 1331–1335.
(8) The pH dependence is consistent with fastest rate at a maximum concentration of **17**. This is in equilibrium with a predominant isomer that has a protonated base group and unprotonated pyridine.
(9) Bayer, E.; Grom, E.; Kattenegger, B.; Uhmann, R. *Anal. Chem.* **1976**, *48*, 1106–1109.
(10) Lam, S.; Chow, F.; Karmen, A. *J. Chromatogr.* **1980**, *199*, 295–305.
(11) Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169–176.
(12) In an experiment with **12** and [2-^{13}C]pyruvic acid in CD_3OD, the product aldimine related to **19** had D, not H, on the C-2 carbon (by ^{13}C NMR) after 40 min. Exchange in the product should be slow, as judged by the chiral induction with **21**, so there is either fast exchange in the intermediate related to **18** (most likely) or a solvent-mediated general acid reaction.

Carbenes and the O–H Bond: 3-Cyclopentenylidene. A Novel Approach to Bis(homocyclopropenyl) Cations†

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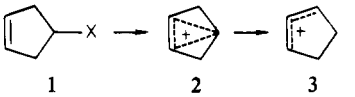
Retention of configuration in the formolysis of an appropriately labeled cyclopent-3-enyl tosylate (**1**-OTs) suggests intervention



of the bis(homocyclopropenyl) cation **2**.[1] All attempts to observe **2** under superacidic conditions were unsuccessful; ionization of **1**-OH or **1**-Cl even at −140 °C gave only the allylic ion **3**.[2] The 1,2-hydride shift leading to **3** was a minor process in the formolysis

† Dedicated to Professor William von Eggers Doering on the occasion of his 65th birthday.
(1) Lambert, J. B.; Finzel, R. B.; Belec, C. A. *J. Am. Chem. Soc.* **1980**, *102*, 3281.
(2) Olah, G. A.; Prakash, G. K. S.; Rawdah, T. N.; Whittaker, D.; Rees, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3935.

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