Association Phenomena. 3. Polyfunctional Catalysis of Acetyl Phosphate Decomposition

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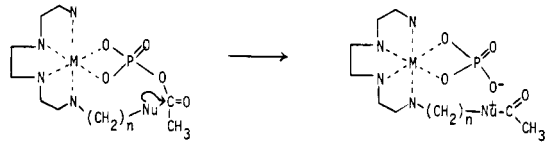
Abstract: The decomposition of acetyl phosphate via hydrolysis and/or aminolysis has been studied with respect to the effects of (a) triethylenetetramines carrying nucleophilic moieties attached to an N terminus, alone and in the presence of metal ions, and (b) oxime triamides (precursors of the N-substituted triethylenetetramines), alone and in the presence of metal ions. The tetramines, including those substituted with benzyl (**6-A**), 2-aminobenzyl (**6-B**), 2-pyridinemethyl (**6-C**), 2-*N*-benzylimidazolemethyl (**6-D**), and 2-imidazolemethyl (**6-E**) groups and the oxime triamides, including those substituted with 2-aminobenzoyl (**9**), 2-pyridinecarbonyl (**5-C**), and 2-imidazolecarbonyl (**5-E**) groups, were synthesized by a new method in which a key intermediate is *N*-(2-hydroxyiminoalkanoyl)ethylenediamine (**4**). The kinetics of acetyl phosphate decomposition have been measured under these various conditions by means of a ferric hydroxamate assay method. With the triethylenetetramines, a significant rate enhancement is observed only with the Cu^{2+} complex of **6-C** (~3-fold). With the oxime triamides, Ni^{2+} has little or no effect, Cu^{2+} with **5-C** accelerates the decomposition as much as 17-fold, and Zn^{2+} with **5-B, 5-C,** and **5-E** decreases the apparent rate of decomposition 5–6-fold. The apparent decrease in rate with Zn^{2+}, however, is the result of a rapid intramolecular transfer of the acetyl group from acetyl phosphate to the oxime group of **9, 5-C,** or **5-E** followed by a much slower hydrolysis of the resulting oxime acetate. Support for this conclusion is provided by (a) isolation of a large amount of zinc phosphate after a short reaction time, (b) determination that the rate of hydrolysis of an independently prepared oxime acetate is comparable with the observed rate of decomposition of acetyl phosphate in the presence of Zn^{2+} and **9, 5-C,** and **5-E,** and (c) failure of an *O*-methyl oxime analogue to show a comparable effect. It is postulated that (a) the rate enhancements, involving intramolecular acetyl transfer to a nitrogen nucleophile (i.e., aminophenyl, pyridyl, or imidazolyl group), may be the result of the formation of mixed chelates in which the phosphate is bound in a four-center structure (requiring a dianionic phosphate) and (b) the apparent rate reductions, involving intramolecular acetyl transfer to an oxygen nucleophile (i.e., oxime group), may be the result of the formation of mixed chelates in which the phosphate is bound in a six-center structure (involving the carbonyl oxygen and requiring only a monoanionic phosphate).

The previous paper in this series[1] describes the effect of triethylenetetramine (trien) complexes of various metals on the rate of decomposition of acetyl phosphate. The present paper extends that work and describes (a) the preparation of several oxime triamides (**5**) and triens (**6**) substituted on a terminal nitrogen with a nucleophilic moiety and (b) the testing of these compounds, alone and in the presence of metal ions, for their effect on the rates of decomposition of acetyl phosphate.

The present work is based on the postulates that (a) mixed chelates comprising triens, acetyl phosphate, and metals, represented by **1,** can exist, (b) nucleophilic moieties separated



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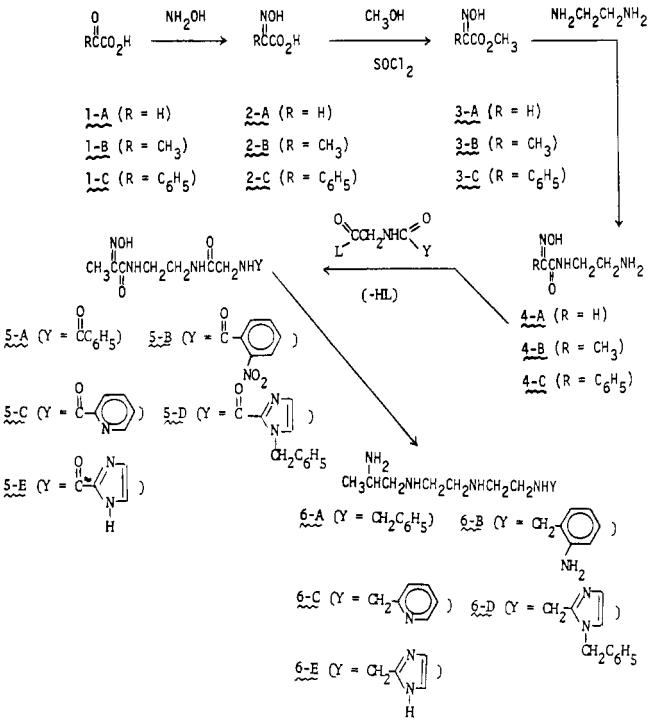
from the terminal nitrogen of trien by one, two, or three methylene groups afford the possibility of intramolecular transfer of the acetyl group from phosphate to nucleophile, and (c) the nucleophilic moieties pyridyl and imidazolyl give *N*-acetylpyridyl and *N*-acetylimidazolyl compounds which should undergo rapid hydrolysis and lead to an overall catalysis of the decomposition of acetyl phosphate via hydrolysis. The results of the work described in the previous paper[1] provide some support for the validity of the first postulate; inspection of space-filling molecular models provides the basis for the second; literature reports of the catalytic action of imidazole and other amines on acetyl phosphate decomposition provide support for the validity of the third.[2]

Synthesis of triens Substituted on a Terminal Nitrogen. Attempts to employ trien as the starting compound and to introduce selectively the appropriate moiety on one of the terminal nitrogens were unsuccessful. Therefore, an alternative approach was adopted in which ethylenediamine provides the "internal" nitrogens of the tetramine backbone and the other two nitrogens, along with the terminal substituent, are introduced sequentially as depicted in Scheme I.

Scheme I. General Scheme for the Synthesis of triens Substituted on a Terminal Nitrogen



The key to the success of this scheme was the preparation of the monosubstituted ethylenediamines, **4,** which permitted the subsequent introduction of a different acyl moiety on the

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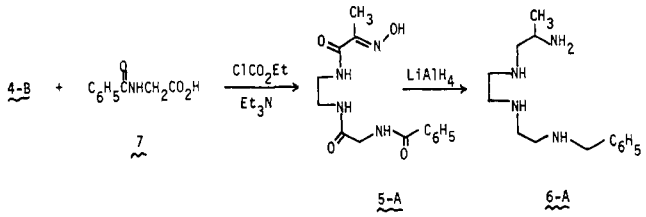
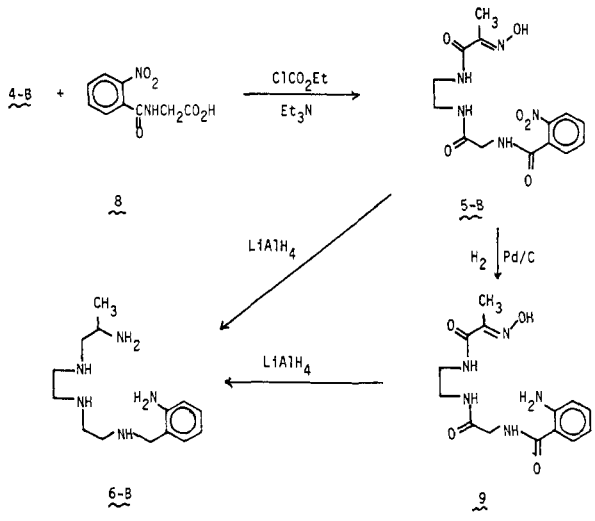
Scheme II. Synthesis of 1-Phenyl-10-methyl-2,5,8,11-tetraazaundecane (6-A)



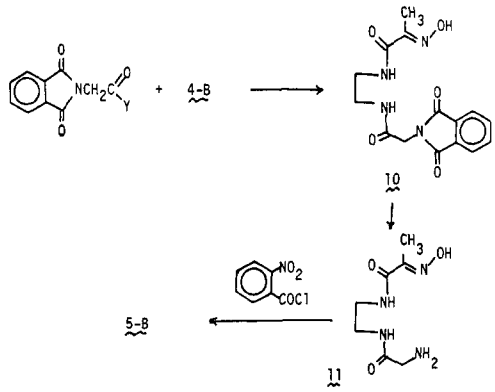
Scheme III. Synthesis of 1-(*o*-Aminophenyl)-10-methyl-2,5,8,11-tetraazaundecane (6-B)



other amino nitrogen and allowed the preparation of the variously substituted oxime triamides, **5**; reduction of the carbonyl functions of **5** yielded the corresponding polyamines, **6**. In the majority of synthetic sequences compound **4-B** was used, prepared by the reaction of the methyl ester of pyruvic acid oxime (**3-B**) with ethylenediamine. The product, obtained in 60–90% yield, proved to be almost completely free of diacyl contaminant, this fortunate circumstance probably being due to the moderate reactivity of **3-B** as an acylating agent and, possibly, the stability of **4-B**.[3] The sensitivity of the reaction in this respect was demonstrated by the relative rates of formation of compounds **4**, which are in the order **4-A** > **4-B** > **4-C**, and the amount of diacyl contaminant, which decreases in the order **4-A** > **4-B** > **4-C**.

1-Phenyl-10-methyl-2,5,8,11-tetraazaundecane (6-A). Of the numerous methods available for the condensation of amines with carboxylic acids,[4] the one found to be most convenient for the present purpose was the mixed anhydride procedure using ethyl chloroformate and triethylamine. By this means hippuric acid (**7**) was condensed with **4-B** to give **5-A** in 79% yield. Reduction of **5-A** with lithium aluminum hydride proceeded very slowly, but after 2 days in refluxing tetrahydrofuran produced 50% tetramine **6-A** (Scheme II).

(1-(*o*-Aminophenyl)-10-methyl-2,5,8,11-tetraazaundecane (6-B). *N*-(*o*-Nitrobenzoyl)aminoacetic acid (**8**), prepared by the method of Hoffmann and Jagnicinski,[5] was condensed with **4-B** by means of the ethyl chloroformate–triethylamine process to yield **5-B.** Because of the tendency for lithium aluminum hydride to reduce aromatic compounds to azo compounds,[6] the nitro group of **5-B** was catalytically reduced to an amino group to give **9** which was then treated with lithium aluminum hydride to yield **6-B.** It was subsequently discovered, however, that **5-B** can be directly reduced to **6-B** with lithium aluminum hydride without the formation of any detectable amount of azo compound. In view of the low yield of **8**, the starting material for the synthesis shown in Scheme III, an alternative synthesis was developed involving the condensation of *N*-phthaloylglycine with **4-B** to yield **10** followed by hydrazinolysis to **11** and treatment with *o*-nitrobenzoyl chloride to yield **5-B.**



1-(2-Pyridyl)-10-methyl-2,5,8,11-tetraazaundecane (6-C). *N*-(2-Pyridinecarbonyl)aminoacetic acid (**12-A**), prepared from picolinic acid and glycine, was condensed with **4-B** by means of the ethyl chloroformate–trimethylamine method or via its cyanomethyl ester **12-B** to yield **5-C.** Direct reduction of **5-C** to **6-C** proved to be unexpectedly difficult, however, and a more circuitous route had to be employed. Although lithium aluminum hydride does not ususually reduce pyridine rings under mild conditions,[6] the strenuous conditions required for the reduction of the oxime triamides caused the complete disappearance of the pyridyl moiety in the product. It is postulated that this is the result of reduction first to a dihydropyridine[7] followed by reduction of the α,β-unsaturated double bond to give a tetrahydropyridine[8] which either polymerizes or trimerizes.[9] Similar difficulties in a related case were circumvented by the use of diborane.[10] However, for diborane to reduce an oxime to an amine it is necessary to first convert the oxime to its *O*-acyl or *O*-alkyl derivative.[11] Treatment of **5-C** with acetyl chloride resulted in acetylation of only the pyridyl nitrogen. In anticipation of a similar selectivity with methylating agents, the *O*-methyl compound **15** was prepared by starting with **13**, the *O*-methyl analogue of **3**, condensing it with ethylenediamine to yield **14**, the *O*-methyl analogue of **4-B**, and treating **14** with **12-A** to yield **15**. (Scheme IV). It was subsequently realized, however, that **5-C** can be directly converted to **15** simply by using dimethyl sulfate in methanolic

Scheme IV. Synthesis of 1-(2-Pyridyl)-10-methyl-2,5,8,11-tetraazaundecane (6-C)

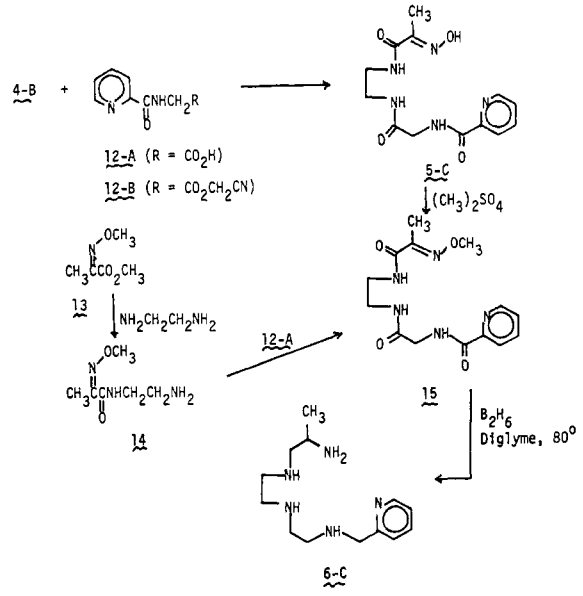
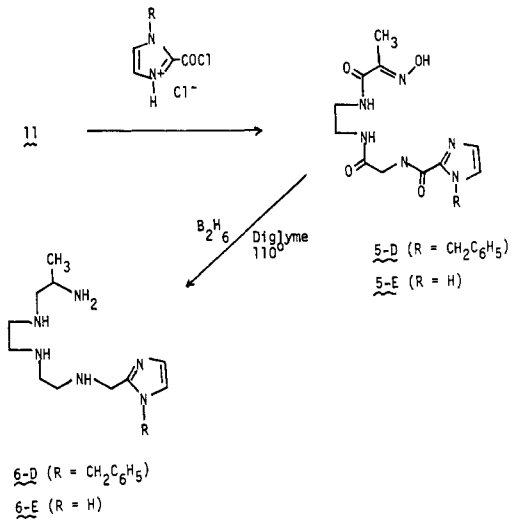


Table I. Rates (k_{obsd}, 10^{-2} min^{-1}) of Decomposition of 0.005 M Acetyl Phosphate in the Presence and Absence of Metal Ions, trien, and the Substituted triens **6A–E**[a]

		Tetramines, 0.01 M					
Metal, 0.01 M	No tetramine	trien	**6-A**	**6-B**	**6-C**	**6-D**	**6-E**
None	1.70 ± 0.04	2.51 ± 0.04	1.84 ± 0.04	1.71 ± 0.03	1.84 ± 0.04	1.77 ± 0.03	2.01 ± 0.04
Mn^{2+}	2.4 ± 0.05	2.83 ± 0.05	1.93 ± 0.04		2.42 ± 0.04	2.40 ± 0.04	3.60 ± 0.07
Co^{2+}	2.4 ± 0.05	3.48 ± 0.07	4.58 ± 0.09	13.2 ± 0.4	2.45 ± 0.04	1.86 ± 0.04	2.30 ± 0.04
Zn^{2+}	2.13 ± 0.04	2.44 ± 0.04	1.82 ± 0.04	1.94 ± 0.04	2.16 ± 0.04	2.13 ± 0.04	2.70 ± 0.05
Ni^{2+}	3.86 ± 0.08	2.34 ± 0.04	2.42 ± 0.04	2.31 ± 0.04	2.30 ± 0.04	2.12 ± 0.04	2.40 ± 0.04
Cu^{2+}	*b*	2.31 ± 0.04	2.11 ± 0.04	1.83 ± 0.04	5.09 ± 0.10	2.04 ± 0.04	2.04 ± 0.04

[a] Collidine–collidine nitrate buffer[16] to maintain pH at 6.5, temperature 50 °C, ionic strength 0.6. [b] In the absence of a trien Cu^{2+} forms a precipitate even in solutions as acidic as pH 5.

Scheme V. Synthesis of 1-(1-Benzyl-2-imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (**6-D**) and 1-(2-Imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (**6-E**)

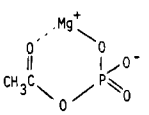


basic solution. Treatment of **15** with diborane in diglyme at 80 °C for 10 h converted it in good yield to **6-C.** Higher temperatures or longer reaction times resulted in reduction of the pyridine ring.

1-(1-Benzyl-2-imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (6-D) and 1-(2-Imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (6-E). A slight variation on Scheme I was used to synthesize **6-D** and **6-E.** Compound **11** was condensed with 1-benzyl-2-imidazolylcarbonyl chloride hydrochloride[12] to give **5-D** which was reduced with diborane in diglyme to yield **6-D.** In similar fashion, 2-imidazolylcarbonyl chloride hydrochloride yielded **5-E** which was reduced to **6-E** (Scheme V). To effect the reduction of the oximino to the amino group in these compounds it was necessary to carry out the reaction at 110 °C; the imidazole ring, in contrast to the pyridine ring, is not reduced under these conditions.

Decomposition of Acetyl Phosphate in the Presence of Substituted triens 6-A–E and Metal Ions. The kinetics of the reactions in the present study were based on the rate of disappearance of acetyl phosphate as measured by its conversion to ferric hydroxamate. Of the several variations that have been described for this assay, the one reported by Koshland[14] as modified by Pechère and Capony[15] was used. Employing this assay, the rates of disappearance of acetyl phosphate from 0.005 M solutions at 50 °C, buffered at pH 6.5 with collidine–collidine nitrate, were measured (a) in the absence of any additional reagents, (b) in the presence of the substituted tetramines **6-A–E,** (c) in the presence of the metal ions Mn^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+}, and Cu^{2+}, and (d) in the presence of the substituted tetramines and the metal ions combined. The results of these studies are shown in Table I. As noted in the work described in the previous paper of this series,[1] slight rate enhancements are observed in the presence of triethylenetetramine alone, metal ions alone, and both of these entities combined; arguments similar to those already adduced[1] serve to explain these results. Of interest in the present context is the effect that the N-terminal substituents of the triens **6-A–E** have on the rate of acetyl phosphate decomposition. In the absence of metal ions, the N-substituted triens all are poorer catalysts than trien itself; k_{trien} calculated from the two data points in Table I is 0.81 min^{-1}, whereas $k_{N\text{-}R\text{-}trien}$ for the N-substituted triens ranges from 0.01 min^{-1} for **6-B** to 0.31 min^{-1} for **6-E.** In the presence of metal ions the only rate enhancements of any significance occur with Co^{2+} and **6-B** and with Cu^{2+} and **6-C.** That with Co^{2+} and **6-B,** however, is uncertain because of experimental difficulties arising from the color of the complex itself and from a time-dependent background value in the ferric hydroxamate assay. Thus, although it appears that catalysis occurs, it may not be as large as the data seem to indicate.

The failure to observe the significant rate enhancements that had been anticipated is probably due to the failure of mixed chelates of structure **1** to form in sufficiently high concentrations. That the tetramine and acetyl phosphate compete for the metal ion is indicated by the sensitivity of the rate of acetyl phosphate decomposition to the ratio of tetramine and metal ion, as shown by the data in Table II. Whether mixed chelates of structure **1** do, in fact, exist remains a matter of speculation, and even the structures of simpler chelate species such as acetyl phosphate–metal complexes are a matter of controversy; to explain the catalytic effect of Mg^{2+} on acetyl phosphate hydrolysis Koshland[14] proposed the formation of a six-center chelate (**16**). Oestreich and Jones,[17] however, argue that a



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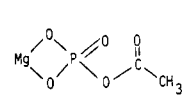

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four-center chelate (**17**) should be considered more likely, and recent work by Kluger and co-workers[18] appears to support this contention. Six-center and four-center chelates have been suggested for the complexes between acetyl phosphate and calcium and magnesium ions, respectively, to explain the different points of hydrolytic attack in the presence of these two ions.[19] Four-center mixed chelates similar to **1** have been proposed to explain the catalysis of methyl phosphate hydrolysis by the chelate of Co^{3+} and trien[20] and the catalysis of acetyl phosphate hydrolysis by pyridine-2-carboxaldoxime-Ni^{2+} complex.[21] Little firm experimental evidence for these mixed chelate structures exists, however, and attempts in the present work to obtain spectral evidence for their presence were unconvincing.

Decomposition of Acetyl Phosphate in the Presence of the Oxime Triamides 9, 5-C, 5-E, and 15 and Metal Ions. In the

Table II. Rates of Decomposition of Acetyl Phosphate in the Presence of Ni^{2+} and **6-E** as a Function of Hydrogen Ion Concentration and Ratio of Metal Ion to Tetramine[a]

[6-E], M	[Ni^{2+}], M	[$AcPO_4^{2-}$], M	pH	k_{obsd}, 10^{-2} min^{-1}
0.01	0.01	0.005	5.03	2.59 ± 0.04
0.01	0.01	0.005	6.50	2.40 ± 0.04
0.01	0.01	0.005	6.97	1.83 ± 0.04
0.01	0.01	0.005	8.20	2.19 + 0.04
None	0.01	0.005	6.5	3.86 ± 0.07
0.005	0.01	0.005	6.5	3.20 ± 0.06
0.01	0.01	0.005	6.5	2.40 ± 0.04
0.015	0.01	0.005	6.5	1.87 ± 0.04

[a] Temperature 50 °C, ionic strength 0.6.

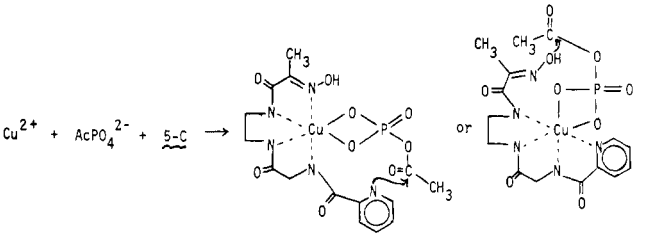
Table III. Rates (k_{obsd}, 10^{-2} min^{-1}) of Decomposition of 0.005 M Acetyl Phosphate in the Presence and Absence of Triamides **9, 5-C, 5-E,** and **15,** with and without Metal Ions[a]

		Triamides, 0.01 M			
Metal, 0.01 M	No triamide	**9**	**5-C**	**5-E**	**15**
None	1.70 ± 0.04	1.75 ± 0.03	1.72 ± 0.03	1.68 ± 0.03	1.72 ± 0.03
Zn^{2+}	2.13 ± 0.04	0.36 ± 0.01	0.21 ± 0.004	0.42 ± 0.01	3.13 ± 0.06
Ni^{2+}	3.86 ± 0.08	3.15 ± 0.06	3.11 ± 0.06	4.10 ± 0.10	2.83 ± 0.05
Cu^{2+}		3.31 ± 0.06	20.5 ± 1.7	5.95 ± 0.27[b]	18.1 ± 0.7

[a] Collidine-collidine nitrate buffer[16] to maintain pH at 6.5 (except where noted), temperature 50 °C, ionic strength 0.6. [b] Obtained at pH 5.3; at higher pH copper hydroxide precipitates.

thought that the superior chelating ability of the tetramines might prevent the formation of the mixed chelates, experiments with several of the oxime triamide precursors **5** of the polyamines **6** were carried out. That these compounds possess chelating properties is indicated by the color changes that are observed when they are added to solutions containing the various metal ions; however, they probably are weaker chelating agents than their analogues. By means of the same procedures employed for the polyamine experiments, the rate of decomposition of acetyl phosphate was measured in the presence of the oxime triamides **9, 5-C, 5-E,** and **15** first in the absence of metals ions and then in the presence of metal ions. The results are shown in Table III. In the absence of metal ions the oxime triamides **9, 5-C, 5-E,** and **15** have no catalytic effect whatsoever on the rate of decomposition of acetyl phosphate. The addition of nickel ion causes no rate change, but the addition of zinc and copper ions results in significant rate changes that are in opposite directions. The oxime triamides **9, 5-C** and **5-E** in the presence of Zn^{2+} appear to markedly diminish the rate of acetyl phosphate decomposition, whereas the oxime triamides **5-C** and **15** in the presence of Cu^{2+} accelerate it, **5-C** showing an optimum acceleration near pH 6.7 (pH 5.08, k = 10.0×10^{-2} min^{-1}; pH 6.28, k = 12.1×10^{-2} min^{-1}; pH 6.72, k = 29.5×10^{-2} min^{-1}; pH 7.50, k = 26.4×10^{-2} min^{-1}).

How best to explain the enhanced rates of acetyl phosphate decomposition in the presence of **5-C** and Cu^{2+} is uncertain. It is tempting, of course, to postulate that the mixed chelate **18** forms and that the pyridyl moiety acts as an internal nucleophile, according to the premise on which this investigation was launched. The dependence of the rate enhancement on the N-terminal moiety provides some support, **5-C** being more effective than **9** or **5-E** (unfortunately, it was not possible to test **5-A** because of its insolubility). The plausibility of this idea is diminished, however, by the low basicity (and nucleophilicity) of the pyridyl moiety in **18;** the pK_a of the pyridyl nitrogen in **5-C** is probably ~2 (pK_a of pyridine-2-carboxamide is 2.10[22]) and chelate formation should lower it further. An alternative possibility is that mixed chelate **19** forms and the oxime moiety acts as an internal nucleophile. If it acts as a nucleophile on oxygen, however, it would be expected to give rise either to an apparent reduction in rate (if intramolecular



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acetyl transfer is rapid, as is observed with Zn^{2+} as the metal ion) or to more complicated kinetics (if intramolecular acetyl transfer is slow) than are observed. Although the hydrogen ion dependence of the rate enhancement in the pH range 5–7.5 might possibly be interpreted in terms of an oxime dissociation (pK_a of 2-pyridylaldoxime methiodide is 8.00[23]), the near identity in rate enhancements with Cu^{2+} in the presence of **5-C** (=NHOH moiety) and **15** (=$NOCH_3$ moiety) seems to rule out this possibility. Thus, the mode of action of Cu^{2+} in the presence of **5-C** and **15** remains unclear and it is hoped that further work will reveal its details.

The apparent inhibition of the acetyl phosphate decomposition in the presence of the Zn^{2+} complexes of **9, 5-C,** and **5-E** is interpreted in terms of a very rapid transfer of the acetyl group from acetyl phosphate to the oxime function followed by slow hydrolysis of the oxime acetate, the rate of the latter process being the one that is measured by the ferric hydroxamate assay. The first indication of this course of events was the precipitate that forms almost immediately upon admixture of the reactants, a precipitate that proved to be zinc phosphate. Additional support is provided by (a) the failure of a comparably slow rate to be observed when **15** (containing a =$NOCH_3$ moiety) is used and (b) the preparation of an oxime acetate of **5-A** and the determination that its rate of hydrolysis alone (k = 0.317×10^{-2} min^{-1}) and in the presence of Zn^{2+} (k = 0.566×10^{-2} min^{-1}) are very similar to those for **9, 5-C,** and **5-E** in the presence of Zn^{2+}. An approximate specific rate of 1.7 min^{-1} for the initial acetyl transfer was obtained by terminating a reaction after 30 s and weighing the amount of zinc phosphate fromed. This represents an ~100-fold en-

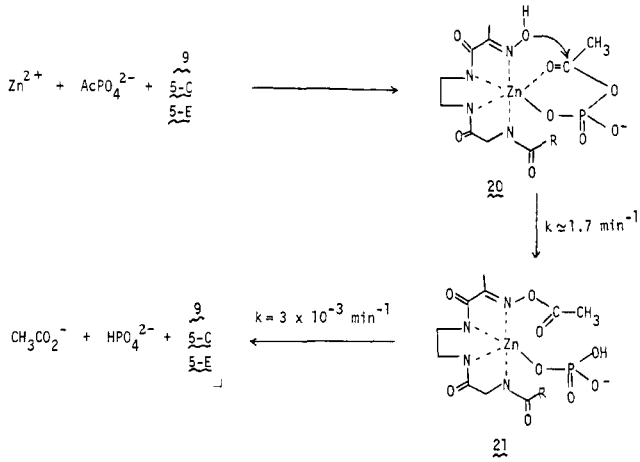
Table IV. Rates (k_{obsd}, 10^{-2} min^{-1}) of Decomposition of 0.005 M Acetyl Phosphate in the Presence and Absence of **5-C** and Zn^{2+} or Cu^{2+} at pH 6.5 and 3.5[a]

	No triamide		**5-C**	
Metal, 0.01 M	pH 6.5	pH 3.5	pH 6.5	pH 3.5
None	1.70 ± 0.03	3.87 ± 0.07	1.75 ± 0.03	3.56 ± 0.07
Zn^{2+}	2.13 ± 0.04	4.31 ± 0.09	0.21 ± 0.01	0.29 ± 0.03
Cu^{2+}			20.5 ± 0.4	1.30 ± 0.04

[a] Temperature 50 °C, ionic strength 0.6.

hancement over the rate of decomposition of acetyl phosphate by water alone and a very much larger enhancement over the rate of reaction of compounds **9**, **5-C**, and **5-E** with acetyl phosphate in the absence of Zn^{2+} (i.e., **9**, **5-C**, and **5-E** show no detectable reaction with acetyl phosphate (see Table III)).

To explain the intramolecular acetyl transfer when Zn^{2+} is the metal ion it is postulated that the six-center chelate **20**



forms, allowing the oxime to serve as an acetyl transfer moiety (to form **21**) and to decrease the overall rate of hydrolysis. Some support for the formation of **20**, which requires only a phosphate monoanion, is provided by the similarity of the rate at which the dianion of acetyl phosphate (i.e., reaction of pH 6.5) and the monoanion of acetyl phosphate (i.e., reaction at pH 3.5) undergo decomposition in the presence of the Zn^{2+} complex of **5-C** as shown in Table IV. On the other hand, the rate of decomposition of acetyl phosphate in the presence of the Cu^{2+} complex of **5-C**, for which a four-center chelate requiring the phosphate dianion might be the effective catalytic species, is significantly diminished at pH 3.5.

Results similar to those for acetyl phosphate decomposition in the presence of Zn^{2+} with **9**, **5-C**, and **5-E** have been obtained by Malmin and Breslow[21] with acetyl phosphate and pyridine-2-carboxaldoxime in the presence of Ni^{2+}. A four-center mixed chelate was proposed to explain these results.

Experimental Section[24]

***N*-(2-Hydroxyiminopropionyl)ethylenediamine (4-B).** To a solution of 132 g (1.5 mol) of pyruvic acid in 75 mL of water was added 106.5 g (1.52 mol) of hydroxylamine hydrochloride in 150 mL of water. The mixture was shaken at room temperature for 4 h, and the white precipitate was collected and washed with water to yield 139 g (91%) of **2-B** as a white powder, mp 180–182 °C (lit.[22] 180–181 °C). A solution of 103 g of this material in 450 mL of methanol was cooled in a Dry Ice–methanol bath to −5 °C and treated dropwise with 78 mL (1.1 mol) of thionyl chloride, keeping the temperature at −5 to −10 °C. The mixture was allowed to warm to 30 °C and was stirred for 2 h. The solution was filtered to remove any insoluble material, and the solvent was then removed under reduced pressure at 40 °C to give 112 g of crude product, mp 67–71 °C. Recrystallization from ethyl ether gave 93 g (80%) of **3-B** as long white needles, mp 71–73 °C (lit.[25] 69 °C). To a solution of 60 g (0.51 mol) of **3-B** in 150 mL of ether was added 31 g (0.52 mol) of ethylenediamine. The mixture was shaken at room temperature for 10 h and filtered, and the white powder washed with ether and acetonitrile to yield 67 g (91%) of crude product, mp 115–130 °C. Recrystallization from acetonitrile–ethanol (10:1) afforded 41 g (61%) of **4-B** as a white powder, mp 145–148 °C. An additional recrystallization from acetonitrile produced an analytical sample: mp 147–148.5 °C; IR (KBr) 3400 (N–H), 2900–2400 (O–H), 1670 (C=O), 1540 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 7.8 (br s, 1, CONH), 5.2 (br s, 3, OH and NH_2), 3.2 (q, 2, J = 6 Hz, $CONHCH_2$), 2.7 (t, 2, J = 6 Hz, CH_2NH_2), 1.9 ppm (s, 3, CH_3); ^{13}C NMR (D_2O) δ 169.8 (8.9%, C=N), 154.9 (13.2%, C=O), 43.5 (84%, CH_2), 42.6 (91%, CH_2), 12.1 ppm (57.6%, CH_3).

Anal. Calcd for $C_5H_{11}N_3O_2$: C, 41.40; H, 7.59; N, 28.95. Found: C, 41.21; H, 7.68; N, 28.97.

***N*,*N*′-Bis(2-hydroxyiminopropionyl)ethylenediamine.** A mixture of 11.7 g (0.1 mol) of methyl pyruvate oxime (**3-B**) and 2.5 g (0.042 mol) of ethylenediamine in 40 mL of methanol was allowed to stand at room temperature for 12 days. The crude product was recrystallized from water to give 7.3 g (76%) of white needles, mp 183–185 °C. Additional recrystallization yielded an analytical sample: mp 184.5–186 °C; IR (KBr) 3400 (N–H), 3300–2400 (O–H), 1670 and 1650 (C=O and C=N), 1540 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 2, OH), 7.9 (br s, 2, NH), 3.35 (br s, 4, CH_2), 1.9 ppm (s, 6, CH_3).

Anal. Calcd for $C_8H_{14}N_4O_4$: C, 41.70; H, 6.09; N, 24.35. Found: C, 41.59; H, 6.22; N, 24.20.

***N*-(2-Hydroxyiminoacetyl)ethylenediamine (4-A).** Methyl glyoxylate oxime (**3-A**), prepared by esterification of glyoxylic acid oxime by the procedure described above for the synthesis of **3-B** was obtained in 95% yield as white crystals, mp 53–55 °C (lit.[26] 55 °C). A mixture of 10.3 g (0.1 mol) of **3-A** and 9.0 g (0.15 mol) of ethylenediamine in 150 mL of acetonitrile was stirred vigorously at room temperature for 4 h. The precipitate was removed by filtration, washed with acetonitrile and ether, and recrystallized from acetonitrile–water (95:5) to give 9.5 g of white powder, mp 140–142 °C. An analytical sample was obtained by an additional recrystallization: mp 142–143 °C dec; IR (KBr) 3350 and 3300 (N–H), 2900–2400 (N–H and O–H), 1670 (C=O), 1560 cm^{-1} (amide II band); ^1H NMR (D_2O) δ 7.6 (s, 1, HC=N), 3.5 (t, 2, J = 6 Hz, CH_2NHCO), 3.0 ppm (t, 2, J = 6 Hz, CH_2NH_2).

Anal. Calcd for $C_4H_9N_3O_2$: C, 36.64; H, 6.92; N, 32.04. Found: C, 36.61; H, 6.80; N, 31.51.

***N*,*N*′-Bis(hydroxyiminoacetyl)ethylenediamine.** A solution of 2.06 g (0.02 mol) of methyl glyoxylate oxime (**3-A**) and 0.6 g (0.01 mol) of ethylenediamine in 20 mL of methanol was allowed to stand at room temperature for 24 h and filtered, and the crude product recrystallized from water to give 1.3 g (65%) of white needles: mp 171–173 °C dec; IR (KBr) 3350 (N–H), 3300–2700 (O–H), 1680 (C=O), 1550 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 7.3 (s, 2, HC=N), 3.25 ppm (br s, 4, CH_2).

Anal. Calcd for $C_6H_{10}N_4O_4$: C, 32.73; H, 5.49; N, 25.45. Found: C, 32.78; H, 5.39; N, 25.15.

***N*-(Phenylhydroxyiminoacetyl)ethylenediamine (4-C).** Methyl benzoylformate oxime (**3-C**), prepared by esterification of benzoylformic acid oxime by the procedure described above, was obtained as white needles in 65% yield after recrystallization from methanol, mp 145–148 °C (lit.[27] 138–139 °C). A solution of 3.6 g (0.02 mol) of **3-C** in 15 mL of ethylenediamine was refluxed for 2 h. The excess ethylenediamine was removed in vacuo at 60 °C, and the residual solid was triturated with 15 mL of acetonitrile to yield 3.2 g (77%) of **4-C** as white needles: mp 190–192 °C; IR (KBr) 3400 (N–H), 3200–2400

(N-H and O-H), 1670 (C=O), 1600 (C=N), 1540 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 8.1 (t, 1, J = 6 Hz, NHCO), 7.4 (s, 5, ArH), 4.9 (br s, 3, OH and NH_2), 3.2 (q, 2, J = 6 Hz, CH_2NHCO), 2.7 ppm (t, 2, J = 6 Hz, CH_2NH_2).

Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.69; H, 6.31; N, 20.12.

***N*-(2-Hydroxyiminopropionyl)-*N'*-(*N*-benzoylaminoacetyl)ethylenediamine (5-A).** In a three-necked round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel were placed 9.0 g (0.05 mol) of benzoylglycine (hippuric acid) and 80 mL of tetrahydrofuran. The mixture was cooled to −10 °C in a Dry Ice-methanol bath, stirred, and treated with 5.01 g (0.05 mol) of triethylamine followed by 5.04 g (0.05 mol) of ethyl chloroformate, added over a period of 5 min. The mixture was stirred for 25 min at −10 °C, and a solution of 7.25 g (0.05 mol) of *N*-(2-hydroxyiminopropionyl)-ethylenediamine (**4-B**) in 50 mL of water was added over a period of 10 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The tetrahydrofuran was removed under vacuum on a steam bath, and the aqueous residue was slowly cooled to room temperature and then in a refrigerator for 2 h. Filtration yielded slightly tan crytals which were washed with water and dried to give 11.3 g (74%) of crude product. Recrystallization from water gave **5-A** as white needles: mp 180–182 °C; IR (KBr) 3500–3000 (N-H and O-H), 1660 (C=O), 1530 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 8.7 (t, 1, J = 6 Hz, CH_2NHCO), 8.0 (m, 4, C-2 and C-6 ArH and NH), 7.6 (m, 3, C-3, C-4, and C-5 ArH), 3.95 (d, 2, J = 6 Hz, NCH_2CO), 3.3 (m, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.03; H, 5.88; N, 18.31.

1-Phenyl-10-methyl-2,5,8,11-tetraazaundecane (6-A). To 300 mL of anhydrous tetrahydrofuran in a 500-mL round-bottomed flask was added 8.0 g (0.21 mol) of lithium aluminum hydride in small portions with stirring. The mixture was cooled in an ice bath, and 9.18 g (0.03 mol) of **5-A** was added in small portions over a period of 15 min with stirring. The mixture was slowly brought to boiling, refluxed for 2 days, and then cooled in an ice bath and treated with 8 mL of water. Filtration yielded a solid which was placed in a Soxhlet thimble and extracted with the filtrate for 24 h. Evaporation of the solvent on a rotary evaporator at 60 °C yielded 3.6 g (50%) of a pale yellow oil: IR (KBr) 3400 (N-H), 2900 (C-H), 1630 and 1500 cm^{-1} (Ar); ^1H NMR (Me_2SO-d_6) δ 7.4 (s, 5, ArH), 3.8 (s, 2, NCH_2Ar) 2.7 (two s, 8, CH_2), 2.9–2.3 (m, 3, NCH and CCH_2), 1.7 (s, 5, NH), 1.0 ppm (d, 3, J = 6 Hz, CH_3).

The **tetrahydrochloride of 6-A** was obtained, after recrystallization from methanol, as a white powder, mp 228–231 °C dec.

Anal. Calcd for $C_{14}H_{30}Cl_4N_4 \cdot {}^1/_4H_2O$: C, 41.96; H, 7.62; N, 13.98. Found: C, 42.05; H, 7.36; N, 13.44.

The **tetra(hydrogen oxalate) of 6-A** was obtained, after recrystallization from water, as a white powder, mp 245–247 °C dec.

Anal. Calcd for $C_{22}H_{34}N_4O_{16}$: C, 43.27; H, 5.61; N, 9.18. Found: C, 43.23; H, 5.60; N, 9.31.

***N*-(2-Hydroxyiminopropionyl)-*N'*-[*N*-(*o*-nitrobenzoyl)aminoacetyl]ethylenediamine (5-B). A. From *N*-(*o*-Nitrobenzoyl)aminoacetic Acid (8).** To a solution of 11.2 g (0.05 mol) of **8** in 100 mL of dry tetrahydrofuran was added 5 g (0.05 mol) of triethylamine. The slurry was cooled to −5 °C, treated with 5 g (0.05 mol) of ethyl chloroformate added dropwise over a period of 5 min, and stirred for 20 min at −5 °C. A solution of 7.25 g (0.05 mol) of **4-B** in 50 mL of water was added over a period of 15 min, and the solution was then warmed to room temperature and stirred overnight. The tetrahydrofuran was removed under vacuum, and the aqueous residue was cooled in an ice bath to give a precipitate which was collected by filtration and recrystallized from boiling water to afford 10.5 g (60%) of white needles: mp 184–186 °C; IR (KBr) 3400–3000 (N-H and O-H), 1670 (C=O), 1530 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 3.85 (d, 1, J = 6 Hz, CH_2NHCO), 3.3 (br s, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{17}N_5O_6$: C, 47.96; H, 4.88; N, 19.95. Found: C, 47.99; H, 4.95; N, 20.08.

B. From *o*-Nitrobenzoyl Chloride and *N*-Aminoacetyl-*N'*-(2-hydroxyiminopropionyl)ethylenediamine (11). To a solution of 1.01 g (5 mmol) of **11** prepared as described below and 1 g of sodium bicarbonate in 20 mL of water was added dropwise 0.92 g (5 mmol) of *o*-nitrobenzoyl chloride[28] in 5 mL of acetonitrile. The mixture was stirred at room temperature for 6 h, concentrated to 15 mL on the steam bath, filtered hot, cooled to room temperature, and placed in the refrigerator overnight. Filtration yielded 0.6 g (57%) of a white solid which was recrystallized from acetonitrile to yield **5-B** as white needles, mp 184–186 °C, identical with the material prepared by method A.

***N*-Aminoacetyl-*N'*-(2-hydroxyiminopropionyl)ethylenediamine (11).** A mixture of 11 g (0.077 mol) of *N*-(2-hydroxyiminopropionyl)-ethylenediamine (**4-B**) and 10 g (0.12 mol) of sodium bicarbonate in 120 mL of water was cooled in an ice bath with stirring, and 15.6 g (0.07 mol) of *N*-phthaloylglycyl chloride[29] was added in several portions. The mixture was stirred for a day at room temperature and stored overnight in the refrigerator. Filtration yielded 15 g (65%) of a white solid, mp 175–185 °C, a small sample of which was recrystallized several times from 95% ethanol to give *N*-phthaloylglycyl-*N'*-(2-hydroxyiminopropionyl)ethylenediamine (**10**) as white needles: mp 224–225 °C; ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 8.4–8.1 (br s, 2, NH), 7.85 (s, 4, ArH), 4.2 (s, 2, NCH_2CO), 3.2 (br s, 4, CH_2), 1.85 (s, 3, CH_3). The entire crude product was mixed with 6.5 g (0.11 mol) of 85% hydrazine hydrate and 200 mL of absolute ethanol and stirred for 2 days at room temperature. The insoluble phthalic acid hydrazide was removed by filtration, and the filtrate was cooled in a freezer for 1 h. Filtration yielded 5.0 g (55%) of white needles, mp 160–163 °C, from which an anlytical sample of **11** was obtained by two recrystallizations from ethanol: mp 161–163 °C; IR (KBr) 3300 (N-H), 2800–2300 (O-H), 1650 (C=O), 1530 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 7.9 (br s, 2, NH), 3.2 (m, 4, CH_2), 3.1 (s, 2, $NHCH_2CO$), 1.85 ppm (s, 3, CH_3).

Anal. Calcd for $C_7H_{14}N_4O_3$: C, 41.58; H, 6.98; N, 27.71. Found: C, 41.56; H, 6.88; N, 27.64.

Alternatively, **11** was obtained by the condensation of 10.2 g (0.05 mol) of *N*-phthaloylglycine in 150 mL of tetrahydrofuran with 7.25 g (0.05 mol) of **4-B** in 50 mL of water in the presence of 5.01 g (0.05 mol) of triethylamine and 5.04 g (0.05 mol) of ethyl chloroformate at −10 °C. The product consisted of 9.2 g (56%) of **10** which was hydrazinolyzed in the fashion described above to yield **11.**

***N*-(2-Hydroxyiminopropionyl)-*N'*-[*N*-(*o*-aminobenzoyl)aminoacetyl]ethylenediamine (9).** A mixture of 0.9 g of 10% palladium/carbon, 8.8 g (0.025 mol) of **5-B**, and 150 mL of methanol was shaken in an atmosphere of hydrogen at 9 psi for 10 min at room temperature. The catalyst was removed by filtration and washed with methanol, and the combined filtrate was evaporated to dryness on a rotary evaporator at 40 °C to give a spongy, crude product which was then treated with 50 mL of acetonitrile. The precipitate that formed was removed by filtration and recrystallized from acetonitrile to give 6.5 g (81%) of **9** as white needles: mp 150–152 °C; IR (KBr) 3500, 3200, and 3100 (N-H and O-H), 1670 and 1640 (C=O), 1520 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 8.4 (t, 1, J = 6 Hz, CH_2NHCO), 8.2–6.3 (m, 6, ArH and NH), 3.85 (d, 2, J = 6 Hz, $NHCH_2CO$), 3.3 (br s, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.18; H, 5.94; N, 21.70.

1-*o*-Aminophenyl-10-methyl-2,5,8,11-tetraazaundecane (6-B). A. From 9. To 100 mL of anhydrous tetrahydrofuran in a 300-mL round-bottomed flask cooled in an ice bath 3 g (0.08 mol) of lithium aluminum hydride was added in small portions, followed by 3.26 g (0.01 mol) of **9** in 60 mL of tetrahydrofuran over a period of 20 min. After refluxing for 2 days, the reaction mixture was cooled in an ice bath and treated with a mixture of 3 mL of water and 3 mL of tetrahydrofuran. The mixture was stirred for 1 h and filtered, and the solid washed three times with boiling tetrahydrofuran. The combined filtrate was evaporated to dryness, and the residue was dried in a vacuum desiccator to give 1.8 g (65%) of a pale yellow, very viscous oil: IR (KBr) 3200 (N-H), 3000 (C-H), 1630 and 1490 cm^{-1} (Ar); ^1H NMR (Me_2SO-d_6) δ 7.2–6.4 (m, 4, ArH), 3.7 (s, 2, NCH_2Ar), 2.6 (s, 8, CH_2), 2.9–2.3 (m, 3, NCH and CCH_2), 2.1 (s, 7, NH), 1.0 (d, 3, J = 6 Hz, CH_3).

The **tetra(hydrogen oxalate) of 6-B** was obtained as a white solid after recrystallization from water, mp 235.5–236 °C.

Anal. Calcd for $C_{22}H_{35}N_5O_{16}$: C, 42.24; H, 5.64; N, 11.20. Found: C, 42.34; H, 5.83; N, 11.53.

B. From 5-B. A solution of 10 g (0.26 mol) of lithium aluminum hydride in 300 mL of anhydrous tetrahydrofuran was treated with 10.5 g (0.03 mol) of **5-B,** and the mixture was refluxed for 3 days. The cooled solution was treated with 15 mL of water mixed with 30 mL of tetrahydrofuran, and the solid that formed was separated by filtration, placed in a Soxhlet thimble, and extracted for 24 h with the

filtrate. Evaporation of the solvent yielded 4.2 g (53%) of a pale tan oil that had IR and NMR spectra identical with those of the material obtained by reduction of **9** and which formed a tetra(hydrogen oxalate), mp 235–236 °C, which showed no depression in melting point upon admixture with the tetra(hydrogen oxalate) described above.

***N*-(2-Hydroxyiminopropionyl)-*N'*-[N-(2-pyridinecarbonyl)aminoacetyl]ethylenediamine (5-C). A. From *N*-(2-Pyridinecarbonyl)-aminoacetic acid (12-A) and 4-B.** A solution of 18 g (0.1 mol) of **12-A**[30] and 10.1 g (0.1 mol) of triethylamine in 300 mL of anhydrous tetrahydrofuran was cooled to −10 °C and treated with 10.8 g (0.1 mol) of ethyl chloroformate followed by a solution of 16 g (0.11 mol) of **4-B** in 80 mL of water. The mixture was worked up as described above for **5-A** to yield 19 g (64%) of crude product, mp 165–168 °C, from which an anlytical sample was obtained by two recrystallizations from water, yielding **5-C** as white plates: mp 170–172 °C; IR (KBr) 3400–3000 (N–H and O–H), 1670 (C=O), 1550 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.6 (s, 1, OH), 8.9 (t, 1, J = 6 Hz, CH_2NHCO), 8.6 (d, 1, J = 5 Hz, C-6 of pyridine), 8.0 (m, 4, C-4 and C-5 of pyridine and NH), 7.6 (m, 1, C-3 of pyridine), 4.0 (d, 2, J = 6 Hz, $NHCH_2CO$), 3.3 (br s, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 51.13; H, 5.64; N, 22.95.

B. From Cyanomethyl *N*-(2-Pyridinecarbonyl)aminoacetate (12-B) and 4-B. A mixture of 4. 5 g (0.025 mol) of **12-A** and 3.8 g (0.038 mol) of triethylamine in 60 mL of ethyl acetate was heated to give a clear solution, cooled, treated with 2.9 g (0.038 mol) of chloroacetonitrile, refluxed for 3 h, and cooled for 30 min in an ice bath. The triethylamine hydrochloride was removed by filtration, the filtrate was washed with 1 N hydrochloric acid and water, then dried, and evaporated to yield 4.0 g (73%) of crude product, mp 74–77 °C. Recrystallization from ethyl acetate-hexane gave **12-B** as white plates: mp 78–80 °C; IR (KBr) 3450 (N–H), 2220 (C≡N), 1760 (ester C=O), 1680 (amide C=O), 1520 cm^{-1} (amide II band); ^1H NMR ($CDCl_3$) δ 8.7–7.4 (m, 5, pyridine and CH_2NHCO), 4.9 (s, 2, OCH_2CN), 4.5 ppm (d, 2, J = 6 Hz, $NHCH_2CO$).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 54.69; H, 4.20; N, 18.88.

A solution of 2.19 g (0.01 mol) of this material was added to a solution of 1.45 g (0.01 mol) of **4-B** in the minimum amount of methanol, and the reaction mixture was allowed to stand at room temperature for 2 days. It was then warmed, treated with 5 mL of ether, cooled for 1 h in a freezer, and filtered to give 1.2 g (40%) of white solid, mp 157–161 °C, which was recrystallized from water to give 1.0 g of **5-C**, mp 165–167 °C, and showed no depression in melting point upon admixture with the material prepared by method A.

***N*-(2-Methoxyiminopropionyl)-*N'*-[*N*-(2-pyridinecarbonyl)aminoacetyl]ethylenediamine (15). A. From *N*-(2-Methoxyiminopropionyl)-ethylenediamine (14) and 12-A.** A solution of 15 g (0.13 mol) of 2-methoxyiminopropionic acid[31] in 100 mL of methanol was cooled to −5 °C, treated with 7.0 g (0.06 mol) of thionyl chloride, and stirred at room temperature for 2 days to yield 13.8 g of a pale yellow oil. Distillation gave 13.2 g (79%) of methyl 2-methoxyiminopropionate (**13**) as a colorless oil: bp 78–80 °C (2 mm); IR (KBr) 3000 (C–H), 1700 (C=O), 1640 cm^{-1} (C=N); ^1H NMR (CCl_4) δ 4.0 (s, 3, $COCH_3$), 3.7 (s, 3, $NOCH_3$), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.71; H, 6.96; N, 10.31.

A 4.0-g (0.03 mol) sample of this material, along with 1.8 g (0.03 mol) of ethylenediamine, was dissolved in 10 mL of acetonitrile, and the solution was refluxed for 7 h to give 14 as an oil which was used without purification: IR (KBr) 3450 (N–H), 1670 (C=O), 1530 cm^{-1} (amide II band); ^1H NMR (D_2O) δ 3.95 (s, 3, OCH_3), 3.5 (t, 2, J = 6 Hz, CH_2NHCO), 2.75 (t, 2, J = 6 Hz, CH_2NH_2), 1.9 ppm (s, 3, CH_3). A solution containing 5.5 g (0.03 mol) of **12-A** in 150 mL of tetrahydrofuran was cooled to −10 °C and treated with 3.1 g (0.03 mol) of triethylamine and 3.3 g (0.03 mol) of ethyl chloroformate and then with the crude sample of **14**, prepared as described above, in 30 mL of water. The reaction mixture was stirred at room temperature for 7 h and worked up to give 4.2 g (47%) of a colorless powder, mp 163–166 °C, from which an analytical sample of **15** was obtained as fine needles after two recrystallizations from water: mp 167–169 °C; IR (KBr) 3400 and 3300 (N–H), 1670 (C=O), 1520 cm^{-1} (amide II band); ^1H NMR ($CDCl_3$) δ 8.7–7.0 (m, 7, pyridine and CH_2NHCO), 4.2 (d, 2, J = 6 Hz, $NHCH_2CO$), 3.95 (s, 3, OCH_3), 3.5 (m, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.13; H, 5.88; N, 21.58.

B. From 5-C. To a boiling solution of 6.1 g (0.02 mol) of **5-C** in 50 mL of methanol were added 10.0 g (0.25 mol) of sodium hydroxide and 34 g (0.25 mol) of dimethyl sulfate, alternately, in three portions. The mixture was refluxed for 90 min, cooled in a refrigerator, and filtered to remove inorganic salts. Evaporation of the solvent and recrystallization of the residue from water gave 5.1 g (80%) of white needles, mp 167–169 °C, having IR and NMR spectra identical with those of **15** prepared by method A and showing no depression in mp upon admixture.

1-(2-Pyridyl)-10-methyl-2,5,8,11-tetraazaundecane (6-C). A solution of 5.0 g (0.13 mol) of sodium borohydride and 3.5 g (0.011 mol) of *N*-(2-methoxyiminopropionyl)-*N'*-[*N*-(2-pyridinecarbonyl)aminoacetyl]ethylenediamine (**15**) in 100 mL of diglyme was cooled to 10 °C and treated with 25 g (0.18 mol) of boron trifluoride etherate, added dropwise over a period of 30 min. The mixture was stirred at room temperature for 30 min, heated to 80 °C over a period of 1 h, and stirred at 80 °C for 10 h. After the mixture was cooled in an ice bath, 3.5 mL of water was added followed by 20 mL of 20% sodium hydroxide, and the mixture was heated to 110 °C and stirred for 90 min. The concentrated solution that resulted was cooled, inorganic salts were removed by filtration and washed with tetrahydrofuran, and the combined filtrate and washings were concentrated to 80 mL, filtered, and evaporated to yield 2.4 g (85%) of **6-C** as a yellow oil: IR (neat) 3400 (N–H), 2900 (C–H), 1600 and 1460 cm^{-1} (Ar); ^1H NMR (Me_8SO-d_6) δ 8.4 (m, 1, C–H of pyridine), 7.8–7.0 (m 3, C-3, C-4, and C-5 of pyridine), 3.8 (s, 2, $ArCH_2$), 2.9 (s, 5, NH), 2.8–2.2 (m, 11, CH_2), 1.0 ppm (d, 3, J = Hz, CH_3).

The **tetra(hydrogen oxalate) of 6-C** was obtained as a white powder after recrystallization from water, mp 235–236 °C dec.

Anal. Calcd for $C_{21}H_{33}N_5O_{16}\cdot\frac{1}{2}H_2O$: C, 40.65; H, 5.52; N, 11.29. Found: C, 40.53; H, 5.54; N, 11.38.

***N*-(2-Hydroxyiminopropionyl)-*N'*-[*N*-(1-benzyl-2-imidazolecarbonyl)aminoacetyl]ethylenediamine (5-D).** Following a published procedure,[13] 15.8 g (0.1 mol) of 1-benzylimidazole[32] in 36 g (0.33 mol) of 37% formalin was placed in a stainless steel bomb and heated at 150 °C for 6 h to give 19.2 g (100%) of 1-benzyl-2-hydroxymethylimidazole as a viscous yellow oil. This was mixed with 400 mL of water, cooled in an ice bath, and treated with 27 g (0.17 mol) of potassium permanganate added in small portions while the temperature was kept below 20 °C. The mixture was stirred at 35 °C for 1 h and then worked up to yield 14.3 g (70%) of 1-benzyl-2-imidazolecarboxylic acid as white plates, mp 106–107 °C dec (lit.[13] 106 °C). A 13.2-g (0.06 mol) sample of this material was added to 80 mL of thionyl chloride in small portions over a period of 15 min. The solution was heated to 1 h at 80–85 °C, cooled in an ice bath for 30 min, and filtered to yield 10.0 g (65%) of 1-benzyl-2-imidazolecarbonyl chloride hydrochloride as a shiny yellow powder: mp 174–179 °C; IR (KBr) 1750 cm^{-1} (COCl). This material rapidly decomposed at room temperature (within 30 min) and had to be used immediately without further purification. A 7.8-g (0.03 mol) sample was added in small portions over a period of 15 min to a stirred solution of 6.1 g (0.03 mol) of **11** in 100 mL of pyridine. The solution was heated for 30 min on a steam bath, concentrated to 30 mL in a rotary evaporator at 80 °C, diluted with hot water to 120 mL, and cooled overnight in a refrigerator. Filtration gave 9.1 g (80%) of crude product, mp 215–218 °C, from which a pure sample of **5-D** was obtained by recrystallization from pyridine-water (1:3) as colorless, fine needles: mp 220–222 °C; IR (KBr) 3300 (N–H), 1600 (C=O), 1550 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 8.5 (t, 1, J = 6 Hz, CH_2NHCO), 8.0 (m, 2, NH), 7.5 (d, 1, J = 1 Hz, imidazole H), 7.3 (s, 5, ArH), 7.1 (d, 1, J = 1 Hz, imidazole H), 5.7 (s, 2, NCH_2Ar), 3.9 (d, 2, J = 6 Hz, NCH_2CO), 3.3 (m 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{18}H_{22}N_6O_4$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.05; H, 5.75; N, 21.57.

1-(1-Benzyl-2-imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (6-D). Using the procedure described above for the reduction of **15** to **6-C**, but carrying out the reaction at 110 instead of 80 °C, 3.9 g (0.01 mol) of **5-D** was reduced with 6.0 g (0.16 mol) of sodium borohydride and 30 g (0.21 mol) of boron trifluoride etherate in 100 mL of diglyme to yield 2.6 g (79%) of a pale yellow oil: IR (neat) 3400 (N–H), 3000 (C–H), 1600 and 1500 cm^{-1} (Ar); ^1H NMR (Me_2SO-d_6) δ 7.15 (s, 5, ArH), 6.95 (d, 1, J = 1 Hz, imidazole H), 6.7 (d, 1, J = 1 Hz, imidazole H), 5.2 (s, 2, CH_2Ar), 3.7 (s, 2, imidazole CH_2), 2.6 (s, 8, CH_2), 2.8–2.2 ppm (m, 3, NCH_2CHN).

The **tetra(hydrogen oxalate) of 6-D** was obtained as a white powder

after recrystallization from water, mp 236.5–238 °C dec.

Anal. Calcd for $C_{26}H_{38}H_6O_{16}$: C, 45.22; H, 5.55; N, 12.16. Found: C, 45.52; H, 5.68; N, 12.45.

The **pentanitrate salt of 6-D** was prepared by adding concentrated nitric acid to a stirred solution of **6-D** in acetonitrile and obtained as a white powder after recrystallization from dimethylformamide–dioxane, mp 214–216 °C dec.

Anal. Calcd for $C_{18}H_{35}N_{11}O_{15}$: C, 33.49; H, 5.47; N. 23.87. Found: C, 33.45; H, 5.48; N, 23.46.

***N*-(2-Hydroxyiminopropionyl)-*N'*-[*N*-(2-imidazolecarbonyl)aminoacetyl]ethylenediamine (5-E).** A suspension of 5.6 g (0.05 mol) of 2-imidazolecarboxylic acid[13] in 100 mL of thionyl chloride was refluxed for 6 h, and the excess thionyl chloride was removed under vacuum to leave 6.7 g (80%) of 2-imidazolecarbonyl chloride hydrochloride as a yellow powder: mp 152–155 °C; IR (KBr) 1700 cm^{-1} (COCl). This was added in small portions over a period of 15 min to a solution of 8.1 g (0.04 mol) of **11** in 80 mL of dry pyridine and worked up as described above for **5-D** to yield 5.9 g (50%) of crude product, mp 241–246 °C, from which 5.6 g of **5-E** was obtained as white needles after recrystallization from water: mp 250–252 °C; IR (kBr) 3400 (N–H), 3200–2600 (O–H), 1670 (C=O), 1550 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 11.7 (s, 1, OH), 8.5–7.8 (m, 3, NH), 7.2 (s, 2, imidazole H), 3.9 (d, 2, J = 6 Hz, NCH_2CO), 3.3 (m, 4, CH_2), 1.9 ppm (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 27.94. Found: C, 44.22; H, 5.39; N, 28.36.

1-(2-Imidazolyl)-10-methyl-2,5,8,11-tetraazaundecane (6-E). By means of the procedure described above for the reduction of **15** to **6-C**, but carrying out the reaction at 100 instead of 80 °C, 4.4 g (0.015 mol) of **5-E** was reduced with 6.0 g (0.16 mol) of sodium borohydride and 30 g (0.21 mol) of boron trifluoride etherate in 100 mL of diglyme to yield 3.1 g (84%) of a pale yellow oil: IR (neat) 3400 (N–H), 1600 and 1460 cm^{-1} (Ar); ^1H NMR (Me_2SO-d_6) δ 6.8 (s, 2, imidazole H), 4.6 (s, 6, NH) 3.7 (s, 2, imidazole CH_2), 2.8–2.2 (s superimposed on m, 11, CH_2 and CH), 1.0 ppm (d, 3, J = 6 Hz, CH_3).

The **penta(hydrogen oxalate) of 6-E** was obtained as a white powder after recrystallization from water, mp 237–239 °C dec.

Anal. Calcd for $C_{21}H_{34}N_6O_{20}$: C, 35.60; H, 5.12; N, 11.86. Found: C, 35.83; H, 4.90; N, 12.12.

The **pentatnitrate of 6-E** was obtained as a white powder after recrystallization from dimethylformamide–dioxane, mp 220–223 °C dec.

Anal. Calcd for $C_{11}H_{29}N_{11}O_{15}$: C, 23.79, H, 5.26; N, 27.74. Found: C, 23.67; H, 5.24; N, 26.80.

***N*-(2-Acetoxyiminopropionyl)-*N'*-[(*N*-benzoylaminoacetyl)]-ethylenediamine (*O*-Acetyl Derivative of 5-A).** A mixture of 3.0 g (0.01 mol) of **5-A** and 50 mL of acetyl chloride was refluxed on a steam bath for 30 min. The excess acetyl chloride was removed under vacuum, and the residue was dissolved in 10 mL of acetonitrile. After treatment with activated charcoal, the solution was heated, ethyl ether was added until the solution became cloudy, the solution was cooled, and the precipitate was separated by filtration. Recrystallization from acetonitrile gave 2.1 g (62%) of white needles: mp 107–109 °C; IR (KBr) 3400 (N–H), 1780 (ester C=O), 1660 (amide C=O), 1550 cm^{-1} (amide II band); ^1H NMR (Me_2SO-d_6) δ 8.8–7.7 (m, 5, C-2 and C-6 ArH and CH_2NHCO), 7.45 (m, 3, C-3, C-4, and C-5 ArH), 3.9 (d, 2, J = 7 Hz, NCH_2CO), 3.3 (m, 4, CH_2), 2.25 (s, 3, CH_3CO), 2.1 ppm (s, 3, CH_3C=N).

Anal. Calcd for $C_{16}H_{20}N_4O_5$: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.23; H, 5.78; N, 15.98.

Dillithium acetyl phosphate was prepared by the method of Stadtman and Lipman[33] as modified by Kurz.[34] Purification by fractional precipitation gave material of 97–99% purity which was stored at 4 °C in a desiccator to prevent decomposition.

Kinetic Measurements. A solution of buffer, catalyst, and metal ion in 30 mL of water was adjusted to an ionic strength of 0.6 (after dilution) by the addition of potassium nitrate, the solution was transferred to a 50 ml glass-stoppered volumetric flask. The flask was kept in the 50 ± 0.05 °C constant-temperature bath until thermal equilibrium was attained, the pH of the solution was adjusted by the addition of nitric acid or potassium hydroxide, and a solution containing ~0.03 g of dilithium acetyl phosphate in 0.5 mL of cold water was added with stirring. Aliquots (2 mL) were withdrawn at appropriate time intervals so that six to ten readings could be obtained during the first three half-lives of the acetyl phosphate decomposition. Each aliquot was immediately added to a test tube containing 4 mL of a 1:1:2 mixture of hydroxylamine hydrochloride (3.6 M), sodium hydroxide (3 M), and acetate buffer (0.1 M, 2:8 HOAc/NaOAc, pH 5.4). After all of the aliquots had been collected, 2 mL of 0.7 M hydrochloric acid and 4 mL of 6% ferric chloride solution were added to each test tube. The tubes were shaken on a vibrator, and the optical densities at 505 nm were read on a Beckman DU spectrometer, using distilled water in the reference cell. Reactions were usually followed to 75–99% completion, times ranging from 7 min to 17 h. Aliquots removed after 6 or more half-lives gave T_∞ values. A plot of the log of the substrate concentration vs time gave straight lines, and the first-order rate constants were calculated using a linear least-squares program[35] on a Hewlett-Packard 9100A calculator. The least-squares program also computed the standard deviation of the points from the line and the variance of the slope of the line. The estimated error for the slope (and, correspondingly, for the rate constants) was taken as twice the standard deviation and was ≤5%.

Semiquantitative Determination of the Rate of Acetyl Transfer from Acetyl Phosphate to 5-C in the Presence of Zn^{2+}. A solution containing 0.05 M collidine, 0.58 M potassium nitrate, 0.01 M zinc chloride, and 0.0125 M **5-C** was placed in the 50 °C constant-temperature bath. After the pH was adjusted to 6.4 by the addition of nitric acid, 0.08 g of dilithium acetyl phosphate dissolved in 0.5 mL of water was added. The white precipitate, which started forming immediately, was collected by filtration after 30 s, washed with a small amount of cold water, and dried at 80 °C for 2 h to give 0.068 g of zinc phosphate tetrahydrate. This accounts for 57% of the phosphate in the starting material and gives a calculated value of 1.69 min^{-1} for the specific rate for the acetyl-transfer step.

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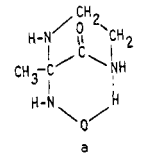

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UniMelt capillary melting point apparatus. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria, and Industrial Testing Laboratories, St. Louis, Mo. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrometer. ^{1}H NMR spectra were obtained on a Varian A-60A spectrometer, unless otherwise noted, with tetramethylsilane (δ 0 ppm), *tert*-butyl alcohol (δ 1.28 ppm), or 99% dimethyl sulfoxide-d_6 (δ 2.51 ppm) as internal standard, depending on the solvent used. ^{13}C NMR spectra were obtained on a JEOL Model FX-60 spectrometer, with tetramethylsilane as an internal standard; we are indebted to Dr. J. L. Ludwig of the Petrolite Corporation of St. Louis for these determinations. The following abbreviations are used to denote NMR spectral characteristics: s, singlet; br s, broad single; d, doublet; t, triplet; m, multiplet. Optical density measurements for the ferric hydroxamate assay were made on a Beckman DU quartz prism spectrometer at 505 nm. pH measurements were made with a Corning Model 12 Research meter using a Corning 07497 glass electrode and a Beckman 39071 calomel electrode with a Carborundum frit. The pH meter was standardized against Beckman Buffer 14268 which has a pH value of 6.83 at 50 °C. The rates of acetyl phosphate decomposition were determined in a Fisher Isotemp Bath Model 15-452 at 50 ± 0.05 °C, unless otherwise noted.

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Chemical Effects of Steric Strains. 22. Rates of Solvolysis of Dimethyl(2-norbornyl)carbinyl *p*-Nitrobenzoates and of the Quaternization of 2-Dimethylaminonorbornanes. A Critical Examination of the Significance of Steric Factors in the Chemistry of *exo*- and *endo*-Norbornyl Derivatives

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Abstract: The techniques previously used to explore the effects of steric strains in strained homomorphs were applied to *exo*- and *endo*-norbornyl derivatives in order to examine the importance of steric effects in the behavior of those derivatives. The solvolysis of dimethyl(*endo*-2-norbornyl)carbinyl *p*-nitrobenzoate proceeds 18 times faster than the exo isomer. A similar factor is observed in the solvolysis of neopentyldimethylcarbinyl *p*-nitrobenzoate which also proceeds 18 times faster than *tert*-butyl *p*-nitrobenzoate. These results are readily interpretable in terms of the relief of steric strain facilitating the solvolysis of both the endo isomer and the neopentyldimethylcarbinyl derivative (a homomorph of di-*tert*-butylmethane). Contrariwise, the rate of reaction of *endo*-dimethylaminonorbornane with methyl iodide proceeds at a rate that is 51 times slower than that of the exo isomer. Similarly, neopentyldimethylamine reacts with methyl iodide at a rate that is 150 times slower than that of *n*-butyldimethylamine. Here reactions proceeding with an increase in steric strain are resisted. Thus, a close parallelism exists between the behavior of the neopentyldimethylcarbinyl system, homomorphs of di-*tert*-butylmethane, and that of the dimethyl(*endo*-2-norbornyl)carbinyl system: steric strain facilitates solvolysis but hinders amine quaternization, as compared to less sterically demanding systems. The implication of these results to the exo:endo rate ratios observed in the solvolysis of 2-norbornyl derivatives is examined.

The high exo:endo rate ratios observed in the solvolysis of highly stabilized tertiary 2-norbornyl derivatives, such as 2-*p*-anisyl-2-norbornyl[2] (284) and 2-*p*-anisyl-2-camphenilyl[2] (44 000), cannot be attributed to σ participation.[3] Such highly stabilized cations cannot possibly form σ bridges involving the 1,6-bonding pair.[4] The sole alternative interpretation now receiving serious consideration is steric hindrance to ionization in the endo isomer.

It has long been apparent from the Goering-Schewene diagram[5] that the difference in energies of the two transition states must be far larger than the small differences in the energies of the ground states. In terms of the steric interpretation, this is accounted for by the fact that in solvolysis the endo leaving group moves from its less strained normal position into the endo cavity, increasing the steric strain and diminishing the usual solvation of the developing anion. Hence, a normal exo rate coupled with a slow endo rate arising from this large increase in the energy of the endo transition state satisfactorily accounts for the high exo:endo rate ratios observed in such stabilized tertitary 2-norbornyl derivatives.[4,6]

It has been suggested that the same steric explanation should be applicable to the high exo:endo rate ratios observed in the secondary derivatives.[4] Recently, Menger and Thanos claimed that the steric explanation is inadequate to account for the observed secondary exo:endo solvolysis rate ratios.[7] They compared the rates of NH proton exchange, nitrogen inversion, and amine quaternization of *exo*- and *endo*-2-dimethylaminonorbornanes and stated "the exo and endo compounds do not display substantial differences as would be expected if the endo dimethylamino group were subjected to unusual steric or solvation effects within the endo cavity".[7]

It appeared to us that a possible weakness in the Menger and Thanos study was the use of phenomena and reactions which have not been calibrated against other known systems with established major steric requirements. Many years ago we examined the effects of steric strains on the behavior of entire families of strained homomorphs.[8] We decided to apply the techniques used in that study to the *exo*- and *endo*-norbornyl systems and to compare the results with those realized in the corresponding study of derivatives related to a typical strained homomorph, di-*tert*-butylmethane (**1**), with established strain of ~5.4 kcal mol^{-1}.[8,9]

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