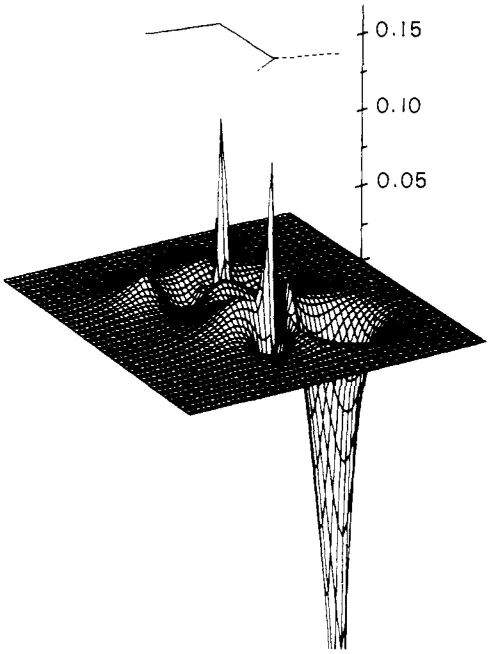

Figure 2. Electron density difference plot for deprotonation of CH_3SH; $\rho(HSCH_2^-)$-$\rho(HSCH_3)$, for H-S-C-(lone pair) plane (SS+d basis).

actly the same pattern, except that polarization at sulfur is stronger than at the C_β of ethyl anion. The pattern of these electron density difference functions suggests strongly that a SH substituent stabilizes a carbanion more than a methyl group because the SH group is more polarizable than CH_3. Arguments based on experimental pK measurements of substituted dithianes[2] have led to the same interpretation of the role of polarization; the Wolfe group[9] have independently arrived at the same conclusion from their SCF calculations.

These qualitative patterns of electron density difference functions may be compared with Mulliken atomic calculations summarized in Table II for the SS basis set. Mulliken population analyses are basis set dependent and relative values are more significant than the absolute populations.

For example, the increase in α-carbon population of only 0.107 electron for $CH_3CH_3 \rightarrow CH_3CH_2^-$ is much less than one would have anticipated for a developing carbanion. Of course, electrons have also polarized away from this carbon. The $CH_3SH \rightarrow {}^-CH_2SH$ case shows a similar pattern. The increase in C_α population is less, consistent with increased polarization, but the increases at H_α and H_β are comparable for both systems. Sulfur apparently gains electrons but the populations above do not tell us how. However, in the ethyl case the electrons gained by CH_2 as a whole are actually wholly on the hydrogens. The peculiarities of Mulliken populations allow us to see the polarization in the CH_2 group invisible in the S atom; that is, we expect the extra electron population in S to be also on outer fringes, exactly as shown in Figure 2.

We conclude that sulfur stabilizes carbanions by polarization rather than by d-orbital conjugation. We plan to explore the generalization of this result to carbanions stabilized by other second-row elements.

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(1) This study was supported in part by NSF Grant No. 29383 and by USPH, NIH Grant No. GM-12855. Some of the computer time used was subsidized by the Computer Center, University of California.
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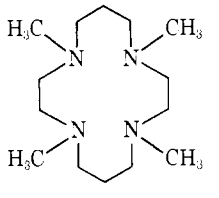
Andrew Streitwieser, Jr.,* James E. Williams, Jr.
University of California, Department of Chemistry
Berkeley, California 94720

Received September 3, 1974

Structure of a Square Pyrimidal Pentacoordinate Complex of Ni(*N*-tetramethylcyclam)$^{2+}$. A Kinetically Determined Ligand Stereochemistry

Sir:

Earlier we reported the preparations of divalent nickel, copper, and zinc complexes of *N*-tetramethylcyclam (TMC, **1**).[1] These complexes, which are prepared by combining the metal salt with the free base in aqueous solution, have chemical behavior that is quite unlike that of the secondary amine analogs such as cyclam itself. They are quite labile, and pentacoordinate species are observed both in solution and in the solid state. Nmr data obtained on $[Zn(TMC)Cl]^+$ in nitromethane solution suggested that the macrocyclic ligand is coordinated in a planar fashion with all four methyl groups on the same side of the metal–nitrogen plane. It was assumed that the nickel and copper complexes also have this stereochemistry, which has been designated the trans I form by Bosnich, *et al.*[2] Kaden has suggested, on the basis of uv-visible spectral data, that the pentacoordinate nickel(II) complexes of TMC are trigonal bipyramidal, which requires that the ligand adopt a folded conformation.[3] An alternative synthesis of $Ni(TMC)^{2+}$, shown as reaction 1, yielded a second stereoisomer.[4] This reaction should yield the thermodynamically most stable of the five possible permethylated products. An X-ray structure determination on a derivative of the product of this reaction has shown it to have the set of nitrogen configurations shown in **2**.[4] This set of nitrogen configurations, the trans III form according to Bosnich,[2] is also the thermodynamically most stable form of metal complexes of the anal-



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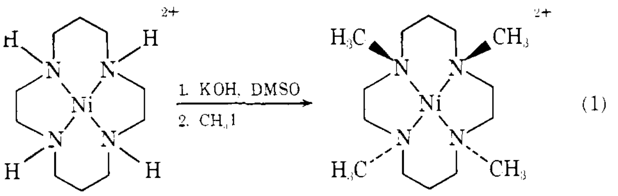

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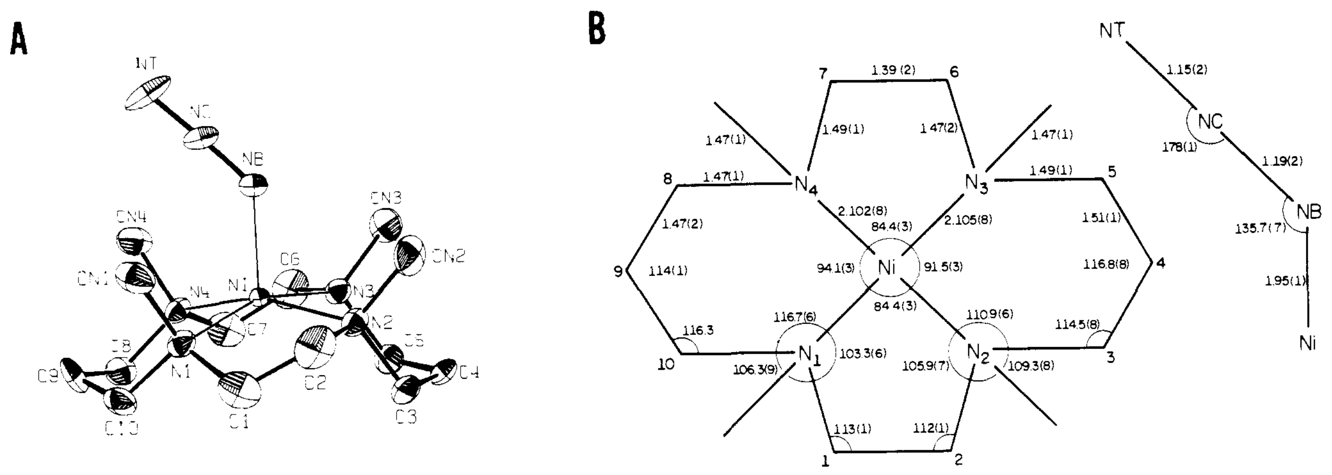


Figure 1. (A) ORTEP drawing of $[Ni(TMC)N_3]^+$. Hydrogen atoms are not shown. Thermal ellipsoids are drawn at the 30% probability level. (B) Bond distances and bond angles for the complex ion shown in A. A crystallographic plane of symmetry passes through C4 and C9. The azide ion lies in this plane.

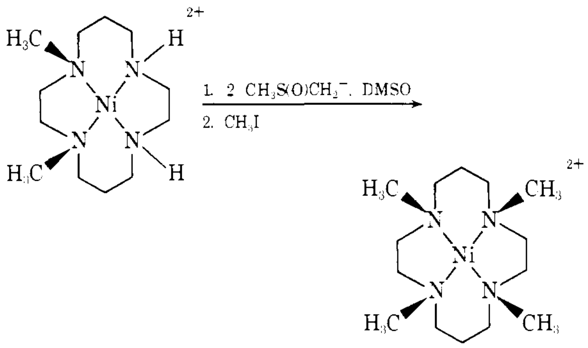
ogous secondary amine ligand[2,5] and certain C-methylated members of the class.[6] Thus, the product obtained by direct interaction of metal ion with tertiary amine must have a kinetically determined stereochemistry.[1,3]

In order to assign unambiguously the stereochemistry of the complexes with kinetically determined stereochemistry, we have performed an X-ray structure determination on $[Ni(TMC)N_3]ClO_4$, which was prepared using preformed **1**. The green crystals that form upon addition of sodium azide to aqueous solutions of the nickel perchlorate complex of **1** are orthorhombic with space group *Pnma*. Cell dimensions are a = 14.298 (15), b = 9.641 (9), and c = 14.765 (12) Å. The experimental density of 1.47 g/cm³ (CCl_4-hexane) indicates the presence of four formula units per unit cell (d_{calcd} = 1.49 g/cm³, formula weight for $NiC_{14}H_{32}N_7ClO_4$ = 456.63). A set of 1469 reflections, observed at the 2σ level, was collected using a Picker FACS-1 automated diffractometer and Mo $K\alpha$ radiation. The structure was solved using heavy atom methods and was refined by full-matrix least-squares techniques (all atoms except hydrogen were given anisotropic temperature factors, hydrogen positions were calculated and these were included as fixed contributions) to a current R of 0.085. For the positions of nuclei in fractional cell coordinates, thermal parameters, and structure factor amplitudes, see paragraph at end of paper regarding supplementary material.

A projection diagram of the pentacoordinate cation, which has C_s crystallographic symmetry, and relevant distances and angles are given in Figure 1. The coordination geometry about the nickel ion is square pyramidal as was previously predicted.[1] The four donor nitrogen atoms of the macrocyclic ligand form a perfect plane, and the nickel ion is 0.33 Å out of this plane toward the azide ion. The perchlorate ion (not shown, there is extensive disorder in the oxygen positions) is not within bonding distance of any atom in the cation. Most bond angles and distances are those expected for complexes of this type except for the C–C bond distance and the N–C–C bond angle in the five-membered chelate ring. These bond distances are *ca.* 0.1 Å shorter than expected and the angles are 2–3° larger than those expected. These anomalous values probably arise from disorder in the carbon atom positions;[7] this hypothesis is supported by the large thermal parameters for these atoms.

Previously we had anticipated that the monodentate ligand would be bonded to the metal ion on the side opposite the nitrogen substituents. However, an examination of space filling models indicates that the metal ion cannot be located above the plane defined by the nitrogen donor atoms on the side opposite the methyl groups without causing severe interactions between those methyl substituents. Bonding of a sixth ligand in the other axial position could occur only if the nickel ion moved into the nitrogen donor plane. Such a movement would cause interaction of the axial donor that is already present with the methyl groups. Similarly, steric arguments suggest that a trigonal bipyramidal stereochemistry, which is observed for a pentacoordinate Cu(II) complex of a 14-membered macrocyclic secondary amine ligand[8] is not possible for the tertiary amine ligand coordinated with the trans I set of nitrogen configurations. The greater lability of the trans I stereoisomer compared to the trans III isomer surely results from the fact that the metal ion is located out of the plane of the donor nitrogen atoms and "stripping" of the ligand from the metal ion does not involve high energy changes in the complex stereochemistry.

The stepwise process by which metal complexes of **1** are formed does not yield complexes containing the thermodynamically most stable form of the ligand. Since there is no low energy process for inversion of a coordinated tertiary nitrogen, as there is for a coordinated secondary amine, isomerization is impossible. Although the trans III isomer is the thermodynamically most stable of all possible isomers, the trans I form must be the most stable of the three stereoisomers that could be formed by reaction 2, since it is the only tetramethylated product.[9] No information is presently available concerning the relative stability of the fifth isomer.



(2)

Acknowledgment. Support of this research by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science

Foundation is gratefully acknowledged. Computer funds were supplied by the University of Illinois Research Board. M.T.M. thanks the National Science Foundation for support through a predoctoral fellowship, 1970–1973.

Supplementary Material Available. Positions of nuclei, thermal parameters, and a listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-192.

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M. J. D'Aniello, Jr., M. T. Mocella, F. Wagner
E. Kent Barefield,* Iain C. Paul
W. A. Noyes Laboratory, School of Chemical Sciences
University of Illinois
Urbana, Illinois 61801

Received August 9, 1974

Very Fast Zinc-Catalyzed Hydrolysis of an Anhydride. A Model for the Rate and Mechanism of Carboxypeptidase A Catalysis

Sir:

One of the most attractive mechanisms[1] for the hydrolysis of peptides or esters by carboxypeptidase A involves two steps and an anhydride (acyl-enzyme) intermediate. In the first step Zn^{2+} of the enzyme electrophilically activates the substrate carbonyl toward nucleophilic attack by a glutamate residue. Departure of an alkoxyl group (with ester substrates) or an amino group (with peptide substrates, assisted by an enzyme tyrosine) results in production of the anhydride between the enzyme glutamate and the scissile carboxyl group. The hydrolysis of this anhydride can be catalyzed only by the Zn^{2+}, the only remaining necessary[2] catalytic group.

There is some direct evidence for a two-step mechanism in the observation[3] that carboxypeptidase catalyzes ^{18}O exchange with the terminal carboxyl group of amino acid derivatives. Such exchange can be interpreted[4] as the catalyzed re-formation of the intermediate anhydride, followed by its hydrolysis with $H_2{}^{18}O$. However, this ^{18}O exchange evidence is not unambiguous evidence for an anhydride intermediate. Furthermore, an intermediate has never been trapped with nucleophiles such as hydroxylamine.[5] An additional question about such an anhydride intermediate is whether indeed simple Zn^{2+} catalysis *could* result in a hydrolysis rate on the enzymatic time scale, the k_{cat}'s[6] for several esters lying in the range of 0.5–230 sec^{-1}.

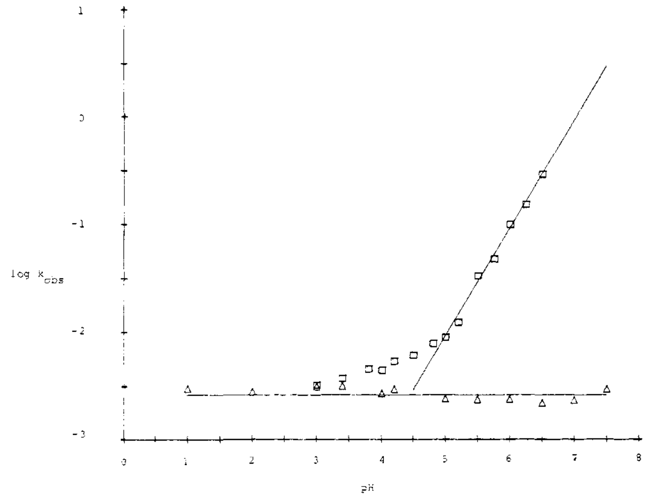

Figure 1. Hydrolysis pseudo-first-order rate constants of anhydride I *vs.* pH: △, I; □, I·Zn^{2+}. All runs at 25.0° with 0.3 *M* buffers having μ = 0.5 *M*. See Table I for experimental details.

Table I. Pseudo-First-Order Hydrolysis Rate Constants[a–c] at pH 7.50[d]

Compound	k_{obsd} (sec^{-1})	k_{rel}
I	$(2.7 \pm 0.5) \times 10^{-3}$	1.0
I·Zn^{2+}	3.0 ± 0.5	10^3
II	$(5.5 \pm 0.5) \times 10^{-3}$	2.0
II·Zn^{2+}	1.5 ± 0.5	5×10^2

[a] Hydrolyses in aqueous 0.3 *M* buffered solutions held at 25° were monitored spectrophotometrically at 400 nm using a Cary 17 or Gilford 2400 spectrophotometer. The least-squares computer-processed kinetic data from two or more runs were averaged for each datum point in Figure 1. Titrimetric kinetic studies with II were also conducted at pH 4.00 and identical results were obtained. [b] Buffers used were 0.3 *M* formate from pH 3.0 to 4.2, 0.3 *M* acetate from pH 4.0 to 5.2, and 0.3 *M* 2-(N-Morpholino)ethane sulfonic acid from pH 5.5 to 7.5. The ionic strength was adjusted with KCl or $NaClO_4$ to μ = 0.5 *M* for all buffers. [c] Buffer concentrations were varied, and the rate constants were corrected for small buffer terms when observed. The zinc-catalyzed hydrolysis of I showed no buffer catalysis from pH 3.0 to 6.5 (the total range studied). [d] Optimum esterase and peptidase activity for carboxypeptidase A has been determined to occur at pH 7.5. Values for the zinc-catalyzed hydrolysis rate constants were extrapolated to pH 7.5 through the use of plots like those shown in Figure 1.

As part of our series of model studies on carboxypeptidase, we have examined the hydrolysis of anhydrides I[7] and II[7] with and without zinc (and other metal ions). We find that rate accelerations of this process do indeed bring it into the rate region mentioned above for the overall enzymatic process itself. Furthermore, we find that the mechanism of this process explains the failure to trap an anhydride intermediate in the enzymatic reaction with nucleophiles other than water, and indeed demonstrates that the large preference of this enzyme for water over other nucleophiles is evidence in favor of the anhydride mechanism.

Since in carboxypeptidase A the natural metal is Zn^{2+} coordinated to two nitrogens and a carboxylate, our principal emphasis has been on the study of the zinc catalyzed reactions of anhydride I, which is fully saturated with Zn^{2+} with metal concentrations greater than 0.005 *M*. The results from the kinetic study are displayed in Figure 1, and the kinetic constants from the studies are listed in Table I. These data show that in the absence of metal the anhydride hydrolysis is independent of pH in the region 1.00–7.50, as with phthalic anhydride.[8] However, with coordinated zinc ion the cleavage is first order in hydroxide above pH 5.00.