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CONTROL OF SITE-SPECIFIC SUBSTITUTION OF AMINOGLYCOSIDES BY TRANSITION METAL CATIONS

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Summary: The site of transition metal-directed acylations of apramycin and related aminoglycosides can be altered simply by changing the metal cation employed in the reaction.

The use of transition metal cations to selectively protect certain amino groups in aminoglycoside antibiotics from acylation has recently been reported.[1-4] Although a number of different transition metal cations were examined in these studies, the site of acylation did not generally depend on the particular cation used.[4]

In contrast to these earlier results and the mechanisms proposed for them, we have found that mono-N-substituted derivatives of apramycin[5] (1) can be selectively and directly prepared in a single reaction in which the site of substitution can be varied simply by changing the metal cation without altering any other reaction variable!

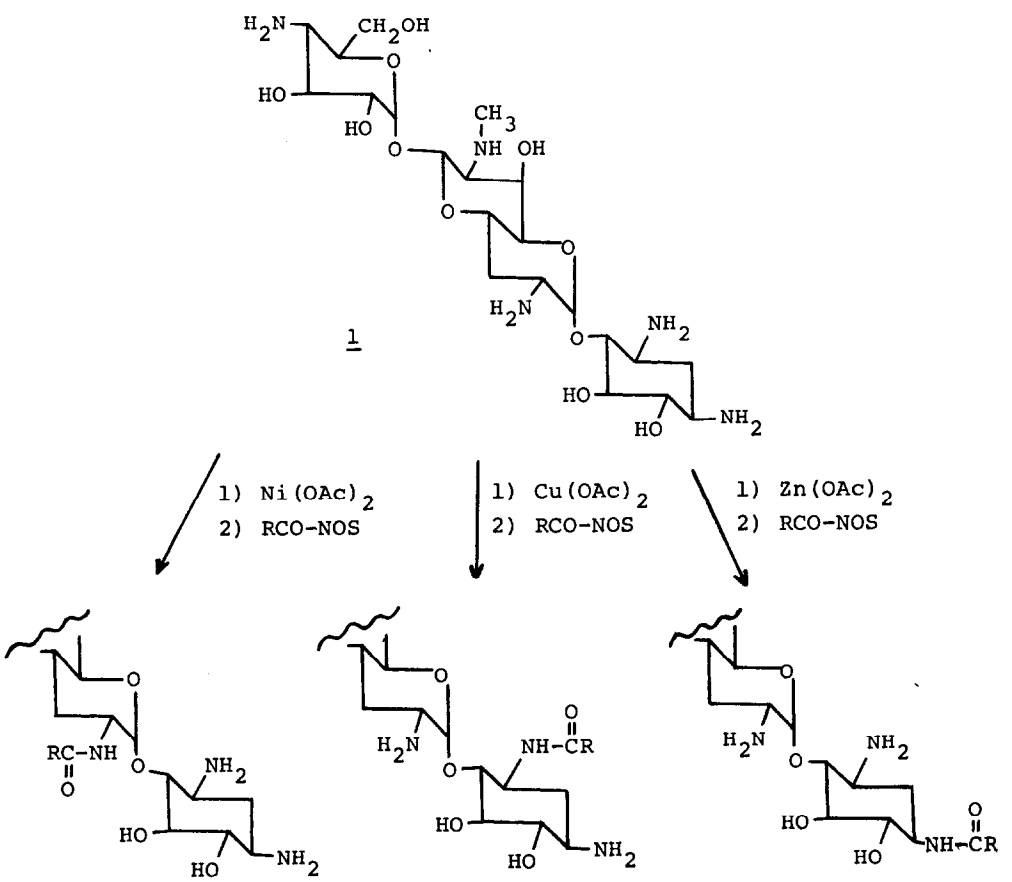
An aqueous solution of apramycin (1) was treated with 4 equiv. $M(OAc)_2$, diluted with 5 volumes DMF and acylated with 1.5 equiv. N-(benzyloxycarbonyl-oxy)-succinimide (CBZ-NOS) overnight at room temperature. Using $Ni(OAc)_2$, 2'-N-CBZ-apramycin was exclusively produced in a very clean reaction. Using $Cu(OAc)_2$, 3-N-CBZ-apramycin was obtained along with a minor amount of di- or tri-N-CBZ product. Using $Zn(OAc)_2$, 1-N-CBZ-apramycin was the major product, although minor amounts of 3-N, 2'-N and 4"-N-CBZ-apramycin were also obtained and substantial (20-30%) amounts of di- or tri-N-CBZ derivatives were formed. However, even with these limitations, the $Zn(OAc)_2$-directed 1-N-acylation was a significant improvement over acylation of apramycin alone (see Table 1); the conversion to 1-N-acyl derivatives was somewhat higher, but more importantly, their isolation free from unwanted isomers was much more readily accomplished. The desired acyl derivatives of apramycin were then isolated in a single step operation (after evaporation of DMF) by chromatography on either Chelex 100 resin[6] or silica gel; the metal salts remained adsorbed on the chromatography support while the aminoglycoside derivatives were eluted with an aqueous NH_4OH gradient (Chelex) or a $MeOH-CH_2Cl_2-NH_4OH$ gradient (silica gel).

Table 1. Yield of Mono-N-CBZ-Apramycin Derivatives[a]

Metal Salt	% 1-N	% 3-N	% 2'-N
None[b]	8	17	15
$Ni(OAc)_2$	-	-	82
$Cu(OAc)_2$	-	87	-
$Zn(OAc)_2$	31	5	5

[a]Reactions carried out with 4 equiv. $M(OAc)_2$ and 1.5 equiv. CBZ-NOS ester in 5:1 DMF-H_2O.

[b]Reaction carried out in water with 1.2 equiv. CBZ-NOS ester.

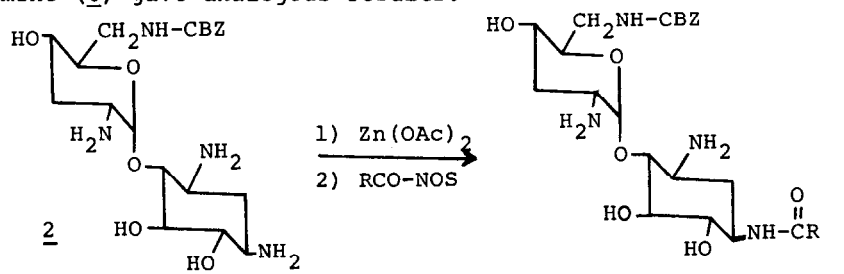


Scheme 1

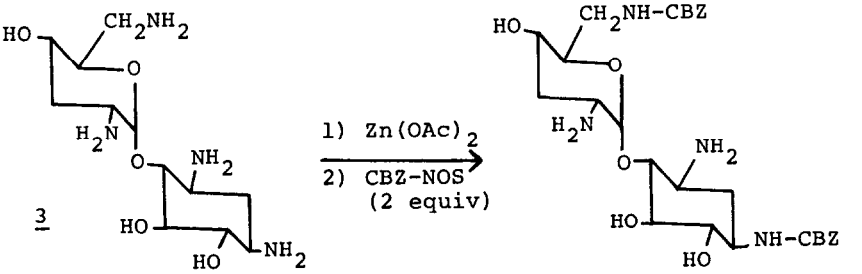
These metal-directed selective acylations have now been successfully carried out with a wide variety of active esters and anhydrides. Very active acylating agents such as acid chlorides led to mixtures of the desired product and the corresponding N-acetyl derivative, apparently by converting the acetoxy ligand into an acetylating agent. In some cases, this problem could be avoided by using an anion other than acetate. Selective alkylation of these metal-apramycin complexes by ethyl iodide has also been demonstrated, although this occurred more slowly than acylation and did not go to completion.

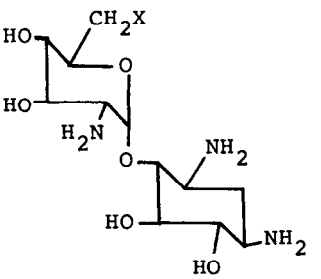
Other 4-O-substituted-2-deoxystreptamine aminoglycosides undergo the same metal-directed acylations described above. Acylation of 6'-N-CBZ-nebramine[7] (2) yielded 1,6'-di-N-CBZ-nebramine with $Zn(OAc)_2$, 3,6'-di-N-CBZ-nebramine with $Cu(OAc)_2$ and 2',6'-di-N-CBZ-nebramine with $Ni(OAc)_2$. Furthermore, using 2.5 equiv. of CBZ-NOS, nebramine (3) itself was cleanly converted to the three di-N-CBZ derivatives described above using the appropriate metal acetate. The free amino group at 6' was apparently not complexed by any of the metals and did not interfere with the selective acylations of the other amino groups. Neamine (5) and its 6'-N-CBZ derivative (4) and paromamine (6) gave analogous results.[8]

Scheme 2

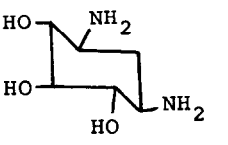


Scheme 3





4 X=NH-CBZ
5 X=NH_2
6 X=OH



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Although the mechanism of the Cu^{+2}-directed acylation may be similar to that proposed previously,[1,2] our studies suggest a fundamentally different mechanism for the Ni^{+2} and Zn^{+2}-directed acylations. 2-Deoxystreptamine (7) was complexed with 4 equiv. of $M(OAc)_2$ in 5:1 DMF-H_2O and acylated with 2 equiv. CBZ-NOS. With $Cu(OAc)_2$, very little acylation occurred, but with $Ni(OAc)_2$ or $Zn(OAc)_2$, complete conversion to di-N-CBZ-2-deoxy-streptamine occurred. Analogous results were obtained with cis-2-amino-cyclohexanol[9] and 2 equiv. $M(OAc)_2$. These experiments confirm that Cu^{+2} effectively complexes amino-alcohols to block N-acylation but indicate that Zn^{+2} and Ni^{+2} complexes, if formed, do not inhibit acylation of the complexed amino groups. Since aminoglycoside-metal complexes are required to explain the selective acylation of aminoglycosides, we conclude that Ni^{+2} and Zn^{+2} cations complex apramycin and nebramine in some manner that directs or promotes acylation of a specific amino group within the complex. A more detailed investigation of these unique reactions and the preparation of derivatives of these aminoglycosides are now in progress.

References and Notes

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(6) Product of Bio-Rad Laboratories, 2200 Wright Avenue, Richmond, California, 94804.

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(8) We thank Dr. J. E. Grady (Upjohn Co.) for a sample of neamine and Dr. M. L. Black (Warner-Lambert Co.) for a sample of paromamine.

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