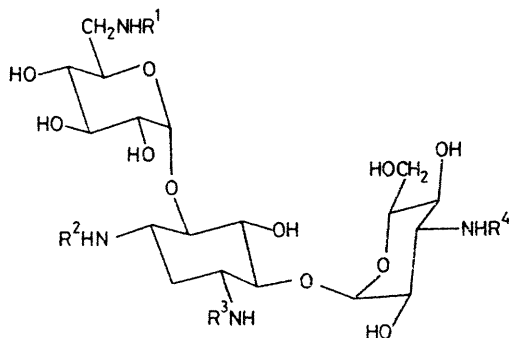


Selective *N*-Acylation of Kanamycin A

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Summary The *N*-acylation of partially trimethylsilylated kanamycin A in acetone has been found to proceed selectively at the 1-*N* position rather than the usual 6'-*N* position.

SELECTIVE chemical modification of aminoglycosides has been hampered by difficulties in separating the activities of the functional groups; thus, direct acylation of kanamycin A yields a mixture of *N*-acylated products, the major component of which is (Ia).¹ We here report a novel procedure for the selective *N*-acylation of kanamycin A to give primarily (Ic).



- (Ia) $R^1 = \text{COCH(OH)}[\text{CH}_2]_2\text{NH}_2$, $R^2 = R^3 = R^4 = \text{H}$
 (Ib) $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{COCH(OH)}[\text{CH}_2]_2\text{NH}_2$
 (Ic) $R^1 = R^2 = R^4 = \text{H}$, $R^3 = \text{COCH(OH)}[\text{CH}_2]_2\text{NH}_2$
 (Id) $R^1 = R^2 = R^3 = \text{H}$, $R^4 = \text{COCH(OH)}[\text{CH}_2]_2\text{NH}_2$

When kanamycin A free base (10 g, 0.0206 mol) containing 1% kanamycin A sulphate was refluxed in acetonitrile (100 ml) with hexamethyldisilazane (HMDS; 7 mol. equiv.) for 5 h, two clear liquid phases were produced. Removal of the acetonitrile and excess of HMDS *in vacuo* gave polytrimethylsilylated kanamycin A as a clear liquid, which was acylated in two ways.

Firstly, a solution of the polytrimethylsilylated kanamycin A in acetone (10% w/v) was treated with 1 mol. equiv. of *N*-[(2*S*)-4-benzyloxycarbonylamino-2-hydroxybutanoyloxy]succinimide (BHBA active ester) at 5 °C for 1 h and the mixture was hydrolysed with water at pH 2.5, hydrogenolysed, and chromatographed. The principal product was (Ia) (*ca.* 50%); smaller amounts of (Ib) (*ca.* 5%), (Ic) (*ca.* 5%), and polyacylated kanamycin A (*ca.* 20%) were also obtained, but (Id) was not detected. About 20% of kanamycin A was recovered.[†]

Secondly, the polytrimethylsilylated kanamycin A in acetone was first stirred, *in vacuo* or under nitrogen, with 10 mol. equiv. of water at 5 °C for 30 min, and the resulting solution was acylated and worked up as in the first experiment. In this case the major product isolated was (Ic) (50%). Small amounts of (Ia) (6%), (Ib) (12%), polyacylated kanamycin A (8%), and unchanged kanamycin A (22%) were obtained. Again (Id) was not detected.

These results indicate that the acylating agent is guided to attack the 1-*N* position only when the polytrimethylsilylated kanamycin A molecule is partially hydrolysed. As far as we are aware this is the first instance of acylation selectivity occurring as a consequence of appropriately placed trimethylsilyl groups. No 3'-*N*-acylation occurs,

[†] A control experiment in which kanamycin A base was acylated with BHBA active ester in 50% aq. tetrahydrofuran gave a similar result, except that (Id) was also produced; yields were (Ia) 45–55%, (Ib) 5–10%, (Ic) *ca.* 5%, (Id) *ca.* 5%, polyacylated kanamycin A 15–20%, and unchanged kanamycin A 10–15%.

presumably because of the bulky flanking SiMe_3 groups. The relative inaccessibility of the 6'-N position to electrophilic attack is more difficult to explain, though models indicate that when the 4'-hydroxy group is trimethyl-

silylated, the 6'- NH_2 group can be shielded by appropriate folding of the sugar rings.

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¹ T. Naito, S. Nakagawa, Y. Abe, S. Toda, K. Fujisawa, T. Miyaki, H. Koshiyama, H. Ohkuma, and H. Kawaguchi, *J. Antibiotics* 1973, **26**, 297.