1972, *50,* 459–464.
(5) Insertion products involving monomeric SiF_2 are more common (Liu, C. S.; Hwang, T. L. *J. Am. Chem. Soc.* **1978,** *100,* 2577–2579 and references therein).
(6) Thompson, J. C.; Wright, A. P. G.; Reynolds, W. F., unpublished work.
(7) Thompson, J. C.; Margrave, J. L.; Timms, P. L. *J. Chem. Soc., Chem. Commun.* **1966,** 566–567.
(8) Liu, C. S. Ph.D. Thesis, University of Toronto, Toronto, 1971.
(9) The observation that the polymer from the *trans*-butene reaction contains the highest proportion of Si_2F_4 units is consistent with the observation that this reaction also gives a higher yield of disilacyclobutane product (III) than any of the other olefin reactions.[6]
(10) A minor product of empirical formula $C_2H_4SiF_2$ has been detected in the mass spectrum of the products of the reaction of SiF_2 with ethylene.[7]

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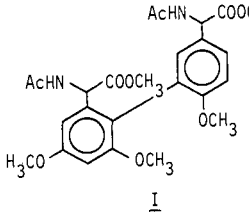
Avoparcin[1]

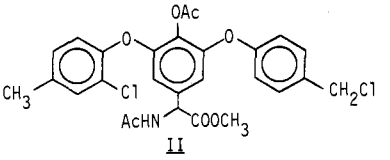
Sir:

Avoparcin, vancomycin, actinoidin, ristomycin, ristocetin, and compound A35512B are a class of complex water-soluble glycopeptide antibiotics with Gram-positive activity which have been isolated over the past 20 years.[2] Vancomycin is the only member of this antibiotic class the structure of which is known with certainty. Recently Williams at Cambridge prepared modified vancomycin (CDP-I) which was suitable for single-crystal X-ray work and thus obtained the unequivocal structure of this material.[3] Avoparcin has commercial importance as a feed additive for agricultural uses. In this communication, we present chemical and spectral evidence that leads us to propose the structure of the aglycone rhamnoside of avoparcin α and β. That avoparcin consists mainly of two components α and β present in about the ratio of 1:3 or 1:4 is readily observed by LC.[4]

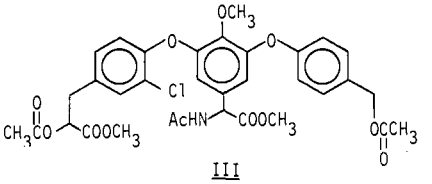
Based on the work of Williams et al., we carried out reductive alkaline hydrolysis (refluxing 11 N NaOH, 20% $NaBH_4$) on avoparcin.[5] Following suitable derivatization and intensive chromatographic efforts, a number of important fragments were obtained, such as **I** (M^+ 502, $C_{25}H_{30}N_2O_9$), II (M^+ 545, $C_{27}H_{25}NO_7Cl_2$), and III (M^+ 671, $C_{33}H_{34}NO_{12}Cl$).[6]



I

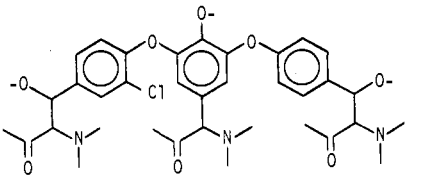


II



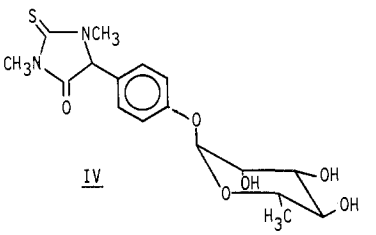
III

The formation of the aromatic methyl groups as well as the benzyl and lactate moieties in II and III suggests a common origin for these groups. They are reasonably explained in terms of the chemistry of the seryl side chains in the partial structure shown below. Such treatment of avoparcin leads to β elimination of one of the benzylic oxygens which gives rise to an enamide which may be hydrolyzed to a keto acid. Reductive conditions would provide the lactate whereas deoxalation would lead to the methylbenzene. The benzyl chloride unit

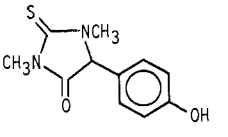


could arise by dealdolization, reduction of the intermediate aldehyde, and introduction of the chlorine during acidification with HCl.

Avoparcin was subjected to the Edman degradation sequence using the reagent methyl isothiocyanate.[7a,b] At the end of the first stage of the normal Edman two-stage cycle, it was possible to isolate the rhamnoside IV (M^+ 382, $C_{17}H_{22}N_2O_6S$).

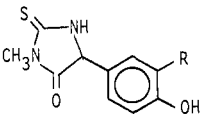


IV



V

If the two-stage cycle is completed normally, V (M^+ 236, $C_{11}H_{12}O_2N_2S$) is isolated. Subjecting the residue to a second complete Edman cycle yields VI (M^+ 256, $C_{10}H_9N_2O_2ClS$) and VII (M^+ 222, $C_{10}H_{10}N_2O_2S$) in about the ratio of 3:1 or 4:1. Because of the abnormality at the end of the first stage of



VI R = Cl
VII R = H

the first Edman cycle,[7c] these products released at the end of two actual Edman cycles arise because, in effect, three full cycles have been completed. Further the isolation of VI and VII in the ratio mentioned most likely means that the major β component contains the chlorinated *p*-hydroxyphenylglycine compared with *p*-hydroxyphenylglycine in the minor α component.

Although there are obvious differences between the ^{13}C NMR spectra of avoparcin (see below) and vancomycin, the general pattern of resonances is similar, especially with respect to the anomeric, aromatic oxycarbon and carbonyl areas, indicating that these antibiotics are structurally related, in agreement with isolation of the identical biphenyl and triphenyl diether (except for chlorine) units from both avoparcin and vancomycin. Further evidence for this relationship comes from the ^1H NMR comparison studies at 270 MHz in Me_2SO-d_6 (courtesy of Walter Krol, Yale University). An essentially pure sample of the β component and a small sample of mostly the α component were prepared by extensive, repetitive chromatography. Even though the spectra are complex, the two meta-substituted protons on the tetrasubstituted ring of the biphenyl have unique chemical shifts at δ 6.30 and 6.44 in vancomycin and 6.31 and 6.44 in avoparcin α and β.[8] The α and β curves are almost identical, except in the aromatic region, with the only difference being the extra chlorine in β. Prominent upfield patterns in the α and β spectra are three sharp three-proton doublets at δ 1.11, 1.17, and 1.23. One of these obviously belongs to rhamnose while the other two are assigned to two ristosamine units (see below). The four-proton complex at δ 2.07 is attributed to the C-2 methylene protons of these ristosamines. The *N*-methyl signal of the phenylsarcosine resonates at δ 2.12.

Thus, on the basis of the work described so far, the subunits of the rhamnoside of avoparcin α and β aglycones are depicted,

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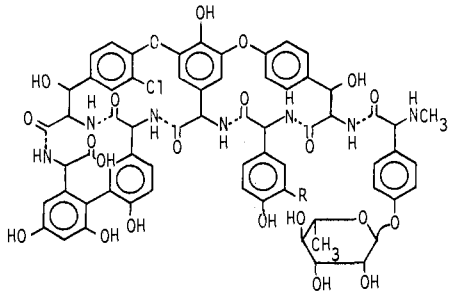
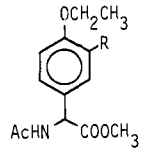


Rhamnoside of Avoparcin α aglycone R = H
Rhamnoside of Avoparcin β aglycone R = Cl

and, by biogenetic analogy with vancomycin, it is logical to include the broken lines indicating how these fragments are connected.

Avoparcin was methylated using methyl iodide and then hydrolyzed to the aglycone, which was again methylated using deuterated methyl iodide and subjected to drastic alkaline hydrolysis. Following suitable derivatization and chromatography, fragment I was isolated, indicating that the phenolic groups of the biphenyl moiety are not glycosylated in the intact antibiotic. Ethylation of avoparcin, followed by hydrolysis, led to the isolation of VIII (M^+ 285, $C_{13}H_{16}NO_4Cl$) and IX (M^+ 251, $C_{13}H_{17}NO_4$), again in about the ratio of 4:1. These results



VIII R = Cl
IX R = H

indicate that the phenolic group of the chlorinated phenylglycine is free and they further support the Edman work which indicates that the avoparcin components differ by a chlorine atom.

The presence of ristosamine in avoparcin was shown by methanolysis of the antibiotic with subsequent conversion of the methyl glycoside into methyl *N,O*-diacetylristosaminide, identical in properties with those described by Bognar et al. for the material isolated from ristocetin.[9] The presence of glucose, mannose, and rhamnose was shown by methanolysis work which yielded the methyl glycosides of D-glucose, D-mannose, and L-rhamnose. Hakomori permethylation of avoparcin, followed by chromatographic resolution of the products from methanolysis of the permethylated material, yielded 1,3,4,6-tetramethylglucose, 1,2,3,4,6-pentamethylmannose, and 1,2,3,4-tetramethylrhamnose.[10] No methylated derivative of ristosamine was isolated. These results indicate that glucose is the only nonterminal neutral sugar and that it is linked glycosidically to another sugar at the C-2 hydroxyl group.

The ^{13}C NMR spectra (70 °C, D_2O, 25.5 MHz) of both α and β are complex; nevertheless they yielded valuable information and confirm that α and β are very closely related. The spectra of both materials show three sharp *C*-methyl signals at ~18 ppm. These belong to the one rhamnose and two ristosamines. There are double signals at 31 and 50 ppm belonging to the C-2 and C-3 carbons, respectively, of the ristosamines. Single signals at these locations were observed in the spectrum of ristocetin which is known to contain ristosamine.[11]

A strong *N*-methyl signal belonging to the terminal amino acid is observed at 33 ppm. Although complex, the 55–85-ppm region includes seven signals typical of amino acid α-CH's. An intense signal at 62 ppm is attributed to the hydroxymethyl groups of glucose and mannose and an isolated signal at 80.5 ppm is assigned to the glycosylated C-2 of glucose, similar to the corresponding signal in the spectrum of vancomycin.[12]

The 90–110-ppm region contains nine signals, four of which belong to aromatic carbons ortho and para to two oxygen substituents, while the other five represent carbohydrate anomeric carbons consistent with the presence of 1 mol each of glucose, mannose, rhamnose, and 2 mol of ristosamine. One of these five is set apart at 94 ppm as in ristocetin, and we have assigned this signal to an α-linked anomeric carbon of one of the ristosamines. The area between 120 and 140 ppm is too complex to be used effectively.

The aromatic oxy carbon region (150–160 ppm) contains nine easily discernible signals. Although the aglycone structure shown contains ten aromatic carbons bound to oxygen, the C-2 of the 1,2,3-trioxygenated center ring of the triphenyl ether moiety resonates between 135 and 140 ppm as indicated by the ^{13}C NMR spectra of II and III. Further, the spectrum of the β component shows three signals at 151.4, 153.1, and 153.7 ppm, with six signals bunched between 156 and 158 ppm, while the α spectrum has two signals at 151.5 and 154 ppm with seven signals between 156 and 158 ppm. A shift of 4 to 5 ppm for an aromatic oxy carbon atom ortho to a chlorine substituent is well known.[13] This further supports the notion of an aromatic chlorine substituent difference between components α and β.

Finally, both spectra contain six distinct carbonyl signals between 168 and 173 ppm and a broader signal at 177 ppm which varies depending upon the pH of the solution. Again this is consistent with the six amide carbons and the free acid group of the aglycone shown.

Except for the rhamnoside linkage, the position of the other sugar moieties are not unequivocal at this stage. Very mild acid hydrolysis of avoparcin yields a microcrystalline degradation product (CDP-I) from the β component (^{13}C and ^1H NMR) which still contains mannose and ristosamine as indicated by further hydrolysis. The ^{13}C spectrum on CDP-I (Me_2SO-d_6, pH 3.5, 70 °C, 25.5 MHz) shows clearly the *C*-methyl signal of ristosamine at 18.5 ppm, a 60.9-ppm signal for the hydroxymethyl group of mannose, and six signals (all doublets in the off-resonance spectrum) at 92.5, 99.0, 103.0, 103.5, 106.0, and 107.5 ppm consistent with the aglycone still bearing 1 mol each of ristosamine and mannose. The absence of a signal between 75 and 85 ppm compared with a clear 80.5-ppm signal in the spectra of the intact antibiotics (glycosylated C-2 of glucose)[12,14] proves the presence of a ristosaminylglucose disaccharide in the intact antibiotic.

Plasma desorption mass spectroscopy (courtesy of Professor R. D. MacFarlane of Texas A & M) on the α component gave a strong quasi-molecular ion ($M + Na^+$) at 1931 ± 2 consistent with the molecular formula $C_{89}H_{101}O_{36}N_9Cl$ (1907) suggested by chemical and spectral studies. Similar determinations on the β component and CDP-I gave quasi-molecular ions ($M + Na^+$) at 1965 ± 2 (consistent with $C_{89}H_{100}O_{36}N_9Cl_2$ (1942)) and 1529 ± 2 (consistent with $C_{71}H_{69}O_{25}N_8Cl_2$ (1504)), respectively.

References and Notes

(1) Avoparcin, formerly called LL-AV290, is marketed in Great Britain in animal feed under the tradename AVOTAN.
(2) (a) M. P. Kunstmann, L. A. Mitscher, J. M. Porter, A. J. Shay, and M. A. Darken, *Antimicrob. Agents Chemother. (1968)*, 242 (1969); (b) M. H. McCormick, W. M. Stark, G. F. Pittenger, R. C. Pittenger, and G. M. McGuire, *Antibiot. Annu.*, 606 (1955–1956); (c) V. A. Shorin, S. D. Yudnitsev, I. A. Kunrat, N. S. Prevner, G. F. Yanze, Ye. S. Kudrina, Ye. G. Topovra, M. G. Brazhnikova, and T. Vsesoyugor, *Konf. Proantibiotikam* (1957); (d) M. G. Brazhnikova, N. N. Lomakina, M. F. Lavrova, I. V. Tolstykh, M. S. Yurina, and L. M. Klyueva, *Antibiotiki*, **8**, 392 (1963); (e) J. E. Philip, J. R. Schenck, and M. P. Hargie, *Antibiot. Annu.*, 699 (1956–1957); (f) M. DeBono, *Abstr. Int. Conf. Antimicrob. Agents Chemother., 17th, 1977* (Oct 1977).
(3) G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams, and G. A. Smith, *Nature (London)*, **271**, 223 (1978).
(4) LC is best carried out on a μ-Bondapak C_{18} column using paired ion chromatography with 1% acetic acid and 20% acetonitrile in water.
(5) (a) K. A. Smith, D. H. Williams, and G. A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2369 (1974); (b) G. A. Smith, K. A. Smith, and D. H. Williams, *ibid.*, 2108 (1975).

(6) ^1H and ^{13}C NMR data consistent with these structures, as well as those of fragments IV–IX, were obtained and will be published later in a full paper. Structures of fragments I and VIII were confirmed by X-ray. The aromatic chlorine in II and III may just as well be on the equivalent position on the right-hand ring.
(7) (a) J. J. Hlavka, P. Bitha, J. H. Boothe, and G. O. Morton, *Tetrahedron Lett.*, 175 (1974); (b) H. C. Beyerman, L. Maat, A. Sinnema, and A. Van Venn, *Recl. Trav. Chim. Pays-Bas*, **87**, 11 (1968); (c) D. T. Elmore, *J. Chem. Soc.*, 3161 (1961).
(8) D. H. Williams and J. R. Kalman, *J. Am. Chem. Soc.*, **99**, 2768 (1977).
(9) R. Bognar, F. Sztaricskai, M. E. Munk, and J. Tamas, *J. Org. Chem.*, **39**, 2971 (1974).
(10) S. Hakomori, *J. Biochem. (Tokyo)*, **55**, 205 (1964).
(11) A ^{13}C NMR spectrum was obtained on SPONTIN, a commercial product of Abbott Laboratories which is a mixture of ristocetin A and B. The spectrum was taken in D_2O at 70 °C. For the most recent work on ristocetin A, see C. M. Harris, J. F. Kibby, J. R. Fehlner, A. B. Raabe, T. A. Barber, and T. M. Harris, *J. Am. Chem. Soc.*, **101**, 437 (1979).
(12) D. H. Williams and J. R. Kalman, *Tetrahedron Lett.*, 4829 (1976).
(13) (a) L. F. Johnson and W. C. Jankowski, "Carbon-13 Spectroscopy", Wiley, New York, 1972, spectrum 248; (b) S. G. Levine, R. E. Hicks, H. E. Gottlieb, and E. Wenkert, *J. Org. Chem.*, **40**, 2540 (1975).
(14) M. Vuilhorgne, S. Ennifar, B. C. Das, J. W. Paschal, R. Nagarajan, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **42**, 3289 (1977).

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A Radical-Chain Mechanism in Substitution Reactions of (Unsaturated Alkyl) Metal Carbonyl Complexes

Sir:

We have previously reported that reactions of the *monohaptocyclopentadienyl* complex, $(\eta^5\text{-}C_5H_5)Fe(CO)_2(\eta^1\text{-}C_5H_5)$ (henceforth abbreviated FpCp), with phosphorus donor ligands, are atypical of (alkyl) metal carbonyl substitution reactions.[1] In addition to the formation of unexpected products in some cases, these reactions are unusually facile: FpCp reacts completely with a variety of phosphines and phosphites over periods varying from several minutes to several days (depending on ligand and solvent), whereas the methyl analogue FpMe is completely inert to all such ligands under the same conditions. Similar behavior has been reported for a number of (hydrido) metal carbonyl substitutions (including FpH[2]); mechanistic investigations on several of these have established that a radical-chain mechanism is responsible for these relatively rapid reactions.[3] We now present evidence that substitution reactions of (unsaturated alkyl) metal carbonyls, including FpCp, can proceed by a closely related radical-chain pathway.

FpCp reacts very slowly in the dark with $P(OPh)_3$ to give the substitution product, $(\eta^5\text{-}C_5H_5)Fe(CO)(P(OPh)_3)(\eta^1\text{-}C_5H_5)$ (Fp′Cp).[1] Irradiation with near-UV light does not cause any significant acceleration of the substitution reaction; instead FpCp is converted into ferrocene.[4] However, if the irradiated solution also contains a small amount of $[(\eta^5\text{-}C_5H_5)Fe(CO)_2]_2(Fp_2)$, substitution is markedly enhanced.[5] This result is similar to observations made for (hydrido) metal carbonyls[3] and suggests formulation of an analogous mechanism, viz:

$$Q\cdot + FpCp \rightarrow QCp + Fp\cdot \quad (1)$$

$$Fp_2 \xrightarrow{h\nu} 2Fp\cdot \quad (2)$$

$$Fp\cdot + L \xrightarrow{\text{fast}} Fp'\cdot + CO \quad (3)$$

$$Fp'\cdot + FpCp \rightarrow Fp'Cp + Fp\cdot \quad (4)$$

In this scheme initiation, either by adventitious impurities (1) or by photocleavage of a metal–metal bond (2) gives the 17-electron fragment Fp. Such 17-electron species have been shown to be highly labile toward substitution.[6] Steps 3 and 4 correspond to chain propagation. The crucial element of this scheme is step 4, which is a homolytic displacement reaction of an *unsaturated* alkyl group. Such a process should be relatively facile, by an addition–elimination sequence, whereas a similar reaction involving a *saturated* alkyl group, as in FpMe, would be highly unfavorable.[7] This would explain the different reactivities of the two complexes. According to this scheme, similar behavior would be anticipated for Fp(allyl) and was in fact found: Fp(allyl) reacts with $P(OMe)_3$ over several hours in the dark, to give the substituted Fp′(allyl);[12] irradiation causes only gradual conversion into $(\eta^5\text{-}C_5H_5)Fe(CO)(\eta^3\text{-allyl})$,[13] while irradiation with added Fp_2 gives complete substitution in 10 min. It is noteworthy that there does not appear to be any direct photosubstitution of either FpCp or Fp(allyl), in contrast to the behavior of saturated alkyl analogues;[14] photolysis under conditions not favoring the chain path leads only to the above-mentioned CO-elimination products, ferrocene and $(\eta^5\text{-}C_5H_5)Fe(CO)(\eta^3\text{-allyl})$, respectively.

While the above provides strong support for the involvement of a radical-chain path, the specific scheme proposed and, in particular, the key step in which the unsaturated alkyl group is transferred from one metal to another remain to be demonstrated. Evidence for the alkyl transfer was obtained, under both photoactivation and dark substitution conditions, by the following crossover experiments.

(i) A solution containing equimolar amounts of FpCp and $[(\eta^5\text{-}C_5H_4CH_3)Fe(CO)_2]_2$ ($MeFp_2$) in benzene was irradiated for 1 h; the NMR showed about a 75% decrease in FpCp and much more complex patterns in the regions for both η^5-Cp ring and CH_3 protons. Chromatography on alumina gave three fractions, corresponding to ferrocene, FpCp, and Fp_2, respectively. However, ^1H NMR showed that *each* fraction contained both unsubstituted $(\eta^5\text{-}C_5H_5)$ and methyl-substituted $(\eta^5\text{-}C_5H_4CH_3)$ compounds. This indicates that the following transfer scheme is taking place:

$$MeFp_2 \overset{h\nu}{\rightleftarrows} 2MeFp\cdot \quad (5)$$

$$MeFp\cdot + FpCp \rightleftarrows MeFpCp + Fp\cdot \quad (6)$$

$$2Fp\cdot \underset{h\nu}{\rightleftarrows} Fp_2 \quad (7)$$

$$FpCp\ (+\ MeFpCp) \xrightarrow{h\nu} \text{ferrocenes} + 2CO \quad (8)$$

(ii) A benzene solution containing equimolar amounts of MeFpCp and Fp(allyl) was treated with $P(OMe)_3$. After 20 min no starting complexes remained; new NMR peaks were present corresponding to Fp′(allyl) as well as the product previously characterized in the reaction of FpCp with $P(OMe)_3$, $CpFe(CO)[P(OMe)_3][PO(OMe)_2]$.[1,15,16] Concentration and extraction with hexane left the latter, which was shown by NMR to be an approximately equimolar mixture of $(\eta^5\text{-}C_5H_5)Fe(CO)[P(OMe)_3][PO(OMe)_2]$ and $(\eta^5\text{-}C_5H_4CH_3)Fe(CO)[P(OMe)_3][PO(OMe)_2]$. This result demonstrates both the transfer of the η^1-Cp group between metal centers and the existence of a common intermediate in the substitution reactions of the two complexes.

Further support for the intermediacy of radicals can be found in reactions of FpCp with $PMePh_2$. In acetone, the major identifiable product is Fp_2;[1] in an acetone–chloroform mixed solvent,[18] the major product is $[(\eta^5\text{-}C_5H_5)Fe(CO)(PMePh_2)_2]Cl$, which was isolated as the PF_6 salt.[12] Abstraction of halogen from halocarbons is typical of metal-centered radicals,[19] including Fp·.[20] No FpCl, Fp′Cl, or

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