STRUCTURES OF AGGLOMERINS

YOSHIHIRO TERUI, RYUJI SAKAZAKI and JUN'ICHI SHOJI

Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka 553, Japan

(Received for publication March 22, 1990)

Structures of a series of new antibiotics, agglomerins A, B, C and D, which are active against a variety of anaerobic bacteria, were determined to be 1-acyl-2,3-dihydroxy-1,3-butadiene-1-carboxylic acid, (1→3)-γ-lactones, *i.e.*, 2-acyl-4-ylidenetetronic acids with different hydrocarbon chains in the acyl group. Their common chromophore exhibited tautomerism in solution. The relationship of their structure to the activity against anaerobes is discussed.

The present report describes the structure of a series of antibiotics, agglomerins A, B, C and D, isolated from the culture broth of a bacterial strain *Enterobacter agglomerans* PB-6042[1]. Several antibiotics mainly active against anaerobic bacteria are known: Bu-2313[2], thiotetromycin[3], clostomicins[4], luminamicin[5], and lustromycin[6]. In order to develop effective anti-anaerobic antibiotics, the correct structures of the active molecules must be known. Since agglomerins display activity against a variety of anaerobic bacteria, their structures were investigated and found to be 1-acyl-2,3-dihydroxy-1,3-butadiene-1-carboxylic acid, (1→3)-γ-lactone which exhibited tautomerism in solution. The compounds differed in the acyl group. The agglomerin congeners were acidic in nature, but they were unstable in the acidic state. Therefore, they were isolated as sodium salts and the structural analyses were conducted with these salts.

Agglomerin A (1)

The molecular formula of agglomerin A (sodium salt, **1a**) is $C_{15}H_{21}O_4Na$[1]. The IR (1735, 1670 and 1630 cm^{-1}) and UV nm 248 (ε 18,842) and 298 (ε 9,242) data[1] and the NMR data described later indicated that the substance probably has an unsaturated lactone and a conjugated ketone. In spite of the acidic property described above, there were no indications of a carboxylic acid or carboxylic acid sodium salt. As assigned in Tables 1~3, the ^{13}C and ^1H NMR data indicated the presence of a nonyl side chain connected to a quaternary carbon. Including this quaternary carbon, **1a** contained five quaternary carbon signals, δ97.1, 153.3, 173.3, 182.4 and 199.3 in $CDCl_3$-CD_3OD (15:1). In DMSO-d_6 these occurred at

Table 1. ^{13}C NMR data of **1a**, **2a**, **3a** and **4a** ($CDCl_3$-CD_3OD (15:1), at 24°C).

Carbon No.[a]	δ value, multiplicity			
	1a	**2a**	**3a**	**4a**
Chromophore				
1	173.3 s	173.3 s	173.3 s	173.2 s
2	97.1 s	97.1 s	97.1 s	97.0 s
3	182.4 s	182.5 s	182.4 s	182.4 s
4	153.3 s	153.4 s	153.5 s	153.6 s
5	90.0 t	89.9 t	89.8 t	89.7 t
6	199.3 s	199.0 s	199.3 s	199.1 s
Side chain				
1′	40.7 t	40.3 t	40.8 t	40.7 t
2′	25.2 t	25.3 t	25.3 t	25.4 t
3′	29.7 t	27.2 t	29.8 t	29.5 t
4′	29.7 t	129.1 d	29.8 t	27.25 t
5′	29.7 t	130.6 d	29.8 t	129.8 d
6′	29.4 t	27.3 t	29.8 t	130.1 d
7′	32.1 t	29.1 t	29.8 t	27.28 t
8′	22.7 t	29.8 t	29.4 t	29.1 t
9′	14.1 q	31.9 t	32.0 t	29.8 t
10′	—	22.7 t	22.7 t	29.8 t
11′	—	14.1 q	14.1 q	31.9 t
12′	—	—	—	22.7 t
13′	—	—	—	14.1 q

[a] With the numbering, see Fig. 6.

Table 2. ^{1}H NMR data of **1a**, **2a**, **3a** and **4a** ($CDCl_3$-CD_3OD (15:1), at 24°C).

Proton No.	δ value, (multiplicity, J=Hz)			
	1a	**2a**	**3a**	**4a**
Chromophore				
5 (a)	5.12 (br s)	5.14 (br s)	5.14 (br s)	5.12 (br s)
5 (b)	4.73 (br s)	4.82 (br s)	4.82 (br s)	4.79 (br s)
Side chain				
1′	2.75 (t, 7)	2.82 (t, 7)	2.81 (m)	2.82 (m)
2′	1.51 (m)	1.62 (m)	1.57 (m)	1.57 (m)
3′	1.2~1.4 (m)	2.10 (m)	1.2~1.4 (m)	1.2~1.4 (m)
4′	1.2~1.4 (m)	*ca.* 5.37 (m)	1.2~1.4 (m)	*ca.* 2.01 (m)
5′	1.2~1.4 (m)	*ca.* 5.37 (m)	1.2~1.4 (m)	*ca.* 5.34 (m)
6′	1.2~1.4 (m)	2.01 (m)	1.2~1.4 (m)	*ca.* 5.34 (m)
7′	1.2~1.4 (m)	1.2~1.4 (m)	1.2~1.4 (m)	*ca.* 2.01 (m)
8′	1.2~1.4 (m)	1.2~1.4 (m)	1.2~1.4 (m)	1.2~1.4 (m)
9′	0.87 (t, 7)	1.2~1.4 (m)	1.2~1.4 (m)	1.2~1.4 (m)
10′	—	1.2~1.4 (m)	1.2~1.4 (m)	1.2~1.4 (m)
11′	—	0.88 (t, 7)	0.88 (t, 7)	1.2~1.4 (m)
12′	—	—	—	1.2~1.4 (m)
13′	—	—	—	0.88 (t, 7)

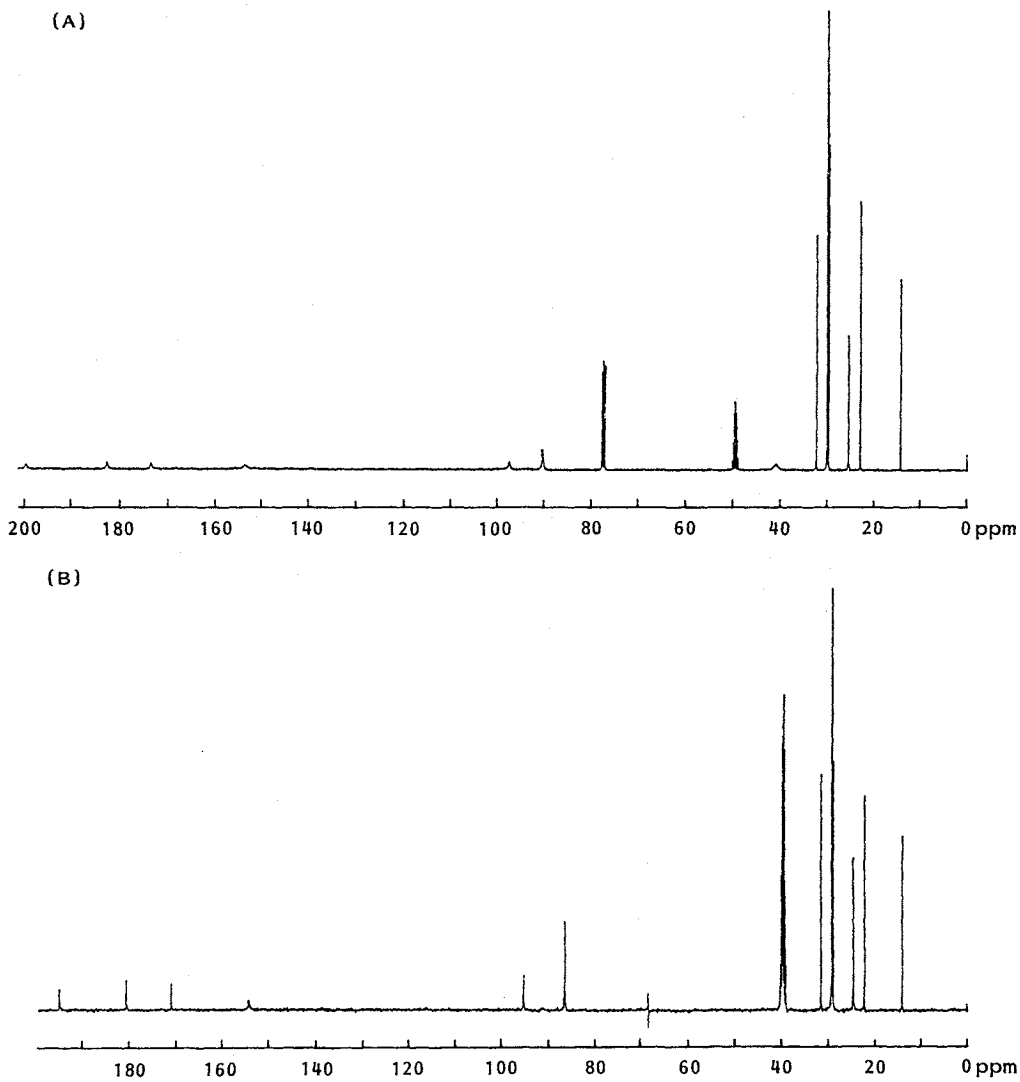
δ 95.0, 154.0, 170.6, 180.3 and 194.6. A methylene carbon gave rise to a signal at δ 90.0 in the mixed solvent or at δ 86.2 in DMSO-d_6 independent of the side chain. The protons of this methylene occur at δ 5.12 and 4.73 in the mixed solvent and at δ 4.81 and 4.58 in DMSO-d_6. Since the side chain does not contain the sodium and oxygens, these together with the quaternary carbons and the methylene are available for the formulation of the chromophore. Although the methylene proton signals appeared as a pair of broad singlets, a small coupling constant (*ca.* J=2 Hz) between them was evidenced by the decrease of the line width in spin decoupling experiments. Line broadening was also observed for some of the carbon signals, particularly the isolated methylene and quaternary carbons and one of the methylenes of the side chain. In the mixed solvent, $CDCl_3$-CD_3OD (15:1), the carbon signals were broader (see Fig. 1). At a higher temperature, the signals sharpened. These observations suggest a chemical shift exchange broadening due to exchange among isomers such as tautomers or conformers. As the material was unstable at elevated temperatures, the ^{13}C-^{1}H correlation was examined at room temperature in DMSO-d_6 solution. Observations of carbon signals under selective irradiation of the isolated methylene protons (δ 4.81 and 4.58) provided evidence that the quaternary carbons with signals at δ 154.0 and 180.3 were located near the isolated methylene. Selective irradiations at the most down-field methylene protons and the secondary down-field

Table 3. ^{13}C and ^{1}H NMR data of **1a** and **2a** (DMSO-d_6 at 24°C).

Carbon No.	δ value (^{13}C), multiplicity and (related δ (^{1}H))	
	1a	**2a**
Chromophore		
1	170.6 s	170.5 s
2	95.0 s	95.0 s
3	180.3 s	180.3 s
4	154.0 s	154.0 s
5	86.2 t (4.81, 4.58)	86.2 t (4.80, 4.56)
6	194.6 s	194.3 s
Side chain		
1′	39.5 t (2.65)	39.3 t (2.66)
2′	24.5 t (1.47)	24.5 t (1.52)
3′	28.9 t (*ca.* 1.24)	26.57 t (1.99)
4′	29.0 t (*ca.* 1.24)	129.8 d (5.33)
5′	29.0 t (*ca.* 1.24)	129.4 d (5.33)
6′	28.7 t (*ca.* 1.24)	26.61 t (1.97)
7′	31.3 t (*ca.* 1.24)	29.1 t (1.29)
8′	22.1 t (*ca.* 1.24)	28.3 t (1.25)
9′	13.9 q (0.86)	31.1 t (1.23)
10′	—	22.0 t (1.25)
11′	—	13.9 q (0.85)

Fig. 1. ^{13}C NMR spectra of agglomerin A sodium salt (**1a**).

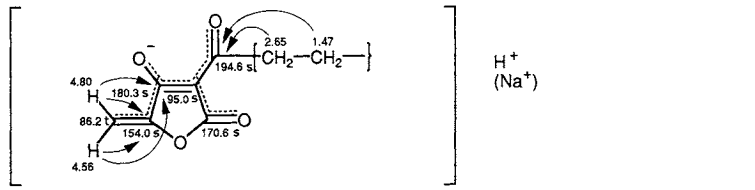
(A) In $CDCl_3$-CD_3OD (15:1) at 24°C. (B) In DMSO-d_6 at 24°C.

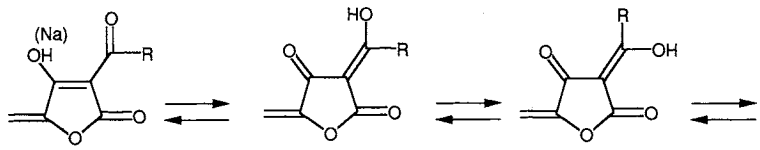


methylene protons in the side chain (δ 2.65 (t) and 1.47 (m), respectively) indicated that the quaternary carbon bearing the side chain had the δ value 194.6. Furthermore, the molecular formula indicated the degree of unsaturation of **1a** to be 5. These data led us to formulate a structure having a chromophore consisting of the unsaturated lactone and conjugated ketone, capable of tautomerism as shown in Fig. 2.

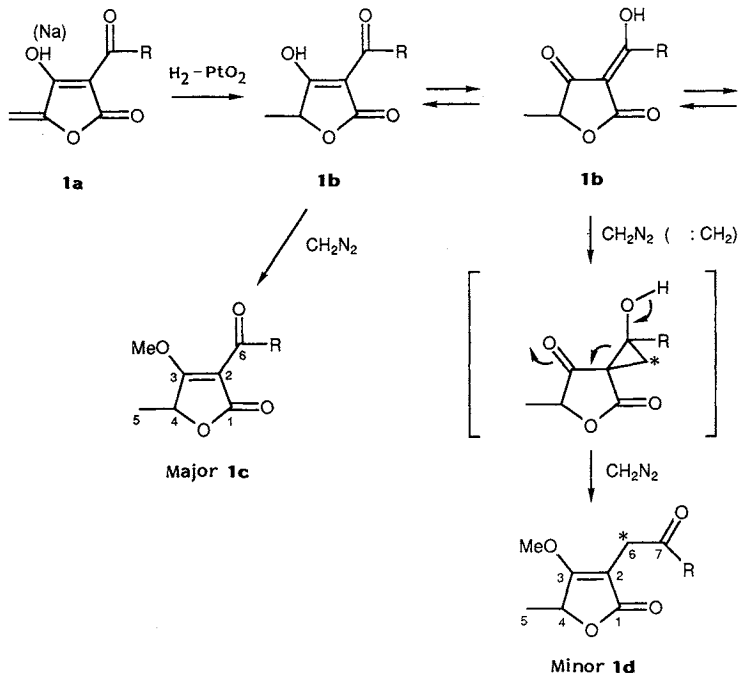
Derivatives of **1a** were prepared, to confirm this structure. At first, **1a** was hydrogenated with platinum oxide catalyst in order to convert the exo-methylene to a methyl group, and the expected compound (**1b**) was obtained. The derivative **1b** also exhibited the broad carbon signals of the chromophore and the adjacent side chain methylene when spectra were recorded in the mixed solvent $CDCl_3$-CD_3OD (15:1). In DMSO-d_6, **1b** exhibited signals corresponding to the three tautomers at room temperature. These signals coalesced at high temperature. This indicates that the exchange rate between tautomers of the hydrogenated product **1b** is slower than that of tautomers of **1a** (see Scheme 1).

Fig. 2. Structure of the chromophore.





Scheme 1.



To obtain a derivative unable to exist as a mixture of tautomers, **1b** was methylated using diazomethane. The reaction gave two products, a major and a minor. Since separation of the components was difficult, a mixture of the two components was analyzed by NMR. All the ^{1}H and ^{13}C NMR signals were sharp and showed no significant changes in temperature variation experiments. The structure of these products was determined by HETCOR experiments[7] focusing on the one-bond and long-range ^{13}C-^{1}H correlation and by selective decoupling experiments. The major and minor components have the structures **1c** and **1d** presented in Scheme 1, respectively. The HETCOR spectrum focusing on the long-range correlation is presented in Fig. 3, and the key correlation leading to the structures are illustrated in Fig. 4. The major product **1c** needs no explanation. We postulate the minor product **1d** to arise *via* the reaction process shown in Scheme 1; addition of carbene originating from diazomethane on a double bond of the tautomer

Fig. 3. Long-range ^{13}C-^{1}H HETCOR spectrum on a mixture of derivatives **1c** and **1d**.

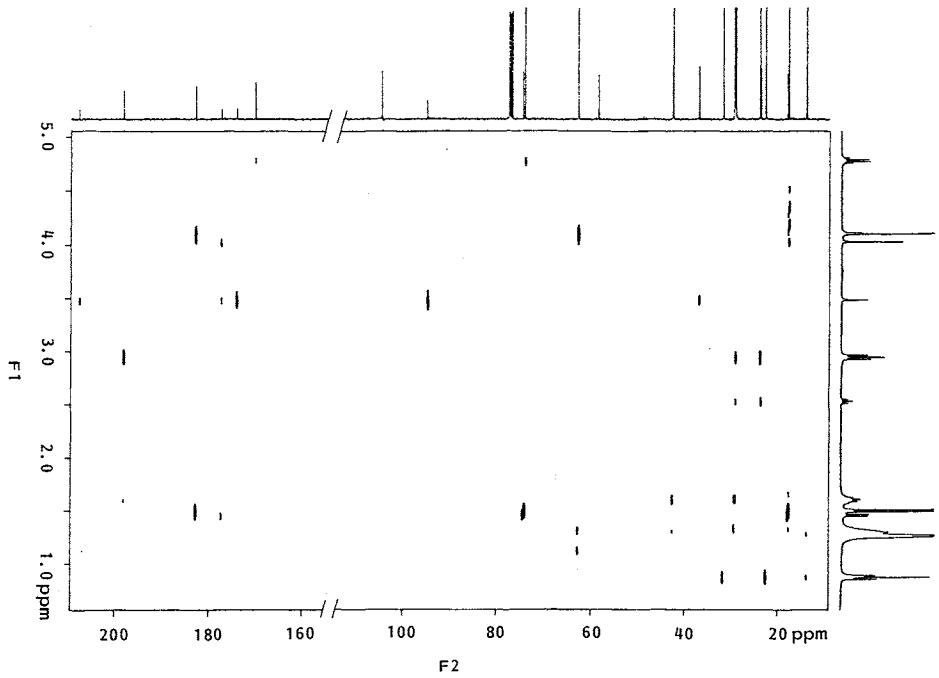
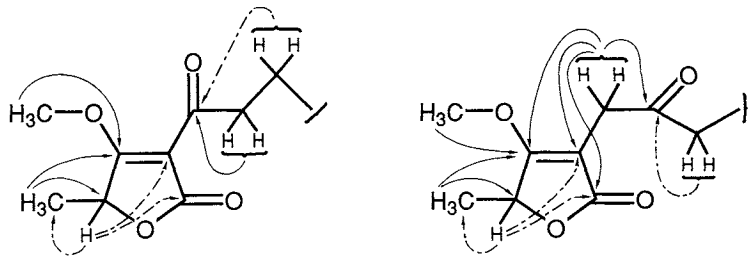


Fig. 4. The key C-H correlation leading to structures **1c** and **1d**.



⟶, from HETCOR; ⟶, from selective decoupling.

formed a cyclopropyl intermediate, and methylation after rearrangement of the intermediate yielded the minor product. The NMR signal assignments of the products are listed in Table 4. Chemical evidence confirmed the structure of the starting material, agglomerin A.

Agglomerins B, C, and D (**2**, **3** and **4**)

The UV and IR data[1] indicate that all the agglomerin congeners (sodium salt, **1a**, **2a**, **3a** and **4a**) probably contain a common chromophore and this was confirmed by the NMR data listed in Tables 1~3 which show common NMR signals assigned to the chromophore. The differences were in the side chain part.

Agglomerin B contained two olefinic carbons in the side chain (δ 130.6 (d) and 129.1 (d) in the mixed solvent or δ 128.8 (d) and 129.4 (d) in DMSO-d_6). Decoupling experiments in ^{1}H NMR spectroscopy and ^{13}C-^{1}H HETCOR spectroscopy clarified the presence of a 4-undecenyl side chain, $(CH_2)_3-CH=CH-(CH_2)_5-CH_3$, (see the assignments in Tables 1~3). The signal of a methylene carbon adjacent to the

chromophore overlaps with the signals of the solvent DMSO-d_6. The HETCOR spectrum shown in Fig. 5, however, confirmed the presence of the carbon. The configuration of the olefin was determined to be *Z* from the δ values of the methylene carbons adjacent to the olefinic part, δ 27.2 and 27.3 in the mixed solvent or δ 26.57 and 26.61 in DMSO-d_6; our unpublished data on the known olefinic compounds showed the corresponding carbon signal of the *Z* type (*i.e. cis*-type) molecule near δ 27 and that of *E* type (*i.e. trans*-type) near δ 32. These findings clarified the structure of **2**.

Agglomerin C has no olefinic carbons in the side chain. Compared with congener A, an increase of two methylene carbons (δ 28.8 t ($\times$ 2) in the mixed solvent) and of the corresponding four protons (δ *ca.* 1.24 (m)) were found in congener C; integration experiments confirmed this. Thus, the presence of an undecyl side chain in **3** was established.

Agglomerin D, like agglomerin B, contained two olefinic carbons in the side chain (δ 130.1 (d) and 129.8 (d) in the mixed solvent), but it differed from **2** by having two more methylenes (δ 29.5 (t) and 29.8 (t)). This was confirmed by integration experiments in both ^{1}H and ^{13}C spectroscopies. Since the carbon exhibiting the δ 29.5 is located between the carbons assigned to 2′ in the side chain (δ 25.4) and to one of

Table 4. ^{13}C and ^{1}H NMR data of **1c** and **1d** ($CDCl_3$ at 24°C).

Carbon No.[a]	δ value (^{13}C), multiplicity (related δ (^{1}H) and multiplicity)	
	1c	**1d**
Chromophore		
1	170.0 s	173.9 s
2	104.4 s	94.7 s
3	182.7 s	172.2 s
3-OMe	62.8 q (4.10 s)	58.6 q (4.03 s)
4	74.1 d (4.79 q)	74.5 d (4.77 q)
5	17.8 q (1.50 d)	18.1 q (1.46 d)
6	197.9 s	37.1 t (3.49 s)
7	—	207.5 s
Side chain		
1′	42.6 t (2.95 t)	42.7 t (2.53 t)
2′	23.9 t (1.61 m)	23.7 t (1.60 m)
3′	29.2 t (1.30 m)	29.1 t (1.30 m)
4′	29.5 t (1.26 m)	29.4 t (1.26 m)
5′	29.5 t (1.26 m)	29.5 t (1.26 m)
6′	29.3 t (1.26 m)	29.3 t (1.26 m)
7′	31.9 t (1.26 m)	31.9 t (1.26 m)
8′	22.7 t (1.30 m)	22.7 t (1.30 m)
9′	14.1 q (0.88 t)	14.1 q (0.88 t)

[a] With the numbering, see Scheme 1.

Fig. 5. One-bond ^{13}C-^{1}H HETCOR spectrum of agglomerin B sodium salt (**2a**).

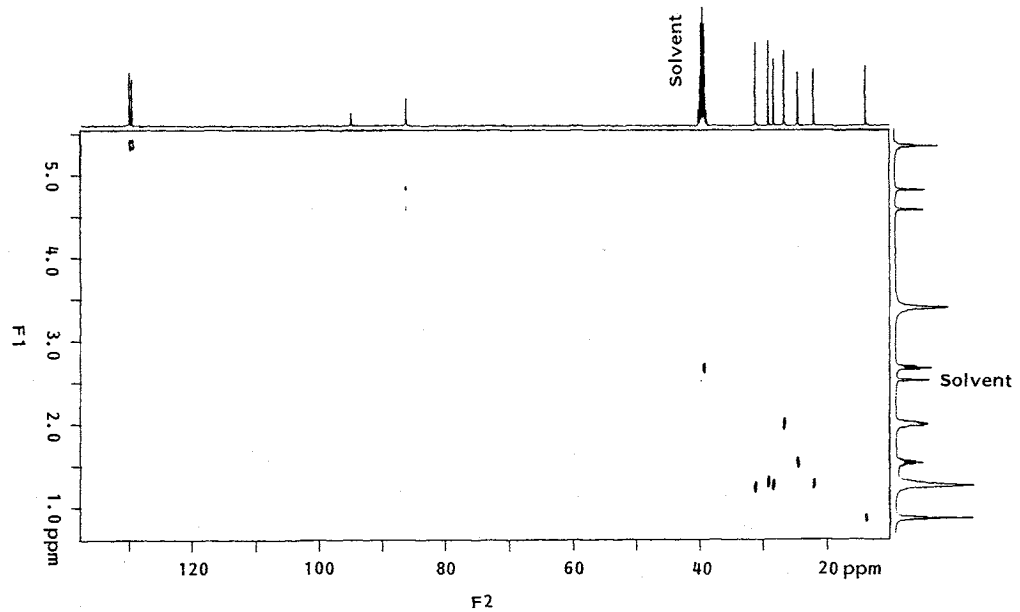
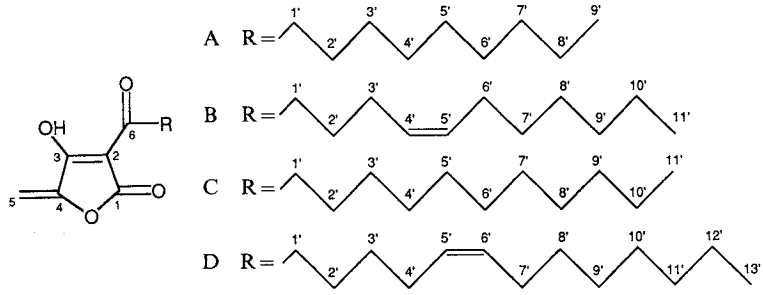


Fig. 6. Structures of agglomerins A, B, C, and D.



the methylenes adjacent to the olefinic part (*i.e.* 4′, δ 27.25) from the relaxation time (T_1) behavior[8], we concluded that a 5-tridecenyl side chain, $(CH_2)_4-CH=CH-(CH_2)_6-CH_3$, was present; for the numbering of the methylene carbons, see Fig. 6. The T_1 values of the methylene carbons 2′, 3′, 4′, and those of the olefinic methine carbons 5′ and 6′ measured at 27°C were 0.941, 1.037, 1.077, and 1.573 and 2.109 seconds, respectively. Including another one adjacent to the olefinic part (*i.e.* 7′, δ 27.28), the other methylene carbons in the side chain exhibited a T_1 value larger than those of the above methylenes with the exception of C-1′. A reliable T_1 value for C-1′ could not be determined because of line broadening. The occurrence of broadening is understandable since the tautomerism occurs in the chromophore part, to which C-1′ is directly connected. T_1 analysis was also very useful for assignments of the side chain carbons of the other congeners.

These findings elucidate the structures of agglomerin congeners presented in Fig. 6, with support from the results of SI mass spectrometries[1]. The acidic property of the agglomerins is ascribable to the resonance effect in the anionic form of the chromophore part, which can stabilize the anion molecule and therefore facilitate release of the hydroxy proton from the agglomerins (see Fig. 2).

As described above, agglomerins were determined to be 1-acyl-2,3-dihydroxy-1,3-butadiene-1-carboxylic acid, (1→3)-γ-lactone, *i.e.*, 2-acyl-4-ylidenetetronic acid. Although there are a good many 4-ylidenetetronic acid analogues from natural sources[9], we know of few 2-acyl-4-ylidenetetronic acids. Dehydrocarolic acid was regarded as the first example of this series[10], but a hydrated form of the substance corresponds to this[11]. A polyether antibiotic tetronomycin contains the 2-acyl-4-ylidenetetronic acid moiety as one of the structural elements of the molecule[12].

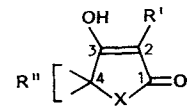
On the Structure Related to the Activity against Anaerobic Bacteria

As presented in the preceding paper[1], agglomerins displayed activity against a variety of anaerobes. The derivative **1b** displayed similar activity. Furthermore, macrolide antibiotics PA-46101 A and B isolated from the culture broth of a strain of *Streptomyces* sp. exhibited activity against anaerobes[13]. They also contained the moiety belonging to the tetronic acid type, like the **1b**.

In the report[3] on thiotetromycin which is active against *Bacteroides fragilis*, ŌMURA *et al.* stated that "the compounds containing tetramic acid, thiotetronic acid or a related moiety may be considered to exhibit selective activity against *B. fragilis*." The structures are known of Bu-2313 analogues[14,15] which contain a tetramic acid moiety or a related moiety and exhibit activity against anaerobes including *B. fragilis*. These data and our findings indicate that the antibiotics containing the T moiety shown in Fig. 7 can exhibit activity against anaerobes, although the selectivity differs depending upon the difference in R′, R″, and X. The T includes 4-ylidene analogues.

Of a series of anti-anaerobic antibiotics, clostomicins seem to be different from the above type. Structures of tiacumicins[16], which were regarded to be identical with clostomicins, have been reported. They do not contain the T moiety, having instead, a substituted phenol group adjacent to the ester carbonyl. The group also can exhibit the acidic property, and its arrangement, *i.e.*, the hydroxy group on the double bond (enol group) and the adjacent carbonyl, is quite similar to that of agglomerins.

Fig. 7. The T moiety effective for activity against anaerobes.



T X=S, O, N or C *etc.*

Coloradocin has been reported to be identical with the anti-anaerobic antibiotic luminamicin[17]. It contains a maleic anhydride moiety somewhat similar to the T moiety. However, we found no group exhibiting the acidic property. Since luminamicin has the acidic property[5], we withhold discussion of it here using the reported structure.

Based on the above observations, we consider that the moiety belonging to the tetronic acid type (*i.e.*, the T in the general formula) or moieties having a function similar to that of the T are effective for activity against anaerobes.

Experimental

Spectral Measurements

The ^{1}H and ^{13}C NMR spectra were recorded with a Varian XL-400 spectrometer operating at 399.948 MHz for ^{1}H and at 100.579 MHz for ^{13}C. In HETCOR experiments, the ^{1}J and ^{n}J values, 140 and 7 Hz, were used to detect the one-bond and long-range C-H correlation. In all the measurements, TMS was used as an internal reference.

Materials and Methods

On the Derivatives

Hydrogenation of Agglomerin A Sodium Salt: In a 20-ml Erlenmeyer flask, agglomerin A sodium salt (50 mg) was dissolved in 8 ml of methanol, and 35 mg of platinum oxide was added. After hydrogenation for 2 hours (H_2, 21 ml), platinum oxide was removed by filtration. The filtrate was concentrated under reduced pressure and subjected to preparative TLC; Merck precoated silica gel plates (F 254 (250), ×6), EtOAc-MeOH (9:1). The UV-sensitive zone (Rf 0.24) was collected and extracted with $CHCl_3$-MeOH (1:1). The extract was concentrated under reduced pressure and the residue was dissolved in EtOAc. After washing with dilute aq $NaHCO_3$ and then with water, the organic layer was dried over Na_2SO_4 and then concentrated. To the concentrated solution, petroleum ether was added, and 22 mg of colorless precipitate **1b** was obtained. NMR data of **1b** (in $CDCl_3$-CD_3OD (15:1) at 24°C) are: ^{1}H δ 4.47 (br, 4-H), 2.81 (br, 1'-H_2), 1.54 (br, 2'-H_2), 1.39 (br, 5-H_3), 1.24 (s-like, 3'~8'-H_2) and 0.87 (t, J=7 Hz, 9'-H_3); ^{13}C δ 200.5 (br s, C-6), 180.2 (br s, C-3), 174.3 (br s, C-1), 96.8 (br s, C-2), 77.3 (br d, C-4), 39.2 (br t, C-1'), 32.0 (t, C-7'), 29.7 (t, C-4' and 5'), 29.6 (t, C-3'), 29.4 (t, C-6'), 25.1 (t, C-2'), 22.7 (t, C-8'), 17.2 (br q, C-5) and 14.1 (q, C-9').

Methylation of the Hydrogenated Product **1b**: According to the procedure described above, 60 mg of **1a** was hydrogenated and the extract from the Rf 0.24 zone in TLC was concentrated. The residue was dissolved in 20 ml of EtOAc and washed with 15 ml of aq HCl (pH 3) and then with water. The EtOAc layer was dried with Na_2SO_4 and then filtered. Under ice-cooling, some excess of methylation reagent (CH_2N_2-ether) was added to the filtrate using the yellow color of the reagent as an indicator. After 10 minutes, the solution was concentrated under reduced pressure and the residue was subjected to HPLC; Nucleosil 10 C_{18} column (20×250 mm) and the mobile phase CH_3CN-20 mM Na_2HPO_4 (pH 7.0) (6:4). The fractions exhibiting a peak at the Rt 22.3 minutes were collected and concentrated under reduced pressure. The residue was extracted with EtOAc. The EtOAc layer was washed with water and dried over

Na_2SO_4. Evaporation of the solvent gave 22 mg of oily substance, a mixture of **1c** and **1d**. Integration in ^1H NMR determined the ratio of **1c** and **1d** to be 4 : 1. SI-MS confirmed M + H peaks 283 and 297 assigned to **1c** and **1d**, respectively.

Acknowledgments

The authors are indebted to Drs. M. MATSUMOTO and T. YOSHIDA of their laboratory for providing useful data on antibacterial activity and to Drs. Y. TAKAYAMA, J. KIKUCHI and F. HAYASHI for assistance with NMR measurements.

References

1) SHOJI, J.; R. SAKAZAKI, T. HATTORI, K. MATSUMOTO, N. UOTANI & T. YOSHIDA: Isolation and characterization of agglomerins A, B, C and D. J. Antibiotics 42: 1729~1733, 1989
2) TSUKIURA, H.; K. TOMITA, M. HANADA, S. KOBARU, M. TSUNAKAWA, K. FUJISAWA & H. KAWAGUCHI: Bu-2313, a new antibiotic complex active against anaerobes. I. Production, isolation and properties of Bu-2313 A and B. J. Antibiotics 33: 157~165, 1980
3) ŌMURA, S.; Y. IWAI, A. NAKAGAWA, R. IWATA, Y. TAKAHASHI, H. SHIMIZU & H. TANAKA: Thiotetromycin, a new antibiotic. Taxonomy, production, isolation, and physicochemical and biological properties. J. Antibiotics 36: 109~114, 1983
4) ŌMURA, S.; N. IMAMURA, R. ŌIWA, H. KUGA, R. IWATA, R. MASUMA & Y. IWAI: Clostomicins, new antibiotics produced by *Micromonospora echinospora* subsp. *armeniaca* subsp. nov. I. Production, isolation, and physico-chemical and biological properties. J. Antibiotics 39: 1407~1412, 1986
5) ŌMURA, S.; R. IWATA, Y. IWAI, S. TAGA, Y. TANAKA & H. TOMODA: Luminamicin, a new antibiotic. Production, isolation and physico-chemical and biological properties. J. Antibiotics 38: 1322~1326, 1985
6) TOMODA, H.; R. IWATA, Y. TAKAHASHI, Y. IWAI, R. ŌIWA & S. ŌMURA: Lustromycin, a new antibiotic produced by *Streptomyces* sp. J. Antibiotics 39: 1205~1210, 1986
7) BAX, A. & G. A. MORRIS: An improved method for heteronuclear chemical shift correlation by two-dimensional NMR. J. Magn. Reson. 42: 501~505, 1981
8) METCALFE, J. C.; N. J. M. BIRDSALL, J. FEENEY, A. G. LEE, Y. K. LEVINE & P. PARTINGTON: ^{13}C NMR spectra of lecithin vesicles and erythrocyte membranes. Nature 233: 199~201, 1971
9) PATTENDEN, G.: Natural 4-ylidenebutenolides and 4-ylidenetetronic acids. Progress in Chemistry of Organic Natural Products 35: 133~198, 1978
10) BRACKEN, A. & H. RAISTRICK: Strudies in the biochemistry of microorganisms. 75. Dehydrocarolic acid, a metabolic product of *Penicillium cinerascens* Biourge. Biochem. J. 41: 569~575, 1947
11) JACOBSEN, J. P.; T. REFFSTRUP, R. E. COX, J. S. E. HOLKER & P. M. BOLL: Revision of the structures of the naturally occurring acyl tetronic acids: Dehydrocarolic acid, terrestric acid and carlic acid. Tetrahedron Lett. 1978: 1081~1084, 1978
12) KELLER-JUSLÉN, C.; H. D. KING, M. KUHN, H.-R. LOOSLI, W. PACHE, T. J. PETCHER, H. P. WEBER & A. VON WARTBURG: Tetronomycin, a novel polyether of unusual structure. J. Antibiotics 35: 142~150, 1982
13) MATSUMOTO, M.; Y. KAWAMURA, Y. YOSHIMURA, Y. TERUI, H. NAKAI, T. YOSHIDA &. J. SHOJI: Isolation, characterization and structures of PA-46101 A and B. J. Antibiotics 43: 739~747, 1990
14) TSUNAKAWA, M.; S. TODA, T. OKITA, M. HANADA, S. NAKAGAWA, H. TSUKIURA, T. NAITO & H. KAWAGUCHI: Bu-2313, a new antibiotic complex active against anaerobes. II. Structure determination of Bu-2313 A and B. J. Antibiotics 33: 166~172, 1980
15) TODA, S.; S. NAKAGAWA, T. NAITO & H. KAWAGUCHI: Bu-2313, a new antibiotic complex active against anaerobes. III. Semi-synthesis of Bu-2313 A and B, and their analogs. J. Antibiotics 33: 173~181, 1980
16) HOCHLOWSKI, J. E.; S. J. SWANSON, L. M. RANFRANZ, D. N. WHITTERN, A. M. BUKO & J. B. MCALPINE: Tiacumicins, a novel complex of 18-membered macrolides. II. Isolation and structure determination. J. Antibiotics 40: 575~588, 1987
17) RASMUSSEN, R. R.; M. H. SCHERR, D. N. WHITTERN, A. M. BUKO & J. B. MCALPINE: Coloradocin, an antibiotic from a new *Actinoplanes*. II. Identity with luminamicin and elucidation of structure. J. Antibiotics 40 : 1383~1393, 1987