

Synthesis and Biological Activities of the *Z* Isomers of Carbapenem Antibiotics

Setsuo Harada,* Shigetoshi Tsubotani, Mitsuko Asai, Kenji Okonogi, and Masahiro Kondo

Central Research Division, Takeda Chemical Industries, Ltd., Jusohomachi-2, Yodogawa-ku, Osaka 532, Japan.

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Naturally occurring carbapenem antibiotics having a double bond in the side chain, when refluxed in chloroform containing quarternary alkylammonium halides, were converted into *Z* isomers in high yields. The mechanism of this new equilibration involves intramolecular proton transfer from the carboxylic acid to the carbon α to the sulfur atom in the side chain as shown by deuterium-labeling experiments. Some *Z* isomers showed stronger protective effects in mice infected by *Escherichia coli* O-111 and more potent synergistic activities with cefotiam in mice infected by *Proteus vulgaris* GN4815 than did the naturally occurring *E* isomers. The decomposition rates of the *Z* isomers in mouse kidney homogenates were about 3-fold slower than those of the *E* isomers.

In previous papers, we described the isolation and chemical structures of new carbapenem antibiotics, C-19393 S₂ (1), H₂ (2), and E₅ (3).¹⁻³ These antibiotics have strong, broad antimicrobial spectra^{2,4} and β -lactamase inhibitory activities^{5,6} as good as the known 5,6-*cis*-carbapenem antibiotics, olivanic acids, MM 17880, MM 13902 (4), and MM 4550 (5),⁷⁻⁹ and epithienamycins A, B (6), C,

the low-field shift in 8 was not the result of a steric difference between *Z* and *E* isomers or the anisotropy of the oxide.

Since 8% of 1 was recovered when it was submitted to this reaction and 9% of 8 was converted to 1 when 8 was subjected to the same condition, this *Z* isomerization can be characterized as an equilibrium reaction. Table I also

Table I. Reaction Conditions and Yields of *Z,E* Isomerization in 1^a

column	ammonium halide ^b	solvent	temp, °C	time, h	yield, %		
					8	1	sum
I	TOMAC	CHCl ₃	ref 1		85	13	98
	TPAC	CH ₂ Cl ₂	ref 6		77	23	100
	TPAB	CHCl ₃	ref 1		38	38	76
	TDMBAC	CHCl ₃	ref 2		49	27	76
	HDMBAC	CH ₂ Cl ₂	ref 16		76	25	101
	TBAC	CH ₂ Cl ₂	ref 4		0.3	16	16
	II	TOMAC	CH ₂ Cl ₂	ref 8		92	8
TOMAC		CH ₂ ClCH ₂ Cl	60-62	0.5	61	14	75
TOMAC		CH ₂ ClCH ₂ Cl	40-42	3	50	18	68
TOMAC		CCl ₃ CH ₃	60-62	3	27	53	80
TOMAC		CCl ₄	60-62	2	13	77	90

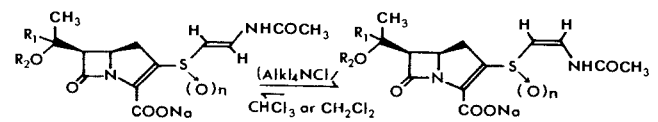
^a One micromole of 1 in H₂O (5 mL) was extracted with 25 μ mol of ammonium halide in the organic solvent (5 mL). The amounts of 8 and 1 in the reaction mixture were determined by HPLC. ^b TPAC = tetra-*n*-pentylammonium chloride; TPAB = tetra-*n*-pentylammonium bromide; TDMBAC = *n*-tetradecyldimethylbenzylammonium chloride; HDMBAC = *n*-hexadecyldimethylbenzylammonium chloride; TBAC = tetra-*n*-butylammonium chloride.

and D (7).¹⁰ However, all of these showed weak or undetectable protective effects in our screening system, except when administered intraperitoneally.

shows the maximum yields with various combinations of reaction conditions. TOMAC was the best of the reagents tested (in column I). When tetrabutylammonium chloride was used, both extraction and reaction yields were very poor. The reactions with other hydrocarbon chlorides (column II) gave clear-cut solvent effects; *Z* isomerization was predominant in dichloromethane and chloroform, but *E* isomerization was predominant in carbon tetrachloride. In 1,2-dichloroethane or 1,1,1-trichloroethane, *Z* or *E* isomerization did not proceed as much as in dichloromethane or carbon tetrachloride. Because of the lack of a sulfated group, about 250 equiv of TOMAC was necessary to extract 2. However, the reaction proceeded easily to give a *Z* isomer of 2 (11) in 92% yield, based on HPLC detection. These two reaction conditions were applied to synthesize the *Z* isomers of 5,6-*cis*-carbapenem antibiotics² in high yields, as shown in Table II. In addition, compound 7, having a 5,6-*trans* orientation, gave a *Z* isomer (18). Moreover, the stereoisomers at the sulfoxide groups of 1 and 2 (19 and 20)³ also afforded the corresponding *Z* isomers (21 and 22). Table II shows their physicochemical properties.

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Table II. Physicochemical Properties of Z Isomers in 5,6-cis-Carbapenem Antibiotics



starting material (E isomer)	R ₁	R ₂	n	config ^b	product (Z isomer)	yield, ^c %	t _R , ^d min (% of MeOH)	UV λ _{max} (H ₂ O), nm (ε)	IR (KBr) ν _{max} , cm ⁻¹ (β-CO)	¹ H NMR (D ₂ O) δ (100 MHz)	
										8-CH ₃	CH=
1	CH ₃	SO ₃ Na	1	R	8	92	5.9 (8)	241 (16 100), 291 (11 200)	1770	1.66, 1.73	5.90, 7.39
2	CH ₃	H	1	R	11	92	7.5 (15)	241 (14 300), 293 (9970)	1760	1.34, 1.45	5.88, 7.40
12 ^e	CH ₃	SO ₃ Na	0		13	92	7.4 (8)	232 (13 000), 307 (12 800)	1775	1.60, 1.68	5.72, 7.20
9	CH ₃	H	0		10	92	6.0 (20)	232 (15 700), 308 (14 500)	1755	1.28, 1.40	5.72, 7.17
19 ^e	CH ₃	SO ₃ Na	1	S	21	88	1.8 (8)	237 (13 300), 292 (9050)	1765	1.65, 1.68	5.85, 7.30
20 ^e	CH ₃	H	1	S	22	83	4.2 (8)	237 (15 600), 290 (10 000)	1765	1.32, 1.41	5.71, 7.27
5	H	SO ₃ Na	1	R	14	88	4.8 (4)	240 (14 600), 292 (10 200)	1770	1.56	5.78, 7.40
3	H	H	1	R	15	78	5.5 (8)	238 (12 100), 291 (8390)	1770	1.38	5.90, 7.40
4	H	SO ₃ Na	0		16	95	5.2 (4)	228 (13 200), 307 (8130)	1750	1.53	5.74, 7.21
6	H	H	0		17	95	7.5 (8)	226 (11 300), 306 (9430)	1760	1.35	5.74, 7.20
7 ^a	H	H	0		18 ^a	93	13.5 (10)	231 (13 700), 308 (12 100)	1755	1.38	5.70, 7.13

^a 5,6-Trans orientation. ^b Configuration at the sulfoxide. ^c HPLC detection. ^d Waters Associates, Radial Pak A/MeOH-0.02 M phosphate buffer (pH 6.3), 2 mL/min. ^e Reference 3.

Table III. Antimicrobial Spectra of 5,6-cis-Carbapenem Antibiotics^a

organism	MIC, μg/mL													
	2	11	20	22	9	10	6	17	1	8	12	13	4	16
<i>S. aureus</i> 308 A-1	0.78	1.56	3.13	3.13	1.56	0.39	0.39	0.2	12.5	6.25	6.25	6.25	0.78	0.78
<i>E. coli</i> T-7	1.56	6.25	25	25	3.13	6.25	>100	>100	12.5	12.5	6.25	100	6.25	25
<i>C. freundii</i> IFO 12681	0.2	1.56	3.13	12.5	0.2	0.78	1.56	1.56	12.5	25	6.25	50	3.13	12.5
<i>K. pneumoniae</i> DT	0.78	3.13	1.56	12.5	0.39	0.78	0.39	0.39	12.5	50	6.25	50	0.78	1.56
<i>E. cloacae</i> IFO 12937	0.78	6.25	25	50	1.56	3.13	>100	12.5	25	50	12.5	100	12.5	50
<i>S. marcesc</i> IFO 12648	0.78	3.13	6.25	25	1.56	3.13	3.13	6.25	12.5	50	12.5	100	1.56	12.5
<i>P. vulgaris</i> IFO 3988	3.13	25	12.5	100	3.13	3.13	3.13	0.78	50	>100	50	100	0.2	0.78
<i>P. mirabilis</i> IFO 3849	1.56	12.5	12.5	50	3.13	3.13	0.78	0.78	50	>100	50	100	0.2	0.39
<i>P. morganii</i> IFO 3168	1.56	12.5	25	100	1.56	3.13	1.56	1.56	50	100	50	100	0.78	3.13
<i>P. aeruginosa</i> IFO 3455	6.25	>100	25	>100	12.5	50	100	25	>100	>100	>100	>100	3.13	6.25
<i>A. calcoacet.</i> IFO 13006	0.78	50	12.5	25	6.25	25	3.13	12.5	25	>100	>100	>100	12.5	25

^a Medium: Trypticase soy agar (BBL Microbiology System, Cockeysville, ME); inoculum size, one loopful of bacterial suspension (10⁸ cfu/mL).

Scheme I

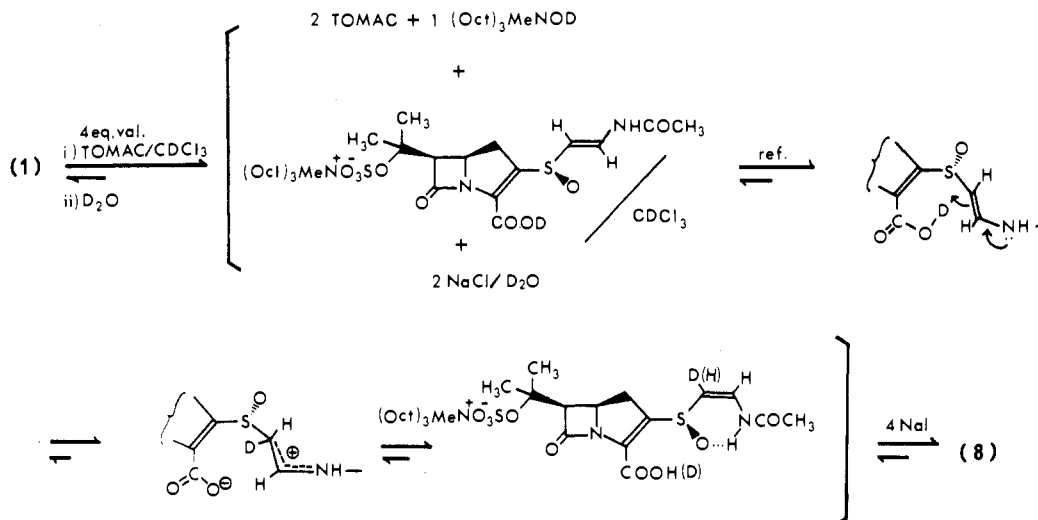


Table IV. Relationships between Protective Effects and Stability in Mouse Kidney Homogenates of 5,6-*cis*-Carbapenem Antibiotics

antibiotic	MIC, ^a μg/mL	ED ₅₀ , ^b mg/kg	T _{1/2} , ^c min
2	≤ 0.1	20	17
11	≤ 0.1	1.56	45
9	≤ 0.1	> 50	8
10	0.2	> 50	19
20	1.56	28.1	90
22	6.25		> 250
6	0.39	> 50	12
17	0.2	17.7	40
1	6.25	> 100	22
8	6.25	> 50	75
12	3.13	> 50	7
13	12.5	> 50	19
19			37
21			~ 275
4	≤ 0.1	> 50	21
16	0.39	> 50	42

^a Test organism: *E. coli* O-111. ^b Intraperitoneal infection with *E. coli* O-111; route, sc. ^c Half-life in 10% mouse kidney homogenate.

Subsequently, we found that the carbapenem antibiotics can be converted to the Z isomers with quaternary alkylammonium halides, which are known as phase-transfer reagents. This paper presents a new Z,E isomerization method of carbapenem antibiotics that yields Z isomers with improved *in vivo* biological activities.

Chemistry. The disodium salt of 1, extracted with dichloromethane containing 4 equiv of tri-*n*-octylmethylammonium chloride (TOMAC), was refluxed for 8 h and afforded a Z isomer (8) in 92% yield, according to HPLC (Table I). The ¹H NMR spectrum (90 MHz) of 8 in Me₂SO-*d*₆ showed vinyl and acid amide proton signals that had shifted to δ 5.50 (d, *J* = 8 Hz, SCH=), 7.08 (dd, *J* = 8 and 10.5, NCH=), and 11.56 (d, *J* = 10.5, NHCO) from the signals for 1 at δ 6.30 (d, *J* = 14, SCH=), 7.24 (dd, *J* = 14 and 10.5, NCH=), and 10.57 (d, *J* = 10.5, NHCO). The coupling constants indicated that the double bond in 8 has a *cis* orientation, and the large low-field shift of the amide signal showed that a hydrogen bond is present between the acid amide and sulfoxide groups. The presence of a hydrogen bond was also supported by the fact that the acid amide signals of the deoxy compound of 1 (9)³ and its Z isomer (10) were observed at 10.28 and 10.12 ppm, respectively. These chemical shifts indicated that

The following findings gave important suggestions for clarifying the mechanism of this reaction. C-19393 S₂ *p*-nitrobenzyl ester (23) did not afford any product under these reaction conditions. Furthermore, when 23 in TOMAC/chloroform solution was refluxed in the presence of 1, 23 was completely recovered; nevertheless, 8 was obtained in good yield. These data demonstrated that the reaction proceeds intramolecularly and that the proton source in the neutral solvent phase may not be the acid amide group but the carboxylic acid group. Compound 1, deuterium substituted in the carboxylic acid portion, was converted in TOMAC/chloroform solution. In the ¹H NMR spectrum of the purified Z isomers, the area of the vinyl proton signal near the sulfoxide was decreased to 58% in comparison with that near the acid amide. This percentage means that at least 84% of the double-bond proton was substituted by the deuterium atom of the carboxylic acid.

The mechanism of this Z,E isomerization proposed on the basis of these data is summarized in Scheme I. Of 4 equiv of TOMAC, 2 equiv of reagent may be consumed to form a sulfate and to eliminate sodium ion from the carboxylate.

This novel reaction method can be characterized as follows: (1) the reaction conditions are mild enough so as not to lead to decomposition in the unstable β-lactam ring in aqueous solution; (2) at equilibrium, the reaction will proceed predominantly in one direction; (3) the presence of the sulfoxide group does not affect this reaction. Z,E isomerization with palladium/carbon or mercuric chloride³ is inferior to this new reaction method in these three aspects.

Biological Activities. The minimum inhibitory concentrations of 5,6-*cis*-carbapenem antibiotics and the E and Z isomers are compared in Table III. The Z isomers showed slightly weaker activity against Gram-negative bacteria than the corresponding E isomers. The MIC differences between 2 and 11 were large, especially in *P. aeruginosa* and *A. calcoaceticus*.

Naturally occurring 5,6-*cis*-carbapenem antibiotics, 4, 6, or 2, when administered subcutaneously to mice infected with *E. coli* O-111, showed poor therapeutic effects, although they had strong *in vitro* antibacterial activity (Table IV). A single injection of 11 showed remarkably greater protective effect than 2. The Z isomer 17 also had a stronger effect than 6.

Merck researchers reported that carbapenem antibiotics

Table V. β -Lactamase Inhibitory Activity and Synergistic Effect of 5,6-*cis*-Carbapenem Antibiotics

antibiotic	I_{50} , ng/mL				antibiotic	MIC, μ g/mL			
	penicillinase of		cephalosporinase of			<i>S. aureus</i>	<i>K. pneum.</i>	<i>S. marcesc.</i>	<i>P. vulgaris</i>
	<i>S. aureus</i>	<i>K. pneum.</i>	<i>S. marcesc.</i>	<i>P. vulgaris</i>					
	1840	TN1698	TN81	GN4413	1840	TN1655	12648	GN4815	
20	540	80	0.78	2.8	ampicillin	100	100		
22	590	110	3.3	14	cefotiam		25	400	
1	210	5.2	55	0.37	+1 ^a	12.5	6.25	6.25	
8	240	1.0	18	0.55	+8	50	3.13	12.5	
14	3.4	0.08	0.34	0.16	+14	50	100	25	
13	1000	28	51	3.8	+13	50	50	25	
16	14	1.8	1.0	0.35	+16	0.78	25	12.5	
11	55	3.8	0.34	1.1	+11	6.25	3.13	12.5	
15	0.55	2.4	0.29	19	+15	6.25	100	50	
10	360	220	5.3	17	+10	12.5	100	12.5	
17	65	320	1.1	1500	+17	1.56	100	25	
							25	400	

^a Antibiotics tested were added at a concentration of 0.1 μ g/mL into the agar plate of ampicillin or cefotiam.

Table VI. Synergistic Protective Effects of C-19393 Derivatives with Cefotiam in Mice Infected with *P. vulgaris* GN4815

antibiotic	dose, ^a mg/kg	ED ₅₀ , mg/kg
cefotiam alone		35.5
1	1.0	12.5
	10	8.87
	100	3.86
cefotiam alone		25.0
8	0.1	18.1
	1.0	6.25
	10	2.41
11	0.1	21.6
	1.0	5.58
	10	1.56

^a Cefotiam and C-19393 derivatives were subcutaneously administered to different locations in mice.

Table VII

starting material (mg)	solvent	time, h	product	yield, %
1 (2670)	CHCl ₃	1.5	8	76
12 (100)	CHCl ₃	2.0	13	57 ^a
5 (12.8)	CH ₂ Cl ₂	8.0	14	25 ^a
4 (20)	CH ₂ Cl ₂	9.0	16	44
19 (10)	CHCl ₃	3.0	21	84

^a QAE-Sephadex A-25 (Cl⁻ type) was used for purification after HP-20 chromatography.

are rapidly hydrolyzed to an inactive form by dehydropeptidase I in the kidneys.¹¹ To clarify stability-protective effect relationships, we measured the comparative stabilities of 5,6-*cis*-carbapenem antibiotics in the mouse kidney homogenate (Table IV). *Z* isomers were found to be stabilized about 3-fold more than the corresponding *E* isomers. This finding may explain the enhancement of the protective effects in 11, 17, and 8 (described below). However, it was difficult to conclude whether or not parallel relationships might be present between the protective effects and stabilities of the renal enzyme(s) because 10 and 16 did not show any therapeutic effect in this experiment situation, although they have strong in vitro antimicrobial activities and improved stabilities.

Another interesting finding was obtained from the stereoisomers at the sulfoxide. Compound 20 was about 5-fold more stable in the homogenate than 2. Furthermore, the *Z* isomers 22 and 21 showed extraordinary stability to the enzyme, but the MIC of 20 and 22 became higher with

Table VIII

starting material (mg)	solvent	time, h	product	yield, %
2 (20)	CHCl ₃	2.5	11	85
9 (50)	CHCl ₃	1.25	10	66
3 (11)	CHCl ₃	2.0	15	54
7 (130)	CHCl ₃	1.5	18	49
20 (7)	CHCl ₃	3.0	22	71

an increase in the stability. In the in vivo studies, 20 showed almost the same protective effect as 2. These findings indicate that the steric structure of the side chain, including the sulfoxide, is very important for the in vivo activities of the antibiotics.

Table V shows the β -lactamase inhibitory activities of the 5,6-*cis*-carbapenem antibiotics. Of eight *Z* isomers, 14 showed the strongest inhibition on penicillinases and cephalosporinases. Compounds having the sulfoxide group showed stronger activities than the other derivatives. Interesting results were obtained on the potentiating action with ampicillin and cefotiam¹² in vitro (Table V). Compounds 1, 8, 11, and 16 decreased the MIC of the two antibiotics to less than one-tenth. Compound 14 did not show any synergistic effect in this test system, although it had a strong inhibitory activity on the enzyme level. The lack of membrane permeability or chemical lability of 14 may be a cause of this synergistic ineffectiveness.

In vivo synergistic effects between C-19393 derivatives and cefotiam with *P. vulgaris* GN 4815 are shown in Table VI. When 1 was subcutaneously administered at a dose of 10 mg/kg, the ED₅₀ of cefotiam decreased to one-fourth. On the other hand, when 8 or 11 was administered at 1 mg/kg, the ED₅₀ decreased to one-fourth. These data demonstrate the presence of a strong potentiating action in vivo between *Z* isomers of C-19393 and cefotiam.

The findings described above clearly show that *Z* isomers with sulfoxide and 8,8-dimethyl groups have superior biological activity than other 5,6-*cis*-carbapenem antibiotics.

Experimental Section

***Z,E* Isomerization. Method I.** A solution of the disodium salt of the compound with a sulfonyloxy group (0.1 mM) in H₂O (2 mg/mL) was extracted with an organic solvent (the same volume with H₂O) containing TOMAC (0.4 mM), and the organic layer was refluxed. The reaction mixture was reextracted with 0.44 mM NaI/H₂O, and the aqueous layer was concentrated after being washed with organic solvent. The concentrate was chromatographed on Diaion HP-20 (Mitsubishi Kasei) by elution with H₂O or MeOH-H₂O. The active fractions detected by HPLC were concentrated to give a *Z* isomer as a freeze-dried white powder (Table VII).

(11) H. Kropp, J. G. Sundelop, R. Hajdu, and F. M. Kahan, *Intersci. Conf. Antimicrob. Agents Chemother.*, 20th, 1980, Abstr. 272.

Method II. (a) A solution of the sodium salt of the compound with a hydroxy group (0.1 mM) in H₂O (50 µg/mL) was extracted with an organic solvent one-half volume × 2) containing TOMAC (25 mM), and the organic solvent layer was refluxed. The reaction mixture was reextracted with 30 mM NaI/H₂O. The purification procedure was similar to that of method I (Table VIII).

(b) To a solution of 6 (144 mg) in DMF (12 mL) was added 5% TOMAC/CH₂Cl₂ (500 mL), and the mixture was refluxed for 22 h. The reaction mixture was extracted with 6% NaI/H₂O (170 mL), and the aqueous layer was treated similarly to give 17 (40.6 mg) as a freeze-dried powder.

The physicochemical properties of the derivatives are shown in Table II.

Determination of in Vitro and in Vivo Antibacterial Activity. The MIC was determined by the agar dilution method.¹² The protective effect in Slc:ICR mice was determined as described previously.¹² The 50% effective dose (ED₅₀) was calculated by the method of Reed and Muench¹³ from the survival rate recorded 5 days after infection.

Determination of β-Lactamase Inhibitory Activity and Antibacterial Synergy Test. The β-lactamase inhibitory activity

- (12) K. Tsuchiya, M. Kida, M. Kondo, H. Ono, M. Takeuchi, and T. Nishi, *Antimicrob. Agents Chemother.*, 14, 557 (1978).
 (13) L. J. Reed and H. Muench, *Am. J. Hyg.*, 27, 493 (1938).

was determined as described previously⁵ and expressed in terms of I₅₀, the concentration required to inhibit β-lactamase activity by 50%. The potentiation of the antibacterial activity of ampicillin and cefotiam by carbapenem antibiotics was examined by the 2-fold dilution method with Mueller-Hinton agar (Difco) as described previously.⁶

Determination of the Stability to Mouse Renal Enzyme(s). The carbapenem antibiotic (50 µg/mL) was incubated in a 10% mouse kidney homogenate at 30 °C. At intervals, we determined the amount of the residual carbapenem antibiotic by assaying the activity to inhibit the β-lactamase.

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Registry No. 1, 76025-74-6; 2, 76035-86-4; 3, 83510-01-4; 4, 57459-82-2; 5, 12795-21-0; 6, 68510-62-3; 7, 68421-49-8; 8, 83916-36-3; 9, 80994-11-2; 10, 83916-37-4; 11, 83916-38-5; 12, 80994-12-3; 13, 83916-39-6; 14, 83916-40-9; 15, 83916-41-0; 16, 83916-42-1; 17, 75443-31-1; 18, 75443-29-7; 19, 83916-43-2; 20, 83916-44-3; 21, 83916-45-4; 22, 83916-46-5; tri-n-octylmethylammonium chloride, 5137-55-3.

Notes

Selection of Test Series by a Modified Multidimensional Mapping Method

Raymond Wootton

Department of Biophysics, Wellcome Research Laboratories, Langley Court, Beckenham, Kent, England. Received May 3, 1982

Maintaining a realistic minimum distance between compounds in a defined multidimensional parameter space ensures well-spread sets of parameter values. It has been suggested, however, that the use of this multidimensional mapping method may lead to series of compounds with high multicollinearities of parameter values. An alternative method, multidimensional mapping by distance and determinant, is discussed here. This method maximizes the determinant of the interparameter correlation matrix as well as maintaining the minimum distance criterion. Its performance is compared with other methods, and it is shown that collinearities may be overcome or maintained at low levels when this method is used.

Multiple linear regression analysis is the most commonly used technique for identifying quantitative relationships between biological activity and the physicochemical parameter values of series of compounds. The chances of establishing such relationships, which will be of use for the prime objective of predicting the activity of further members of the series, depend critically upon there being sufficient variation in the parameter values and no seriously high interparameter correlations (collinearities) for the compounds used to derive the relationships. Multidimensional mapping (MM) is a technique that has been used to help achieve these goals in the design of series of compounds.^{1,2} Good variation is ensured by maintaining a set minimum distance between compounds in the scaled multidimensional parameter space, and low collinearities are achieved by choosing compounds close to the center of gravity in space of the compounds already selected. This

method has been criticized in two recent papers^{3,4} on the grounds that insufficient weight is given to ensuring lack of correlation between parameters. Martin and Panas³ examined the physicochemical properties of a series of methoxychlor analogues² that were designed partly with the help of this method and concluded that its use resulted in a computer-designed series of compounds with too high a degree of multicollinearity. In fact, in this practical application of QSAR methodology, three different methods of computer-aided compound choice were used, and the analysis of Martin and Panas is therefore oversimplified. If the properties of the compounds are examined in greater detail, it becomes clear that the MM method does not, of itself, lead to high multicollinearities and, indeed, goes some way toward decreasing collinearities already present in a data set.

However, if, as was the case for the methoxychlor analogues, there are very high collinearities for the compounds already made, then it may be necessary to adopt an alternative strategy to aid compound choice. Franke et al.⁴

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