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

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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.

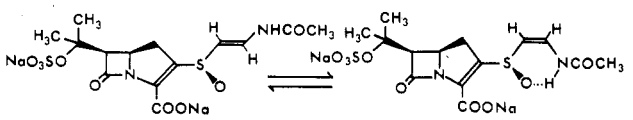
In previous papers, we described the isolation and chemical structures of new carbapenem antibiotics, C-19393 S_2 (**1**), H_2 (**2**), and E_5 (**3**).[1-3] These antibiotics have strong, broad antimicrobial spectra[2,4] and β-lactamase inhibitory activities[5,6] as good as the known 5,6-*cis*-carbapenem antibiotics, olivanic acids, MM 17880, MM 13902 (**4**), and MM 4550 (**5**),[7-9] and epithienamycins A, B (**6**), C, and D (**7**).[10] However, all of these showed weak or undetectable protective effects in our screening system, except when administered intraperitoneally.

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 carpapenem 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 Me_2SO-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 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

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



C-19393 S_2 (1) C-19393 Z-S_2 (8)

column	ammonium halide[b]	solvent	temp, °C	time, h	yield, % 8	1	sum
I	TOMAC	$CHCl_3$	ref	1	85	13	98
	TPAC	CH_2Cl_2	ref	6	77	23	100
	TPAB	$CHCl_3$	ref	1	38	38	76
	TDMBAC	$CHCl_3$	ref	2	49	27	76
	HDMBAC	CH_2Cl_2	ref	16	76	25	101
	TBAC	CH_2Cl_2	ref	4	0.3	16	16
II	TOMAC	CH_2Cl_2	ref	8	92	8	100
	TOMAC	CH_2ClCH_2Cl	60-62	0.5	61	14	75
	TOMAC	CH_2ClCH_2Cl	40-42	3	50	18	68
	TOMAC	CCl_3CH_3	60-62	3	27	53	80
	TOMAC	CCl_4	60-62	2	13	77	90

[a] One micromole of **1** in H_2O (5 mL) was extracted with 25 μmol 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.

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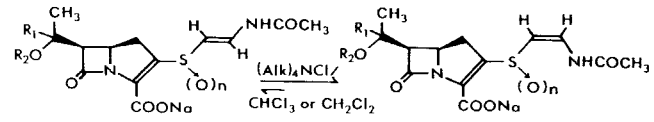
Table II. Physicochemical Properties of *Z* Isomers in 5,6-*cis*-Carbapenem Antibiotics



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_2O), nm (ϵ)	IR (KBr) ν_{max}, cm^{-1} (β-CO)	^1H NMR (D_2O) δ (100 MHz) 8-CH_3	^1H NMR (D_2O) δ (100 MHz) CH=
1	CH_3	SO_3Na	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_3Na	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_3Na	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_3Na	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_3Na	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
S. aureus 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
E. coli T-7	1.56	6.25	25	25	3.13	6.25	>100	>100	12.5	12.5	6.25	100	6.25	25
C. freundii 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
K. pneumoniae 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
E. cloacae IFO 12937	0.78	6.25	25	50	1.56	3.13	>100	12.5	25	50	12.5	100	12.5	50
S. marcesc 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
P. vulgaris IFO 3988	3.13	25	12.5	100	3.13	3.13	3.13	0.78	50	>100	50	100	0.2	0.78
P. mirabilis 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
P. morganii IFO 3168	1.56	12.5	25	100	1.56	3.13	1.56	1.56	50	100	50	100	0.78	3.13
P. aeruginosa IFO 3455	6.25	>100	25	>100	12.5	50	100	25	>100	>100	>100	>100	3.13	6.25
A. calcoacet. 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 (10^8 cfu/mL).

Scheme I

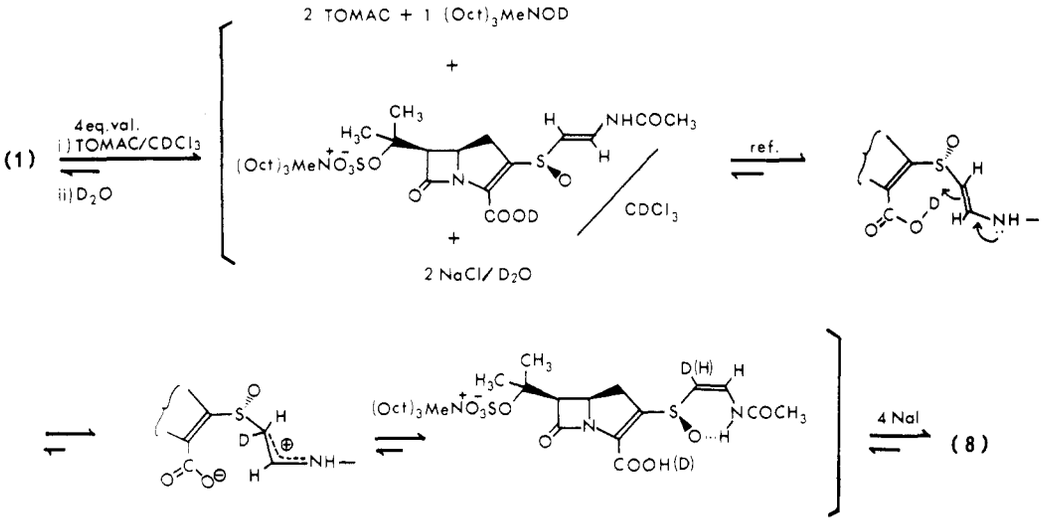


Table IV. Relationships between Protective Effects and Stability in Mouse Kidney Homogenates of 5,6-*cis*-Carbapenem Antibiotics

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.

subjected to the same condition, this *Z* isomerization can be characterized as an equilibrium reaction. Table I also 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 antibiotics[2] 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.

The following findings gave important suggestions for clarifying the mechanism of this reaction. C-19393 S_2 *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/chlorform 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 chloride[3] 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

	I_{50}, ng/mL					MIC, μg/mL			
	penicillinase of		cephalosporinase of						
antibiotic	*S. aureus* 1840	*K. pneum.* TN1698	*S. marcesc.* TN81	*P. vulgaris* GN4413	antibiotic	*S. aureus* 1840	*K. pneum.* TN1655	*S. marcesc.* 12648	*P. vulgaris* 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	1.56
8	240	1.0	18	0.55	+8	50	3.13	12.5	0.78
14	3.4	0.08	0.34	0.16	+14	50	100	25	50
13	1000	28	51	3.8	+13	50	50	25	1.56
16	14	1.8	1.0	0.35	+16	0.78	25	12.5	1.56
11	55	3.8	0.34	1.1	+11	6.25	3.13	12.5	1.56
15	0.55	2.4	0.29	19	+15	6.25	100	50	400
10	360	220	5.3	17	+10	12.5	100	12.5	25
17	65	320	1.1	1500	+17	1.56	100	25	400

[a] Antibiotics tested were added at a concentration of 0.1 μg/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_2Cl_2	8.0	**14**	25[a]
4 (20)	CH_2Cl_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

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

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 cefotiam[12] 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 ED_{50} of cefotiam decreased to one-fourth. On the other hand, when **8** or **11** was administered at 1 mg/kg, the ED_{50} 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 H_2O (2 mg/mL) was extracted with an organic solvent (the same volume with H_2O) containing TOMAC (0.4 mM), and the organic layer was refluxed. The reaction mixture was reextracted with 0.44 mM NaI/H_2O, 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 H_2O or MeOH–H_2O. The active fractions detected by HPLC were concentrated to give a *Z* isomer as a freeze–dried white powder (Table VII).

Method II. (a) A solution of the sodium salt of the compound with a hydroxy group (0.1 mM) in H_2O (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/H_2O. 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/CH_2Cl_2 (500 mL), and the mixture was refluxed for 22 h. The reaction mixture was extracted with 6% NaI/H_2O (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 (ED_{50}) was calculated by the method of Reed and Muench[13] from the survival rate recorded 5 days after infection.

Determination of β-Lactamase Inhibitory Activity and Antibacterial Synergy Test. The β-lactamase inhibitory activity was determined as described previously[5] and expressed in terms of I_{50}, 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.

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This paper first appeared on pages 271–275. It is being reprinted due to errors introduced during the production cycle

Notes

Oscillations in Some Linear Free Energy Relationships Derived from Partition Coefficients of Phenols between Octanol and Water

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In the partition of some resorcinol alkyl ethers between water and 1-octanol, the values of ΔG_{trs} do not increase in a regular way. Odd and even chain alkyl compounds show different, regular increases in ΔG_{trs} for addition of each methylene group. The unrecognized occurrence of this phenomenon in earlier data is pointed out, and its possible significance in medicinal chemistry is discussed.

It has long been assumed[1] that partition coefficients for the transfer of solutes, in particular drugs, between water and a nonaqueous, lipid-like phase are linearly related to the chain length for an homologous series. "Hansch" analysis[2] has been used for some years to correlate the biological activity for a series of drugs with π values (log P/P_0, where P is the partition coefficient for a member of an homologous series and P_0 is that for the "parent" member of the series). The values of P for many of these compounds are now calculated from group contributions,[3] fragmental constant,[4] or molecular connectivity schemes.[5] Clearly, the basis for such calculation schemes is that there exists a *linear* relationship between $f(P)$ and the degree of substitution; i.e., there exists a linear Gibbs energy relationship similar to the Hammett equation.[6] Thus, for the resorcinol monoethers it is assumed[2] that log P increases by 0.5 for each incremental methylene group in the side chain. Moreover, Tanford[7] has shown that the Gibbs

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