On the Relationship between the Chemical Structure and the Carcinogenicity of Polycyclic Aromatic Compounds and Heterocyclic Nitrogen Compounds, as Studied by ^{13}C NMR

Yohko SAKAMOTO* and Yuko SAKAMOTO
School of Pharmaceutical Sciences, Toho University, Funabashi, Chiba 274
(Received May 25, 1988)

Synopsis. The relationship between the chemical structure and the carcinogenicity of eighty polycyclic aromatic compounds and heterocyclic nitrogen compounds was investigated by ^{13}C NMR. The averaged chemical shifts of the carcinogenic polycyclic aromatic compounds were within the range from δ 126.80 to 127.87, while those of the carcinogenic heterocyclic nitrogen compounds were within the range from δ 129.48 to 132.12. The carcinogenicity of several compounds were predicted according to the index.

The information on the electronic structure and electronic state of polycyclic aromatic compounds was obtained by the calculation of the averaged chemical shifts for all the carbons in the ring structure of the molecules, as has been described previously.[1]

The purpose of this paper is to confirm the previous "carcinogenic index" in eighty polycyclic aromatic compounds, either carcinogenic, noncarcinogenic or undetermined.

Polycyclic Aromatic Hydrocarbons 1—51: It has been reported that compounds **1** and **2** are carcinogenic.

The averaged chemical shifts of these carcinogenic compounds are within the index range from δ 127.11 to 127.87, as has reported in a previous paper.[1]

The averaged chemical shift of two other carcinogenic compounds, **3** and **4**, were δ 126.99 and 126.80 respectively. Thus, we can expand the upper limit of the "carcinogenic index" at a high field from δ 127.11 to 126.80.

Compounds **5—8** and **10—13**, previously reported to be noncarcinogenic,[2,3] were confirmed to be out of the "carcinogenic index".

All the fluorene compounds **10—13** can similarly be expected to be noncarcinogenic.

Compounds **14—22**, **24**, **31**, and **37—46** have been reported to be either carcinogenic or noncarcinogenic, depending on the reports.[2-4] According to the "index range", the possibility that compounds **15**, **16**, **18**, **19**, **24**, **31**, **37**, **39**, **42**, and **46** are carcinogenic is high. On the other hand, the possibility that compounds **14**, **17**, **20—22**, **38**, **40**, **41**, and **43—45** are carcinogenic is low.

Compound **9**, previously reported to be noncarcinogenic,[3] fell in the borderline region of the "carcinogenic index", where the judgement of carcinogenicity was difficult.

Heterocyclic Nitrogen Componds 52—80: The averaged chemical shifts in the carcinogenic compounds **52—60** were within the range from δ 129.48 to 132.12.

Table 1. The Averaged ^{13}C NMR Chemical Shifts over All the Ring Carbons of Polycyclic Aromatic Hydrocarbons, and Their Carcinogenicities

Compound	Averaged chemical shift δ/ppm	Predicted carcinogenicity[a]	Carcinogenicity[b] literature
Dibenzo[*a*,*l*]pyrene (**1**)	127.47	+	+ (2, 3)
Phenanthro[4,5-*bcd*]thiophene (**2**)	127.64	+	+ (3)
Dibenzo[*a*,*i*]pyrene (**3**)	126.99	+	+ (2, 3, 4)
Dibenzo[*a*,*h*]pyrene (**4**)	126.80	+	+ (2, 3, 4)
Benzo[*e*]pyrene (**5**)	126.66	−	− (2)
Picene (**6**)	126.08	−	− (2)
Coronene (**7**)	125.78	−	− (2)
1-Methylbenz[*a*]anthracene (**8**)	129.47	−	− (2)
Benzo[*b*]chrysene (**9**)	127.12	+	− (3)
Fluorene (**10**)	130.52	−	− (3)
Fluoranthene (**11**)	129.08	−	− (3)
Benzo[*b*]fluorene (**12**)	124.58	−	− (3)
Benzo[*ghi*]fluoroanthene (**13**)	128.75	−	− (3)
Benzo[*c*]phenanthrene (**14**)	128.40	−	± (3, 4)
Anthanthrene (**15**)	126.97	+	± (2, 4)
Benzo[*ghi*]perylene (**16**)	126.79	+	± (2, 3)
Cyclopenta[*cd*]pyrene (**17**)	128.29	−	± (2, 3)
Benzo[*b*]triphenylene (**18**)	127.26	+	± (3)
Chrysene (**19**)	127.10	+	± (3)

Table 1. (Continued)

Benzo[*c*]chrysene (**20**)	127.92	−	± (3)
Indeno[1,2,3-*cd*]pyrene (**21**)	128.17	−	± (3, 4)
Perylene (**22**)	128.32	−	± (3, 4)
Rubrene (**23**)	130.57	−	
Dibenzo[*a,j*]anthracene (**24**)	127.06	+	± (2, 3, 4)
9-Phenylanthracene (**25**)	129.83	−	
9,10-Diphenylanthracene (**26**)	130.64	−	
9,10-Dihydroanthracene (**27**)	129.94	−	
Acenaphthylene (**28**)	129.15	−	
Acenaphthene (**29**)	130.96	−	
1,2,2a,3,4,5-Hexahydroacenaphthylene (**30**)	132.36	−	
1-Methylphenanthrene (**31**)	127.66	+	± (4)
2-Methylphenanthrene (**32**)	128.23	−	
3-Methylphenanthrene (**33**)	128.20	−	
3,6-Dimethylphenanthrene (**34**)	128.68	−	
1,2,3,4-Tetrahydrophenanthrene (**35**)	128.56	−	
1,2,3,4,5,6,7,8-Octahydrophenanthrene (**36**)	131.94	−	
1-Methylchrysene (**37**)	127.44	+	± (3)
2-Methylchrysene (**38**)	128.49	−	± (3)
3-Methylchrysene (**39**)	127.76	+	± (3)
4-Methylchrysene (**40**)	128.61	−	± (3)
5-Methylchrysene (**41**)	128.34	−	± (3)
6-Methylchrysene (**42**)	127.38	+	± (3)
Benzo[*b*]naphtho[1,2-*d*]thiophene (**43**)	129.62	−	± (3)
Benzo[*b*]naphtho[2,1-*d*]thiophene (**44**)	131.53	−	± (3)
Benzo[*b*]naphtho[2,3-*d*]thiophene (**45**)	128.04	−	± (3)
Benzo[2,3]phenanthro[4,5-*bcd*]thiophene (**46**)	127.83	+	± (3)
Dibenzo[*a,e*]fluoroanthrene (**47**)	128.78	−	
Benzo[*a*]fluoroanthene (**48**)	129.44	−	
Benzo[*b*]fluoroanthene (**49**)	128.68	−	
Benzo[*j*]fluoroanthene (**50**)	129.25	−	
Benzo[*k*]fluoroanthene (**51**)	129.31	−	
Acridine (**52**)	132.12	+	+ (4)
Benz[*a*]acridine (**53**)	130.67	+	+ (4)
Benz[*c*]acridine (**54**)	130.85	+	+ (4)
10-Azabenzo[*a*]pyrene (**55**)	129.48	+	+ (3)
Dibenz[*a,c*]acridine (**56**)	129.58	+	+ (3)
Dibenz[*a,h*]acridine (**57**)	130.19	+	+ (3)
Dibenz[*a,j*]acridine (**58**)	129.95	+	+ (3)
Dibenz[*c,h*]acridine (**59**)	130.33	+	+ (3)
Dibenz[*a,i*]acridine (**60**)	130.24	+	+ (4)
2-Methylpyridine (**61**)	137.49	(−)[c]	
3-Methylpyridine (**62**)	137.95	(−)	
4-Methylpyridine (**63**)	140.39	(−)	
2,3-Dimethylpyridine (**64**)	138.57	(−)	
2,4-Dimethylpyridine (**65**)	139.98	(−)	
2,5-Dimethylpyridine (**66**)	138.77	(−)	
3,4-Dimethylpyridine (**67**)	139.90	(−)	
3,5-Dimethylpyridine (**68**)	138.96	(−)	
3-Ethyl-4-methylpyridine (**69**)	140.80	(−)	
Quinoline (**70**)	133.38	(−)	
Quinazoline (**71**)	138.50	(−)	
Phenanthridine (**72**)	130.56	+	
Benzo[*f*]quinoline (**73**)	130.70	+	
Benzo[*h*]quinoline (**74**)	131.03	+	
2-Methylquinoline (**75**)	133.51	(−)	
4-Methylquinoline (**76**)	133.40	(−)	
2,4-Dimethylquinoline (**77**)	134.03	(−)	
2,6-Dimethylquinoline (**78**)	134.36	(−)	
5,6,7,8-Tetrahydroquinoline (**79**)	138.71	(−)	
Quinoxaline (**80**)	136.90	(−)	

a) − for noncarcinogenic and + for carcinogenic. b) Carcinogenicity reported previously. It may be based on biochemical evidence or molecular orbital calculation. −: for noncarcinogenic, +: for carcinogenic, ±: for either noncarcinogenic or carcinogenic. c) (−): the carcinogenicities of these compounds were assigned by adopting the noncarcinogenic range for the chlorinated monocyclic aromatic compounds.

The carcinogenicity of the other compounds **61—80** have not been determined. Compounds **72, 73,** and **74** may be expected to be carcinogenic, according to the above "index range". The "carcinogenic index" of the heterocyclic nitrogen compounds (δ 129.48—132.12) was similar to that of chlorinated monocyclic aromatic compounds (δ 127.76—132.64);[1] both were shifted to a lower field than that from the polycyclic aromatic compounds (δ 126.80—127.87).

There have been no reports on attempts to determine the noncarcinogenic range of noncarcinogenic heterocyclic nitrogen compounds.

However, compounds **61—71** and **75—80** may be expected to be noncarcinogenic by analogy with the chlorinated monocyclic aromatic compounds.

The polar atoms attract the electrons in the ring by the δ-I effect. Thus, the averaged chemical shifts of heterocyclic and chlorinated compounds move downfield as a whole compared with those of polycyclic aromatic compounds, resulting in the difference in the "carcinogenic index" between the two types of compounds.

The present study, like the previous report,[1] shows a close relationship among the carcinogenicity, the averaged chemical shifts, and the electronic structure in aromatic hydrocarbons. Thus, the "index" will be useful in predicting whether or not compounds are carcinogenic.

The authors are heartily grateful to Professor Taichi Ohmoto of Toho University for his encouragement.

References

1) Y. Sakamoto and S. Watanabe, *Bull. Chem. Soc. Jpn.*, **59**, 3033 (1986).

2) E. L. Cavalieri, E. G. Rogan, R. W. Roth, R. K. Saugier, and A. Hakam, *Chem.-Biol. Interactions*, **47**, 87 (1983).

3) "Spectral Atlas of Polycyclic Aromatic Compounds," ed by W. Karcher, R. J. Fordham, J. J. Dubois, P. G. J. M. Glaude, and J. A. M. Ligthart, D. Reidel Publishing Company (1983).

4) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans., Vol. 32, *IARC*, Lyon, 1983.

5) A. C. Allison and T. Nash, *Nature (London)*, **197**, 758, (1963).