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Correlations between Topological Resonance Energy of Methyl-Substituted Benz[*c*]acridines, Benzo[*a*]phenothiazines and Chrysenes, and their Carcinogenic or Antitumor Activities

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Abstract. *In order to clarify the effects of methyl substitution on the carcinogenic activity, each resonance energy (RE) of benz[c]acridines, benzo[a]phenothiazines, chrysene, and their methyl derivatives was calculated by Aihara's TRE theory. Some correlations seem to exist between the values of resonance energy per π-electron for the cationic species - with the lack of the atom having the highest approximate superdelocalizability (Sr'(E)) from their parents skeleton - and carcinogenic activity.*

The concern need to protect our environment from powtants is of rising worldwide. We have studied the relationship between their antitumor activities of benzo[*a*]phenothiazines or carcinogenic activities of benz[*c*]acridines, and the values of the resonance energy per π-electron (REPE) (1,2). We calculated the values of REPE for the parent molecules and species lacking a double bond in the K-region or M-region of the parent skeleton, and applied this in the prediction of their carcinogenicity. In all cases, the values of the REPE for the compounds lacking a double bond in the K-region were greater than those of the corresponding parent compounds (Figure 1), whereas the values of the REPE for compounds lacking a double bond in the M-region were smaller than those of their parent compounds (Figure 1). Some methyl-benz[*c*]acridines and arenes (3) are strongly carcinogenic, whereas their derivatives are inactive (4-6). Generally, the carcinogenic mechanism of these compounds is very complicated; with the parent molecules undergo the various metabolic transformations. Consequently, the chemical and physical properties of all metabolic intermediates are taken into accounts in order to predict their carcinogenicity, as the presumed ultimate carcinogenic areas of arenes such as dihydrodiols and epoxides are highly reactive (7). Theoretical calculations by a semiempirical molecular orbital method such as parametric method 3 (PM3), have difficulty in predicting the carcinogenicity of all metabolic intermediates. The purpose of this paper was to show the relationship between the antitumor activity of methylbenzo[*a*]phenothiazines or carcinogenicity of methylchrysenes, and the values of REPEs calculated by ω-technique on the mechanism of the antitumor effect, or carcinogenicity caused by methyl substituents of the parent compounds (not metabolites) (8). Interestingly, a good relationship was found between the antitumor activity (and carcinogenicity), and the cationic REPE values for the species (without sulfur (S), nitrogen (N) and carbon (C) atoms) having the values of the highest approximate superdelocalizability (Sr'(E)) on each parent skeleton existed.

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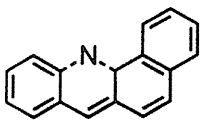
Key Words: Effect of methyl substitution, resonance energy per π-electron, benz[*c*]acridine, benzo[*a*]phenothiazine.

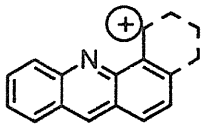
Calculations

Calculatons of Aihara's topological resonance energy (TRE) were carried out by the ω-technique which evaluated the heteroatom parameters for the amine nitrogen, the imine nitrogen, the ether oxygen,

Structures for REPE ($Sr'^{(E)}$) and REPE (B) of benz[*c*]acridines (**1-12**)



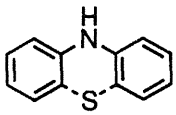
Structures for REPE ($Sr'^{(E)}$)



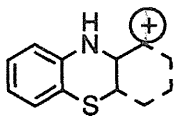
Structures for REPE (B)

Structures for REPE ($Sr'^{(E)}$) and REPE (B) of phenothiazines (**13-21**)

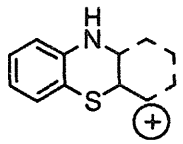
phenothiazine (**13**)



Structures for REPE ($Sr'^{(E)}$) of **13**

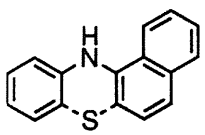


structure for REPE (B) (0.0172ß) of **13**

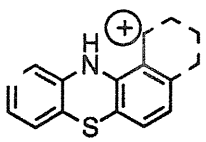


structure for REPE (B) (0.0172ß) of **13**

benzo[*a*]phenothiazines (**14-17**)

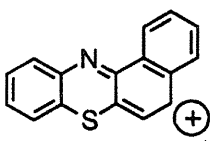


Structures for REPE ($Sr'^{(E)}$) of **14-17**



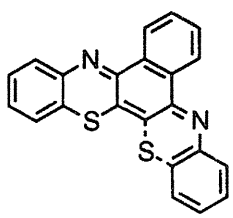
Structures for REPE (B) of **14-17**

5-oxo-5*H*-benzo[*a*]phenothiazines (**18-20**)



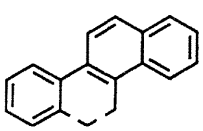
Structures for REPE ($Sr'^{(E)}$) of **18-20**

5*H*-benzo[*a*][1,4]benzothiazino [3,2- *c*]phenothiazines (**21**)

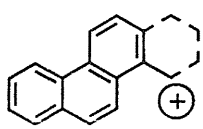


Structures for REPE ($Sr'^{(E)}$) of **21**

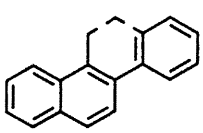
Structures for REPE ($Sr'^{(E)}$) and REPE (B) of chrysenes (**22-32**)



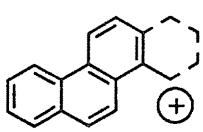
Structures for REPE ($Sr'^{(E)}$) of **22,25,27,29,30,32**



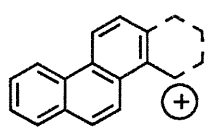
Structures for REPE (B) of **22,23,26-32**



Structures for REPE ($Sr'^{(E)}$) of **23,24,26,28,31**



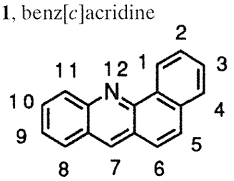
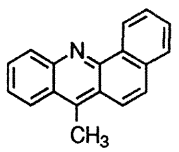
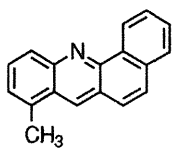
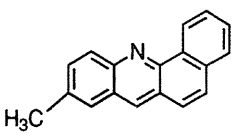
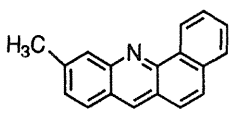
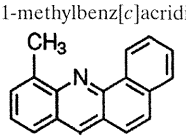
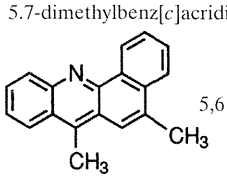
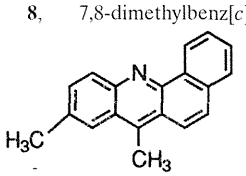
Structures for REPE (B) of **24**



Structures for REPE(B) of **25**

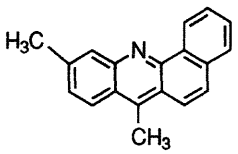
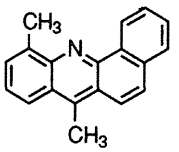
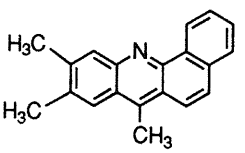
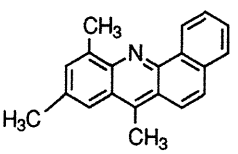
Figure 1. *Structures of REPE($Sr'^{(E)}$) and REPE(B) of benz[c]acridines (**1-12**), phenothiazine (**13**), benzo[a]phenothiazines (**14-21**) and chrysenes (**21-32**).*

Table I. *Bond-order, REPEs and* $Sr^{\cdot(E)}$ *of benz[c]acridines (1-8).*

Compd's No. and structure	Bond[1]	Bond-order (ß unit)[2]	REPE (P) (in ß unit)[3]	Approximate superdelocalizability (in ß unit)				ΔPS[8]	ΔPB[9]	Carcinogenicity index[10]
				Position[4]	$Sr^{\cdot(E)}$ [5]	REPE ($Sr^{\cdot(E)}$)[6]	REPE(B)[7]			
1, benz[*c*]acridine 	5,6	0.782	0.0344	12	0.993	0.0304	0.0252	0.0040	0.0092	-
2, 7-methylbenz[*c*]acridine 	5,6	0.781	0.0306	12	1.042	0.0272	0.0223	0.0034	0.0083	+
3, 8-methylbenz[*c*]acridine 	5,6	0.782	0.0306	12	1.011	0.0269	0.0222	0.0037	0.0084	-
4, 9-methylbenz[*c*]acridine 	5,6	0.782	0.0308	12	0.998	0.0270	0.0224	0.0038	0.0084	-
5, 10-methylbenz[*c*]acridine 	5,6	0.782	0.0306	12	1.010	0.0269	0.0222	0.0037	0.0084	-
6, 11-methylbenz[*c*]acridine 	5,6	0.782	0.0308	12	1.000	0.0270	0.0223	0.0038	0.0085	-
7, 5.7-dimethylbenz[*c*]acridine 	5,6	0.779	0.0279	12	1.019	0.0246	0.0201	0.0033	0.0078	-
8, 7,8-dimethylbenz[*c*]acridine 	5,6	0.781	0.0279	12	1.049	0.0245	0.0201	0.0034	0.0078	+

[1]Bond: Position with the biggest bond-order. [2]Bond-order: Bond-order (in ß unit) at the position with the biggest bond-order. [3]REPE (P): Resonance energy per π-electron (in ß unit) of parent. [4]Position: Position with the biggest approximate superdelocalizability in parent. [5]$Sr^{\cdot(E)}$: Approximate superdelocalizability in parent. [6]REPE ($Sr^{\cdot(E)}$):REPE except the position of the biggest $Sr^{\cdot(E)}$ in parent. [7]Carbocation species derived from the ring-opening of the bay-region diol-epoxide. [8]ΔPS: REPE(P)-REPE ($Sr^{\cdot(E)}$). [9]ΔPB=REPE(P)-REPE(B). [10]Carcinogenkity index (Ref. 4,12,13): +: carcinogenic; -: noncarcinogenic.

Table I. (continued). *Bond-order, REPEs and $Sr'^{(E)}$ of benz[c]acridines (9-12).*

Compd's No. and structure	Bond[1]	Bond-order (ß unit)[2]	REPE (P) (in ß unit)[3]	Approximate superdelocalizability (in ß unit)				ΔPS[8]	ΔPB[9]	Carcinogenicity index[10]
				Position[4]	$Sr'^{(E)}$ [5]	REPE ($Sr'^{(E)}$)[6]	REPE(B)[7]			
9, 7,10-dimethylbenz[*c*]acridine 	5,6	0.781	0.0277	12	1.059	0.0244	0.0200	0.0033	0.0077	+
10, 7,11-dimethylbenz[*c*]acridine 	5,6	0.781	0.0279	12	1.051	0.0246	0.0201	0.0033	0.0078	+
11, 7,9,1.0-trimethylbenz[*c*]acridine 	5,6	0.781	0.0255	12	1.066	0.0222	0.0182	0.0033	0.0073	+
12, 7,9,11-trimethylbenz[*c*]acridine 	5,6	0.781	0.0257	12	1.055	0.0223	0.01B3	0.0034	0.0074	+

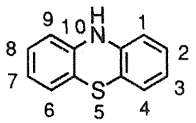
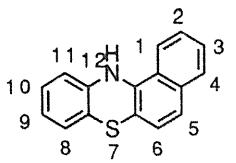
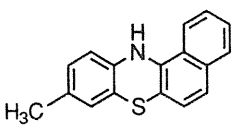
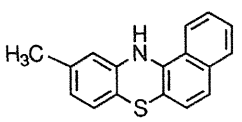
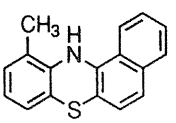
and the ketone oxygen (9). In this paper, we adopted these data values with some other heteroatom parameters. For these calculations, the FACOM M770 computer in the Josai University Information Sciences Center was used (Figure 1).

Results and Discussion

Relationship between carcinogenic activity, and REPE (ΔPS and ΔPB) on twelve benz[c]acridines (1-12) with two analogs (1s-12s and 1b-12b). The REPE values of twelve benz[*c*]acridines (**1-12**) and their corresponding analogs ($\mathbf{1_k}$-$\mathbf{12_k}$ and $\mathbf{1_M}$-$\mathbf{12_M}$) - without a double bond in the K-, or M-region, were calculated by a standard Hückel orbital method (HMO) (10). Firstly, the calculated REPE values for the K-region of benz[*c*]acridines lacking a double bond ($\mathbf{1_k}$-$\mathbf{12_k}$) were higher than those of the corresponding parent benz[*c*]acridines ($\mathbf{1_P}$-$\mathbf{12_P}$). Secondly, the REPE values of M-region benz[*c*]acri-dines without a double bond ($\mathbf{1_M}$-$\mathbf{12_M}$) were lower than those of the corresponding parent benz[*c*]acridines ($\mathbf{1_P}$-$\mathbf{12_P}$). However, in comparison with both REPE values, the substitution effect by the methyl group (s) cannot represent the relationship between carcinogenic activity, and the corresponding REPE value of benz[*c*]acridine (**1**) and methylbenz[*c*]acridines (**2-12**). Thirdly, 7-methylbenz[*c*]acri-dine (**2**) with strong carcinogenicity showed the difference (ΔPK=-0.0017ß) between REPE ($\mathbf{2_P}$=0.0317ß) of 7-methylbenz[*c*]acridine (**2**) and REPE ($\mathbf{2_k}$=0.0334ß) of 7-methylbenz[*c*]acridine (**2**). Non-carcinogenic 9-methyl-benz[*c*]acridine (**4**) showed the difference (ΔPK=-0.0018ß) between REPE ($\mathbf{4_P}$=0.0315ß) of 9-methylbenz[*c*]acridine (**4**) and REPE ($\mathbf{4_K}$=0.0333ß) of 9-methylbenz[*c*]acridine (**4**). The two ΔPK's difference between ΔPK=-0.0017ß of carcinogenic 7-methylbenz[*c*]acridine (**2**) and ΔPK=-0.0018ß of noncar-cinogenic 9-methyl-benz[*c*]acridine (**4**) was very close. Similarly, the substituent effect induced by the methyl group (s) in twelve methylchrysenes (**22-32**) did not show clear differences between carcinogenicity, and the ΔPKs of eight carcinogenic (**22, 26-32**) and three noncarcinogenic methyl-chrysenes (**23-25**) (10). Due to this, the above REPE calculations employed an ω-technique, instead of a standard HMO method.

Table I shows the bond-order, resonance energies per π-electron (REPE(P)s), approximate superdelocalizability ($Sr'^{(E)}$) in the parent compound, REPE($Sr'^{(E)}$) (REPE value minus the position of the highest $Sr'^{(E)}$ in the parent compound), REPE(B) (carbocation species derived from the ring-opening of the bay-region diol-epoxide), the REPE value difference (ΔPS) between the parent compound's REPE

Table II. *Bond-order, REPEs and Sr'$^{(E)}$ of phenothiazine (13) and benzo[a]phenothiazines (14-17).*

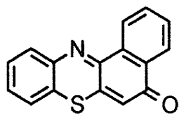
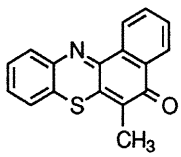
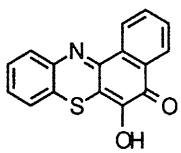
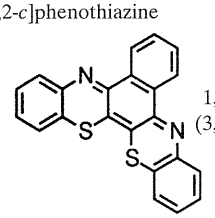
Compd's No. and structure	Bond[1]	Bond-order (ß unit)[2]	REPE (P) (in ß unit)[3]	Approximate superdelocalizability (in ß unit)				ΔPS[8]	ΔPB[9]	Carcinogenicity index[10]
				Position[4]	Sr'$^{(E)}$ [5]	REPE (Sr'$^{(E)}$)[6]	REPE(B)[7]			
13, phenothiazine 	3,4 (6,7)	0.666	0.0311	5	1.130	0.0371	0.0172 0.0172	-0.0060	0.0139	-
14, 12*H*-benzo[*a*]phenothiazine 	1,2	0.724	0 0306	7	1.130	0.0360	0.0245	-0.0054	0.0061	-
15, 9-methyl-12*H*-benzo[*a*]phenothiazine 	1,2	0.724	0.0278	7	1.267	0.0324	0.0220	-0.0046	0.0056	+
16, 10-methyl-12*H*-benzo[*a*]phenothiazine 	1,2	0.724	0.0278	7	1.164	0.0323	0.0221	-0.0045	0.0057	-
17, 11-methyl-12*H*-benzo[*a*]phenothiazine 	1,2	0.724	0.0278	7	1.127	0.0324	0.0220	-0.0046	0.0058	-

[10]Antitumor activity index (Ref. 14,15): +: antitumor; -: nonantitumor.

value and REPE value of the twelve cationic species ($\mathbf{1_S}$-$\mathbf{12_S}$) without the nitrogen atom having the highest Sr'$^{(E)}$ of the corresponding parent skeleton. The REPE value difference (ΔPB) between the parent compound's REPE value, and the REPE value of carbocation species ($\mathbf{1_B}$-$\mathbf{12_B}$) derived from the ring-opening of the bay-region diol-epoxide, and their carcinogenicity of a benz[*c*]acridine (**1**) and eleven methylbenz[c]acridines (**2-12**), was also calculated.

Both REPE values of cationic species ($\mathbf{1_S}$-$\mathbf{12_S}$) and REPE values of carbocation species ($\mathbf{1_B}$-$\mathbf{12_B}$) were apparently lower than those of the corresponding parent's REPE, for example, the REPE difference (ΔPS) between the parent compound's REPE(P) ($\mathbf{1_P}$=0.0344ß) and the REPE(Sr'$^{(E)}$) ($\mathbf{1_S}$= 0.0304ß) of the noncarcinogenic benz[*c*]acridine (**1**) was 0.0040ß. The REPE difference (ΔPS) between the parent compound's REPE(P) ($\mathbf{2_P}$=0.0306ß) and REPE(Sr'$^{(E)}$) ($\mathbf{2_S}$=0.0272ß) of carcinogenic 7-methylbenz[*c*]acridine (**2**) was 0.0034ß. The REPE difference (ΔPB) between the parent compound's REPE(P) ($\mathbf{1_P}$=0.0344ß) and REPE(B) ($\mathbf{1_B}$=0.0252ß) of noncarcinogenic benz[*c*]acridine (**1**) was 0.0092ß. The REPE difference (ΔPB) between the parent compound's REPE(P) ($\mathbf{2_P}$=0.0306ß) and REPE(B) ($\mathbf{2_B}$=0.0223ß) of carcinogenic 7-methylbenz[*c*]acridine (**2**) was 0.0083ß. Among the twelve benz[*c*]acridines (**1-12**), their REPE differences (ΔPS=0.0037ß to 0.0040ß) of five noncarcinogenic benz[*c*]acridines (**1,3-6**) were higher than the REPE differences (ΔPS= 0.0033ß to 0.0034ß) of the six carcinogenic benz[c]acridines (**2,8-12**) except a noncarcinogenic 5,7-dimethylbenz[*c*]acridine (**7**, ΔPS=0.0033ß). Similarly, the REPE differences (ΔPB=0.0084ß to 0.0092ß) of the five noncarcinogenic benz[*c*]acridines (**1,3-6**) were higher than the REPE differences (ΔPB=0.0073ß to 0.0083ß) of the six carcinogenic benz[*c*]acridines (**2,8-12**) except a noncarcinogenic 5,7-dimethylbenz[*c*]acridine (**7**, ΔPB= 0.0078ß). The methyl substituent (s) in the benz[*c*]acridine skeleton has a tendency to reduce the ΔPB value because the lower degree of the REPE differences (ΔPB=0.0073ß to 0.0085ß) of eleven methylbenz[*c*]acridines (**2-12**) was

Table II (continued 1). *Bond-order, REPEs and Sr'$^{(E)}$ of phenothiazine (13) and benzo[a]phenothiazines (18-21).*

Compd's No. and structure	Bond[1)]	Bond-order (ß unit)[2)]	REPE (P) (in ß unit)[3)]	Approximate superdelocalizability (in ß unit)			ΔPS[8)]	ΔPB[9)]	Carcinogenicity index[10)]
				Position[4)]	Sr'$^{(E)}$ [5)]	REPE (Sr'$^{(E)}$)[6)]			
18, 5-oxo-5*H*-benzo[*a*]phenothiazine 	6,6a	0.704	0.0256	13	1.279	0.0254	0.0002	-	over
19, 9- 6-methyl-5-oxo-5*H*-benzo[*a*]phenothiazine 	6,6a	0.703	0.0232	13	1.269	0.0231	0.0001	-	±
20, 6-hydroxy-5-oxo-5*H*-benzo[*a*]phenothiazine 	6,6a	0.702	0.0231	13	1.253	0.0231	0	-	±
21, 5*H*-benzo[*a*][1,4]benzothiazino [3,2-*c*]phenothiazine 	1,2 (3,4)	0.685	0.0264	10 (11)	1.902	0.0295	-0.0031	-	±

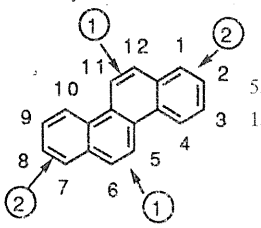
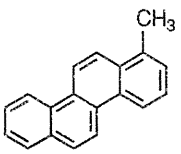
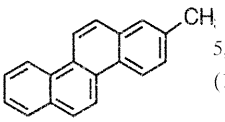
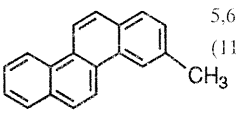
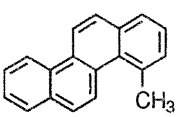
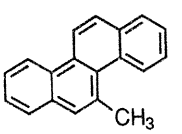
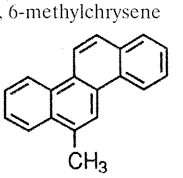
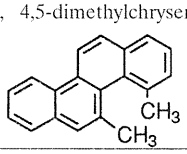
[7]REPE(B): The values of REPE(B) of 5-oxo-5H-benzo[a]phenothiazines **18-21** by a convergent ω-method have not a convergency.
[10]Antitumor activity index (Ref. 14,15): +: antitumor; -: nonantitumor.

apparently found in comparison with the REPE difference (ΔPB=0.0092ß) of non-methylsubstituted benz[c]acridine (**1**). Increasing the number of the methyl (mono, di, trimethyl) substituent (s) lowered the ΔPB values (Table I) (4,12,13). This suggests that there is a relationship between percentage hypochromism and pKa value of benz[*c*]acridines (11).

Relationship between antitumor activity and REPEs of phenothiazine (13) and benzo[a]phenothiazines (14-21). Table II shows the bond-order, resonance energies per π-electron (REPE(P)s), approximate superdelocalizability (Sr'$^{(E)}$) in parent, REPE(Sr'$^{(E)}$)(REPE value except the position of the highest Sr'$^{(E)}$ in parent), REPE(B) (carbocation species derived from the ring-opening of the bay-region diol-epoxide), the REPE value difference (ΔPS) between the parent's REPE value and REPE value of the twelve cationic species (**13_S-21_S**) with lack of the sulfur atom or the ketone oxygen having the highest Sr'$^{(E)}$ of the corresponding parent skeleton. The REPE value difference (ΔPB) between the parent's REPE value and REPE value of carbocation species (**13_B-21_B**) derived from the ring-opening of the bay-region diol-epoxide, and their antitumor activity in one phenothiazine (**13**) and eight benzo[*a*]phenothiazines (**14-21**) was also calculated (Table II).

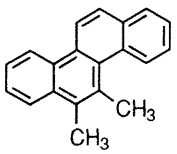
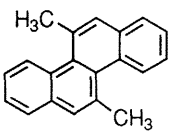
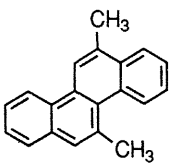
The REPE (Sr'$^{(E)}$) values of the cationic species (**13_S-17_S**, and **21S**) were higher than the REPE(P) values of the corresponding parent compounds (**13_P-17_P,** and **21_P**). For example, the REPE differences (ΔPS=-0.0060ß) between phenothiazine (**13p**, REPE(P)=0.0311ß) and its cationic species (**13s**, REPE (Sr'$^{(E)}$)=0.0371ß) was -0.0060ß and the REPE differences (ΔPS=-0.0060ß) between 9-methylbenzo[*a*]phenothiazine (**15p**, REPE(P)=0.0278ß) and its cationic species (**15s**, REPE(Sr'$^{(E)}$)=0.0324ß) was -0.0046ß as well. On the other hand, the REPE(Sr'$^{(E)}$) values of the cationic species (**18_S-20_S**) were lower than the REPE(P) values of the corresponding parent compounds (**18_P-20_P**), whereas the REPE difference (ΔPS) between REPE(P) value of 6-hydroxy-5-oxo-5*H*-benzo[*a*]phenothiazine (**20_P**, REPE (P)=0.0231ß), and REPE (Sr'$^{(E)}$) value of its cationic species (**20_S**, REPE (Sr'$^{(E)}$)=0.0231ß) was -0.0000ß. Interestingly,

Table III. *Bond-order, REPEs and* $Sr^{\cdot(E)}$ *of chrysenes (22-29).*

Compd's No. and structure	Bond[1]	Bond-order (ß unit)[2]	REPE (P) (in ß unit)[3]	Approximate superdelocalizability (in ß unit)				ΔPS[8]	ΔPB[9]	Carcinogenicity index[10]
				Position[4]	$Sr^{\cdot(E)}$ [5]	REPE ($Sr^{\cdot(E)}$)[6]	REPE(B)[7]			
22, chrysene 	5,6 1,2	0.754 0.712	0.0382	6	0.572	0.0312	0.0301	0.0070	0.0081	±
monomethylchrysenes										
23, 1-methylchrysene 	5,6 1,2	0.754 0.754	0.0344	12	0.572	0.0275	0.0267	0.0069	0.0077	-
24, 2-methylchrysene 	5,6 (11,12)	0.754	0.0344	12	0.577	0.0276	0.0268	0.0068	0.0076	-
25, 3-methylchrysene 	5,6 (11,12)	0.754 0.754	0.0344	6	0.575	0.0276	0.0267	0.0068	0.0077	-
26, 4-methylchrysene 	5,6 (11,12)	0.754 0.754	0.0344	12	0.576	0.0276	0.0266	0.0068	0.0078	+
27, 5-melhylchrysene 	11,12 5,6	0.754 0.751	0.0344	6	0.600	0.0281	0.0268	0.0063	0.0076	++
28, 6-methylchrysene 	11,12 5,6	0.754 0.751	0.0344	12	0.588	0.0278	0.0268	0.0066	0.0076	+
dimethylchrysenes										
29, 4,5-dimethylchrysene 	11,12 5,6	0.754 0.751	0.0312	6	0.591	0.0253	0.0240	0.0059	0.0072	+

[10]Carcinogenicity index (Ref. 16): +: carcinogenic; -: noncarcinogenic.

Table III. (continued 1). *Bond-order, REPEs and Sr'$^{(E)}$ of chrysenes (30-31).*

Compd's No. and structure	Bond[1]	Bond-order (ß unit)[2]	REPE (P) (in ß unit)[3]	Approximate superdelocalizability (in ß unit)				ΔPS[8]	ΔPB[9]	Carcinogenicity index[10]
				Position[4]	Sr'$^{(E)}$ [5]	REPE (Sr'$^{(E)}$)[6]	REPE(B)[7]			
30, 5,6-dimethylchrysene										
	11,12	0.754	0.0312	6	0.612	0.0254	0.0241	0.0058	0.0071	+
	5,6	0.748								
31, 5,11-dimethylchrysene										
	5,6 (11,12)	0.751	0.0312	6,12	0.594	0.0253	0.0241	0.0059	0.0071	++
	1,2 (10,11)	0.712								
32, 5,12-dimethylchrysene										
	11,12	0.751	0.0312	6	0.618	0.0254	0.0241	0.0058	0.0071	+
	5,6	0.751								

the cationic species ($\mathbf{1_S}$-$\mathbf{12_S}$) of carcinogenic benz[*c*]acridines are more unstable than their parent molecules ($\mathbf{1_P}$-$\mathbf{12_P}$), because the REPE(P) values ($\mathbf{1_P}$-$\mathbf{12_P}$) of benz[*c*]acridines (**1-12**) were higher than the REPE(Sr'$^{(E)}$) value of the corresponding cationic species ($\mathbf{1_S}$-$\mathbf{12_S}$). Conversely, the cationic species ($\mathbf{13_S}$-$\mathbf{17_S}$, and $\mathbf{21_S}$) of six benzo[*a*]phenothiazines (**13-17, 21**) are more stable than their parent molecule's ($\mathbf{13_P}$-$\mathbf{17_P}$, and $\mathbf{21_P}$), because the REPE(Sr'$^{(E)}$) values of cationic benzo[*a*]phenothiazines ($\mathbf{13_S}$-$\mathbf{17_S}$, and $\mathbf{21_S}$) were higher than REPE(P) values of the corresponding parent species ($\mathbf{13_P}$-$\mathbf{17_P}$, and $\mathbf{21_P}$). Moreover, the three cationic 5-oxo-5*H*-benzo[*a*]phenothiazines ($\mathbf{18_S}$-$\mathbf{20_S}$) were also stable, because the REPE(Sr'$^{(E)}$) values ($\mathbf{18_S}$-$\mathbf{20_S}$) of the cationic species of 5-oxo-5*H*-benzo[*a*]phenothiazines (**18-20**) showed almost same REPE(P) values as the corresponding parent species ($\mathbf{18_P}$-$\mathbf{20_P}$) (Table II) (14,15).

Relationship between carcinogenic activity, and REPE (ΔPS and ΔPB) on chrysenes (22-32). The effect of the substitution by a methyl group (s) on the carcinogenic activity of chrysene (**22**) and eleven methylchrysenes (**23-32**) was measured. 5-Methylchrysene (**27**) and 5,11-dimethylchrysene (**31**) have the strongest carcinogenicity of chrysene (**22**) and the eleven methylchrysenes (**23-32**)(16).

Table III shows the bond-order, resonance energies per π-electron (REPE(P)s), approximate superdelocalizability (Sr'$^{(E)}$) in the parent compound, REPE(Sr'$^{(E)}$) (REPE value minus the position of the biggest Sr'$^{(E)}$ in parent), REPE(ß) (carbocation species derived from the ring-opening of the bay-region diol-epoxide), the REPE value difference (ΔPS) between the parent compound's REPE value and the REPE value of twelve cationic species ($\mathbf{22_S}$-$\mathbf{32_S}$) minus the carbon atom having the highest Sr'$^{(E)}$ of the corresponding parent skeleton. The REPE value difference (ΔPB) between the parent compound's REPE value and REPE value of the carbocation species ($\mathbf{22_B}$-$\mathbf{32_B}$) derived from the ring-opening of the bay-region diol epoxide, and the carcinogenic activity in one chrysene (**22**) and ten methylchrysenes (**23-32**), was also calculated. Furthermore, when both the carbon at C-5 and the methyl group at C-5 were removed at the same time for the ω-calculation, their behavior of 5,6-dimethylchrysene (**30**) and 5,12-dimethylchrysene (**32**) was different from the molecular orbital conditions of two other dimethyl chrysenes (**29, 31**), as the π-electron and the numbers of the orbitals of 5,6-dimethylchrysene (**30**) and 5,12-dimethylchrysene (**32**) differed from those of two other dimethyl chrysenes (**29, 31**). Therefore, both the carbon itself at C-5 and the methyl group at C-5 were treated as a floating atom and a floating group for the ω-calculation, for the correction to the same environmental condition on four dimethylchrysenes (**29-32**) (Table III).

The REPE(Sr'$^{(E)}$) values of the cationic species ($\mathbf{22_S}$-$\mathbf{32_S}$) were lower than the REPE(P) values of the corresponding parent compounds ($\mathbf{22_P}$-$\mathbf{32_P}$). For example, the REPE differences (ΔPS) between parent 5,11-dimethylchrysene (**31**, REPE(P)=0.0312ß) and its cationic species (**31**, REPE (Sr'$^{(E)}$)=0.0253ß) was 0.0059ß and the REPE differences (ΔPS) between 1-methylchrysene (**23**, REPE(P)=0.0344ß)

and its cationic species (**23**, REPE(Sr'$^{(E)}$)=0.0275ß) was 0.0069ß.

As with to benz[*c*]acridines, the cationic species ($\mathbf{22_S}$-$\mathbf{32_S}$) and carbocation species ($\mathbf{22_B}$-$\mathbf{32_B}$) of chrysenes (**22-32**) were more unstable than their parent molecules ($\mathbf{22_P}$-$\mathbf{32_P}$), because the REPE(P) values ($\mathbf{1_P}$-$\mathbf{12_P}$) of benz[*c*]acridines (**1-12**) were higher than the REPE(Sr'$^{(E)}$) value of the corresponding cationic species ($\mathbf{1_S}$-$\mathbf{12_S}$). It is thus concluded that the REPE difference value (ΔPS) lower than 0.0066ß is neccesary for the carcinogenicity of methylchrysenes, except 4-methylchrysene (**26**, ΔPS=0.0068ß) to be apparent.

The methyl group at the C-6 or C-12 positions was treated as floating atom, which was not bonded to the carbon atom at the 6 or 12 position.

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