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Radical Productions and π-Spin Density by UHF/PM3 Method on Benz[*c*]acridines and Benzo[*a*]phenothiazines

26

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Abstract. *On the calculated π-spin density (ϱ^{π}) of benz[c]acridines [1-12], benz[c]acridines [2,8-12] with alternately value of π-spin density (ϱ^{π}) on angular ring, large negative π-spin density at C-1 and C-3 positions and large positive π-spin density at C-2 and C-4 positions indicates their carcinogenicity, except for 7-methylbenz[c]acridine [7]. Benz[c]acridines [1,3-6] which do not follow were not carcinogenic. Radical producing benzo[a]phenothiazines [13-16] and non-radical producing benzo[a]phenothiazines [17-19] gave calculated π-spin density (ϱ^{π}) which was positive in radical producing benzo[a]phenothiazines [13-16] at N-12 position, and had the opposite π-spin density in non-radical producing benzo[a]phenothiazines [17-19].*

Some benz[*c*]acridines and benzo[*a*]phenothiazines produce radicals (1-3). Using both McLachlan-Hückel molecular orbital (McLachlan-HMO) and Hückel methods on benz[*c*]acridines, all the carcinogenic benz[*c*]acridines were shown to have elevated π-spin density at their 12th nitrogen atom as compared with noncarcinogenic benz[*c*]acridines. Electron spin resonance (ESR) spectroscopy, however, revealed that both carcinogenic and noncarcinogenic benz[*c*]acridines produced no detectable amounts of the radical (3). The radical modulation activity of ^{12}*H*-benzo[*a*]phenothiazine might explain at least in part the ability of this compound to induce monocytic differentiation and apoptosis in human myelogenous leukemic cell lines (1) and the induction of human leukemic cell differentiation by benzo[*a*]phenothiazines might be initiated by radical mediated reactions (2). The purpose of this paper is to clarify the relationship between the radical productions and the π-spin density (ϱ^{π}) by UHF/PM3 method on benz[*c*]acridines and benzo[*a*]phenothiazines.

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Key Words: π-Spin density (ϱ^{π}), UHF/PM3 method, carcinogenicity, antitumor activity, benz[*c*]acridines, benzo[*a*]-phenothiazines.

Materials and Methods

Materials. Benz[*c*]acridines [**1-12**] and benzo[*a*]phenothiazines [**13-20**] were synthesized as previously described (Figure 1) (4).

Calculation. π-Spin density (ϱ^{π}) of benz[c]acridines [**1-12**] and benzo[a]phenothiazines [**13-20**] was calculated by unrestricted Hartree-Fock/Parametric Method 3 (UHF/PM3 method) (5). The geometry of the cation radical species was optimized with respect to all geometrical parameters using Broyden-Fletcher-Goldfarb-Shanno algorithm incorporated into the program. For these calculations, the FACOM M330 computer in the Josai University Information Sciences Center was used. π-Spin density (ϱ^{π}) was defined as the α-Spin density minus the β spin density.

Results and Discussion

Benz[c]acridines [1-12]. The UHF/PM3 optimized geometry was almost planar. The C-C bonds of benz[*c*]acridines were 1.412-1.492Å and the formular double bonds were 1.374-1.386Å except the central bonds such as C4a-C12b and C7a-C11a were 1.415-1.419Å. The C11a-N12 and N12-C12a were 1.362-1.410Å and 1.327-1.359Å, respectively.

Relationship between π-spin density (ϱ^{π}) and carcinogenicity of benz[c]acridines [1-12]. A clear rule at C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-12a and C-12b positions could be found (Figure 2).

First, by clockwise rotation on an angular ring or naphthalene moiety, the distribution of the π-spin density (ϱ^{π}) at C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-12a and C-12b positions on carcinogenic benz[*c*]acridines [**2, 8, 9, 10, 11** and **12**] changed alternately from negative π-spin density to positive π-spin density. Whereas noncarcinogenic benz[*c*]acridines [**1, 3, 4, 5, 6** and **7**] did not obey to this rule.

Second, benz[*c*]acridine carcinogenicity must involve large negative values of the π-spin density at both C-1 and C-3 positions, and the large positive values of the π-spin density at both C-2 and C-4 positions. Additionally, the π-spin density at C-2 position of carcinogenic benz[*c*]acridines [**2, 8, 9, 10, 11** and **12**] was much larger than the π-spin density of noncarcinogenic benz[*c*]acridines [**1, 3, 4, 5, 6** and **7**] and the π-spin density at C-4 position of carcinogenic benz[*c*]acridines

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[**2**, **8**, **9**, **10**, **11** and **12**] was much larger than that of noncarcinogenic benz[*c*]acridines [**1**, **3**, **4**, **5**, **6** and **7**].

Therefore, a) Active singlet oxygen might attack M-region at C-3 and C-4 positions or bay-region at C-1 and C-2 positions of benz[*c*]acridines, producing a benz[*c*]acridine-oxygen adduct (or complex). Then, a benz[*c*]acridine-adduct could change to become carcinogenic. b) The π-spin density

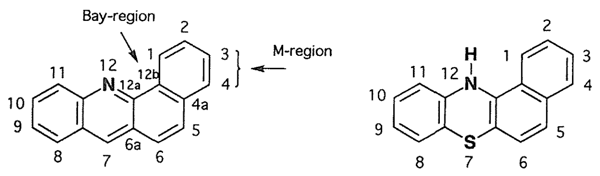
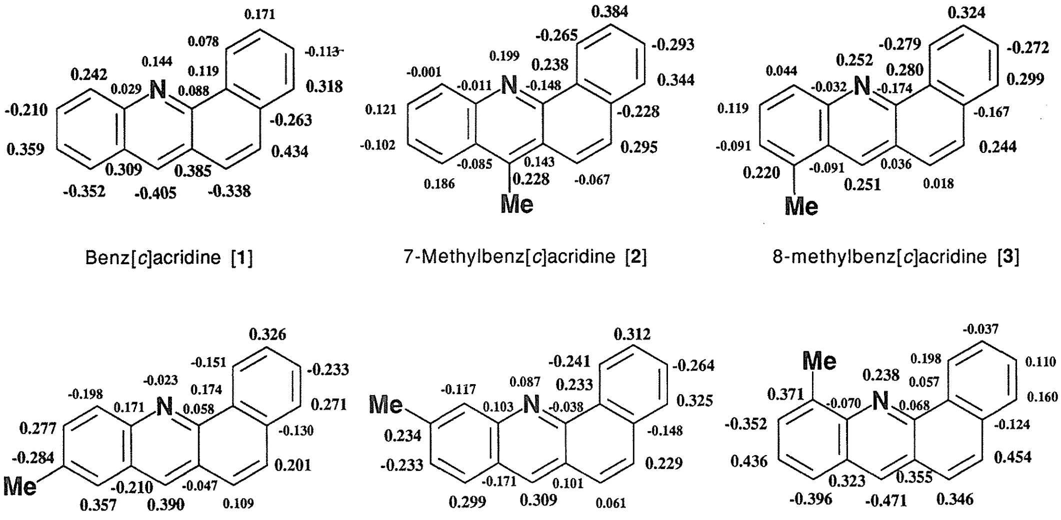
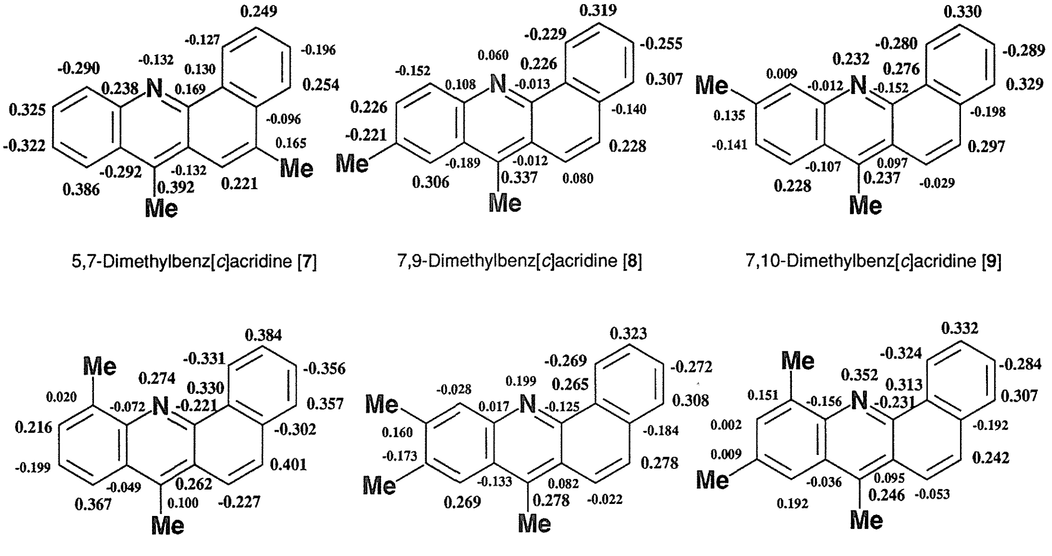


Figure 1. *Benz[c]acridines and benzo[a]phenothiazines.*



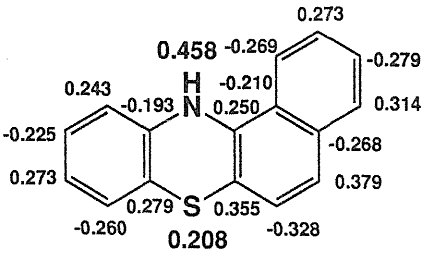
Benz[*c*]acridine [**1**]
7-Methylbenz[*c*]acridine [**2**]
8-methylbenz[*c*]acridine [**3**]
9-methylbenz[*c*]acridine [**4**]
10-methylbenz[*c*]acridine [**5**]
11-methylbenz[*c*]acridine [**6**]

Figure 2. *π-Spin densities of benz[c]acridines [1-6] calculated by UHF/PM3 method.*

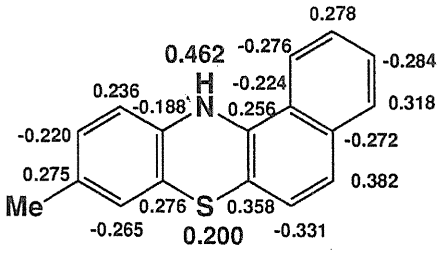


5,7-Dimethylbenz[*c*]acridine [**7**]
7,9-Dimethylbenz[*c*]acridine [**8**]
7,10-Dimethylbenz[*c*]acridine [**9**]
7,11-Dimethylbenz[*c*]acridine [**10**]
7,9,10-Trimethylbenz[*c*]acridine [**11**]
7,9,11-Trimethylbenz[*c*]acridine [**12**]

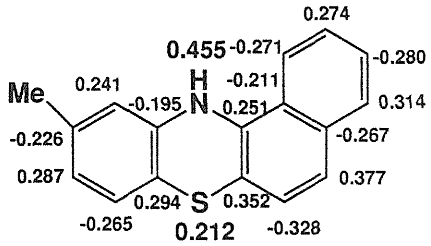
Figure 2 *(cont.1). π-Spin densities of benz[c]acridines [7-12] calculated by UHF/PM3 method.*



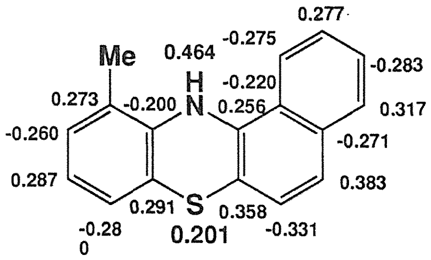
12*H*-Benzo[*a*]phenothiazine [13]



9-Methyl-12*H*-benzo[*a*]phenothiazine [14]

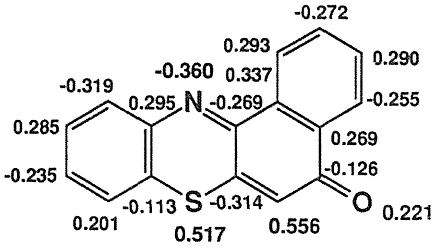


10-Methyl-12*H*-benzo[*a*]phenothiazine [15]

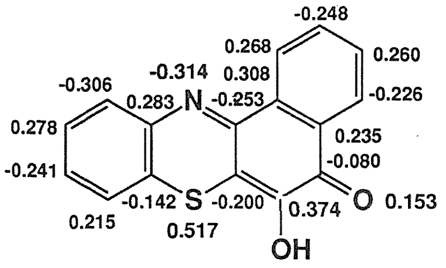


11-Methyl-12*H*-benzo[*a*]phenothiazine [16]

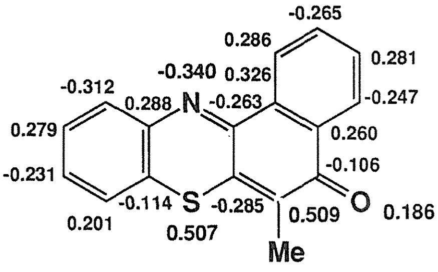
Figure 3. *π-Spin densities calculated by UHF/PM3 method of benzo[a]phenothiazines [13-16] which produce potent radicals(s).*



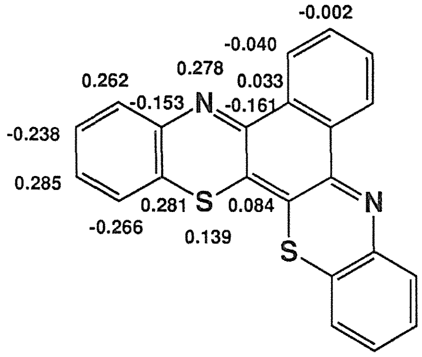
5-Oxo-5*H*-benzo[*a*]phenothiazine [17]



6-Hydroxy-5-oxo-5*H*-benzo[*a*]phenothiazine [18]



6-Methyl-5-oxo-5*H*-benzo[*a*]phenothiazine [19]



5*H*-Benzo[*a*][1,4]benzothiazino-
[3,2-*c*]phenothiazine [20]

Figure 3 *(cont.1). π-Spin densities calculated by UHF/PM3 method of benzo[a]phenothiazines [17-20] which produce potent weak or no radicals(s).*

(ϱ^{π}) of each position on twelve benz[*c*]acridines had roughly average density. Therefore, it might be supposed that twelve benz[*c*]acridines did not produce a significant radical intensity in the ESR condition of our study. c) A linear relationship between a distribution of π-spin density (ϱ^{π}) by UHF/PM3 method and carcinogenicity of benz[*c*]acridines was shown in this study.

Benzo[a]phenothiazines [13-20]. The geometry study of benzo[*a*]phenothiazines [**13-20**] was carried out with optimization of all geometrical parameters with no assumption. In all cases, the UHF/PM3 optimized geometry was planar. The C-C bonds of benzo[*a*]phenothiazines [**13-16**] were 1.402-1.445Å and the double bonds were 1.380-1.394Å, except for the central bonds such as C4a-C12b, C6a-C12a, and C7a-C11a which were 1.414-1.418Å. The C11a-N12 and N 12-C12a were 1.402-1.104Å and 1.385-1.386Å, respectively. The C6a-S7 and S7-C7a were 1.730-1.737Å.

Relationship between the radical intensity and π-spin density (ϱ^{π}) at N-12 position of benzo[a]phenothiazines. First, the relationship between the radical intensity and π-spin density (ϱ^{π}) calculated by UHF/PM3 method at N-12 position of benzo[*a*]phenothiazines was discussed (Figure 3). Significant radical producing benzo[*a*]phenothiazines [**13-16**] had the π-spin density (ϱ^{π}) of 0.458, 0.462, 0.455, and 0.464, respectively. A positive π-spin density means that α-spin density is larger than β-spin density. Whereas, non-radical producing benzo[*a*]phenothiazines [**17-19**] had a π-spin density (ϱ^{π}) of -0.360, -0.314 and -0.340, respectively. A negative π-spin density means that β-spin density is larger than α-spin density. Between radical producing benzo[*a*]phenothiazines [**13-16**] and non-radical producing benzo[*a*]phenothiazines [**17-19**], the (+) π-spin density (ϱ^{π}) of radical producing benzo[*a*]phenothiazines [**13-16**] at N-12 position had the opposite values of (-) π-spin density of non-radical producing benzo[*a*]phenothiazines [**17-19**].

Relationship between radical intensity and π-spin densitv (ϱ^{π}) at S-7 position of benzo[a]phenothiazines. The positive π-spin density at S-7 position of benzo[*a*]phenothiazines [**13-16**] was 0.208, 0.200, 0.212 and 0.201, respectively. Whereas, non-radical producing benzo[*a*]phenothiazines [**17-19**] had the π-spin density of 0.517, 0.517 and 0.507, respectively.

Apparently, benzo[*a*]phenothiazines [**17-19**] had a larger π-spin localization than benzo[*a*]phenothiazines [**13-16**].

Interestingly the carcinogenicity or noncarcinogenicity on benz[*c*]acridines [**1-12**] could be easily predicted by the plus-minus rule of π-spin density of benz[clacridines [**1-12**] benzo[*a*]phenothiazines, however, could not be followed using the above rule. Second, it is thought that a singlet oxygen might attack the sites of bay-region (C-1 - C2) or M-region (C-3 - C4) of benz[*c*]acridines and by the reactions of the radicals benz[*c*]acridines become carcinogenic. This study should be continued to further clarify the site attacked by the radicals, *i.e.*, singlet oxygen and other radical species.

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