Notes

A Study on the Relationships between Molecular Structure and Antitumor Activity I: 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU) and 3-(N-phenylacetylamino)-2,6-piperidinedione (Antineoplaston A10)

Min Joo Lee*, Sam Kyu Lee, Seong Hoon Kim†, and Yoo Hang Kim†

Department of Chemistry, Changwon National University, Changwon, Kyungnam 641-773, Korea
†Department of Chemistry, Inha University, Inchon 402-751, Korea

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The chloroethylnitrosoureas are important cytotoxic agents against the hematological and solid cancers.[1] The PCNU is an interesting compound as clinically active agent which has 3- to 4-fold higher alkylating activity than other anticancer nitrosourea drugs such as 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).

Several studies show close relationship between antitumor activity of nitrosoureas and their alkylating activity.[2,3] The solubility of the nitrosoureas also affects their antitumor activity.[4] On the basis of high alkylating activity and favorable solubility, PCNU is expected to have excellent cilincal activity.

Antineoplaston A10 is a natural compound isolated from human urine and plasma and has been shown to have remarkable antitumor activity and toxicity.[5,6] X-ray crystal structure[7] and the Raman and IR spectra[8] of synthetic Antineoplaston A10 have been obtained. Also semi-empirical MNDO calculations[9] have been performed on its derivative, 3-acetylamino-2,6-piperidinedione. From these studies it was found that the A10 molecule has structural resemblance to base pairs in a DNA helix. And it is possible that A10 may intercalate between base pairs of DNAs and interact via hydrogen bonding with them.

Interestingly, PCNU and Antineoplaston A10 have closely related structural features as shown in Figure 1. The aminopiperidinedione moiety in both molecules indicates that the biological activity may be associated with this moiety.

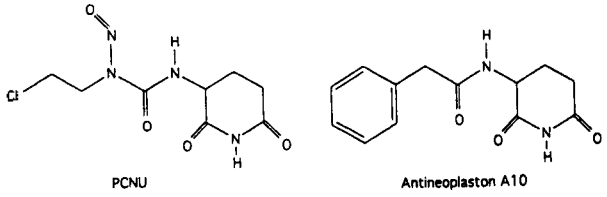

Figure 1. The structure of PCNU, 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea, and Antineoplaston A10, 3-(N-phenylacetylamino)-2,6-piperidinedione.

The purpose of this work is to get basic data for elucidating the relationship between structure and antitumor activity of these compounds by calculating the structural parameters and total atomic charges. Therefore, in order to characterize the geometrical and chemical properties, *ab initio* calculations have been carried out to obtain the optimized structure and atomic charges for both molecules. All of these results are discussed herein.

Ab initio Calculations

These calculations were performed with the Gaussian-92 /DFT program[10] using the RHF/4-31G basis set for obtaining the optimized geometries and atomic charge distributions of both PCNU and antineoplaston A10.

Before the full geometry optimization of the whole molecule is attempted, the geometry optimization of three moieties-*i.e.*, glutarimide, amido, and piperidinedione fragments-has been carried out with the reported experimental[7,11] and MNDO[9] data as the starting values.

In the next step the optimized glutarimide and amido fragments have been connected and optimized. Then, this optimized glutarimide-amido structure has been connected to the optimized structure of piperidinedione fraction and all parameters of Antineoplaston A10 are relaxed and completely optimized. The same procedures were used for the PCNU too.

Results and Discussion

PCNU. In Table 1 are presented structural parameters, rotational constants, dipole moment and total energy for PCNU, and in Figure 2 are given total atomic charges of it. Some important geometrical parameters, which may affect the strength of the hydrogen bonding between the drug and the receptors and/or the insertion ability of the drug into the DNA double helix, of the skeleton are r (C_1-C_6) = 1.531, r (C_2-C_1) = 1.511, r (N_3-C_2) = 1.370, r (C_4-N_3) = 1.384, r (C_5-C_4) = 1.503, r (C_6-C_5) = 1.528, r (N_{15}-C_1) = 1.440, r (C_{17}-N_{15}) = 1.344 and r (N_{19}-C_{17}) = 1.415 Å. The total atomic charges of fairly polar atoms are C_2 = 0.859, N_3 = −1.001, C_4 = 0.825, O_7 = −0.592, H_8 = 0.420, O_9 = −0.603, N_{15} = −0.903, H_{16} = 0.428, C_{17} = 1.137, O_{18} = −0.606, and N_{19} = −0.754. The distances between O_7·····H_8, O_9·····H_8, O_{18}·····H_{16} are 2.472, 2.442, and 3.136 Å, respectively.

Antineoplaston A10. In Table 2 are presented structural parameters, rotational constants, dipole moment and total energy for Antineoplaston A10, and in Figure 3 are given total atomic charges of it. Some structurally important geometrical parameters, which may affect the strength of the hydrogen bonding between the drug and the receptors and/or the insertion ability of the drug into the DNA double helix, of the skeleton are r (C_1-C_6) = 1.531, r (C_2-C_1) = 1.523, r (N_3-C_2) = 1.373, r (C_4-N_3) = 1.378, r (C_5-C_4) = 1.502, r (C_6-C_5) = 1.527, r (N_{15}-C_1) = 1.442, r (C_{17}-N_{15}) = 1.351 and r (C_{19}-C_{17}) = 1.516 Å. The total atomic charges of fairly polar atoms are

Table 1. Structural parameters, rotational constants, dipole moment and total energy for PCNU[a]

Parameter[b]	RHF/4-31G	Parameter[b]	RHF/4-31G	Parameter[b]	RHF/4-31G
r (C_1-N_{15})	1.440	∠ (C_1-N_{15}-C_{17})	120.6	τ (C_1-N_{15}-C_{17}-O_{18})	6.5
r (C_2-C_1)	1.511	∠ (C_2-C_1-N_{15})	108.8	τ (C_2-C_1-N_{15}-C_{17})	−207.1
r (N_3-C_2)	1.378	∠ (N_3-C_4-C_5)	116.4	τ (N_3-C_4-C_5-C_2)	−0.2
r (N_3-C_4)	1.384	(C_4-C_5-C_6)	112.6	τ (C_4-C_5-C_6-C_1)	52.4
r (C_4-C_5)	1.503	∠ (C_5-C_6-C_1)	109.4	τ (C_5-C_6-C_1-C_2)	−58.1
r (C_5-C_6)	1.528	∠ (C_6-C_1-N_{15})	113.9	τ (C_6-C_1-N_{15}-C_{17})	−83.9
r (C_6-C_1)	1.531	∠ (O_7-C_4-N_3)	120.0	τ (O_7-C_4-N_3-C_2)	−179.9
r (O_7-C_4)	1.211	∠ (H_8-N_3-C_4)	115.7	τ (H_8-N_3-C_4-C_2)	−182.8
r (H_8-N_3)	0.998	∠ (O_9-C_2-N_3)	121.3	τ (O_9-C_2-N_3-C_4)	173.4
r (O_9-C_2)	1.214	∠ (H_{10}-C_1-C_2)	107.6	τ (H_{10}-C_1-C_2-N_3)	−81.8
r (H_{10}-C_1)	1.085	∠ (H_{11}-C_6-C_1)	108.8	τ (H_{11}-C_6-C_1-C_2)	181.2
r (H_{11}-C_6)	1.079	∠ (H_{12}-C_6-C_1)	109.5	τ (H_{12}-C_6-C_1-C_2)	63.6
r (H_{12}-C_6)	1.084	∠ (H_{13}-C_5-C_4)	107.6	τ (H_{13}-C_5-C_4-N_3)	97.5
r (H_{13}-C_5)	1.086	∠ (H_{14}-C_5-C_4)	107.5	τ (H_{14}-C_5-C_4-N_3)	−147.8
r (H_{14}-C_5)	1.079	∠ (N_{15}-C_{17}-N_{19})	114.0	τ (N_{15}-C_{17}-N_{19}-N_{20})	−147.8
r (N_{15}-C_{17})	1.344	∠ (H_{16}-N_{15}-C_{17})	120.8	τ (H_{16}-N_{15}-C_{17}-O_{18})	187.2
r (H_{16}-N_{15})	0.994	∠ (O_{18}-C_{17}-N_{19})	122.6	τ (O_{18}-C_{17}-N_{19}-N_{20})	35.1
r (C_{17}-N_{19})	1.415	∠ (N_{20}-N_{19}-C_{17})	123.3	τ (O_{21}-N_{20}-N_{19}-C_{17})	16.0
r (O_{18}-C_{17})	1.216	∠ (O_{21}-N_{20}-N_{19})	118.0	τ (C_{22}-N_{19}-N_{20}-C_{17})	168.0
r (N_{20}-N_{19})	1.354	∠ (C_{22}-N_{19}-N_{20})	112.9	τ (H_{23}-C_{22}-N_{19}-N_{20})	192.2
r (O_{21}-N_{20})	1.194	∠ (H_{23}-C_{22}-N_{19})	108.6	τ (C_{24}-C_{22}-N_{19}-N_{20})	68.5
r (C_{22}-N_{19})	1.463	∠ (C_{24}-C_{22}-N_{19})	113.2	τ (H_{25}-C_{22}-N_{19}-N_{20})	−50.8
r (H_{23}-C_{22})	1.077	∠ (H_{25}-C_{22}-N_{19})	108.1	τ (H_{26}-C_{24}-C_{22}-H_{23})	61.3
r (C_{24}-C_{22})	1.510	∠ (H_{26}-C_{24}-C_{22})	111.8	τ (Cl_{27}-C_{24}-C_{22}-H_{23})	−55.1
r (H_{25}-C_{22})	1.083	∠ (Cl_{27}-C_{24}-C_{22})	110.9	τ (H_{28}-C_{24}-C_{22}-H_{23})	187.6
r (H_{26}-C_{24})	1.074	∠ (H_{28}-C_{24}-C_{22})	112.8	A	718.4
r (Cl_{27}-C_{24})	1.895			B	233.1
r (H_{28}-C_{24})	1.073			C	193.6
				μ	3.329
				$-E$	1284.298926

[a] Bond lengths in Å, bond angles in degrees, rotational constants (A, B, C) in MHz, dipole moment (μ) in Debyes and energy (E) in Hartrees. [b] For the definition of atom numbers, see Figure 2.

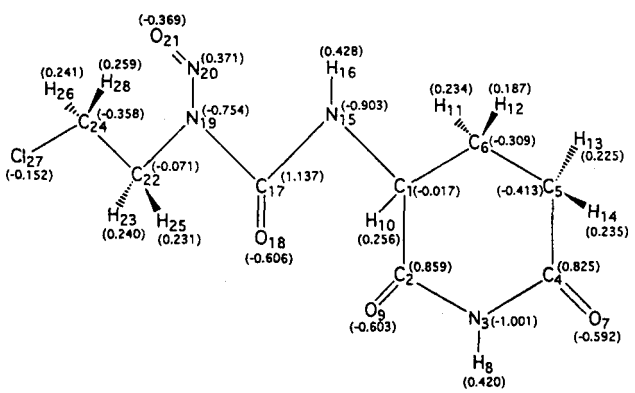

Figure 2. Structural model and atom numbering of 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU). The numbers in parentheses are the atomic electronic charges calculated in this work.

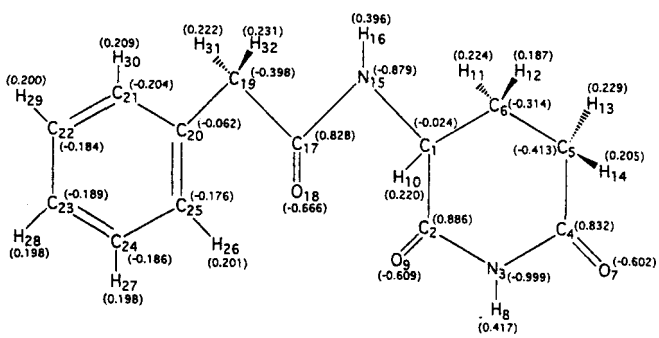

Figure 3. Structural model and atom numbering of 3-(N-phenylacetylamino)-2,6-piperidinedione (Antineoplaston A10). The numbers in parentheses are the atomic electronic charges calculated in this work.

C_2=0.886, N_3=−0.999, C_4=0.832, O_7=−0.602, H_8=0.417, O_9=−0.609, N_{15}=−0.879, H_{16}=0.396, C_{17}=0.828, O_{18}=−0.666, and C_{19}=−0.398. The distances between O_7·····H_8, O_9·····H_8, O_{18}·····H_{16} are 2.472, 2.442, and 3.136 Å, respectively.

From these results one can see that the atoms O_7, O_9,

Table 2. Structural parameters, rotational constants, dipole moment and total energy for Antineoplaston A10[a]

Parameter	RHF/4-31G	Parameter	RHF/4-31G	Parameter	RHF/4-31G
r (C_1-C_6)	1.531	∠ (N_3-C_2-C_1)	116.3	τ (C_4-N_3-C_2-C_1)	−2.58
r(C_2-C^1)	1.523	∠ (C_4-N_3-C_2)	128.5	τ (C_5-C_4-N_3-C_2)	3.16
r (N_3-C_2)	1.373	∠ (C_5-C_4-N_3)	116.1	τ (C_6-C_5-C_4-N_3)	−29.4
r (C_4-N_3)	1.378	∠ (C_6-C_5-C_4)	112.3	τ (O_7-C_4-N_3-C_2)	181.3
r (C_5-C_4)	1.502	∠ (O_7-C_4-N_3)	120.4	τ (H_8-N_3-C_2-C^1)	179.7
r (C_6-C_5)	1.527	∠ (H_8-N_3-C_2)	115.6	τ (O_9-C_2-N_3-C_4)	180.5
r (O_7-C_4)	1.213	∠ (O_9-C_2-N_3)	120.9	τ (H_{10}-C^1-C_2-O_9)	87.6
r (H_8-N_3)	0.997	∠ (H_{10}-C^1-C_2)	105.6	τ (H_{11}-C_6-C^1-C_5)	121.5
r (O_9-C_2)	1.211	∠ (H_{11}-C_6-C^1)	109.1	τ (H_{12}-C_6-C^1-C_5)	−120.9
r (H_{10}-C^1)	1.086	∠ (H_{12}-C_6-C^1)	108.8	τ (H_{13}-C_5-C_6-C_4)	120.9
r (H_{11}-C_6)	1.078	∠ (H_{13}-C_5-C_6)	111.7	τ (H_{14}-C_5-C_6-C_4)	−120.0
r (H_{12}-C_6)	1.081	∠ (H_{14}-C_5-C_6)	110.6	τ (N_{15}-C^1-C_2-O_9)	−27.1
r (H_{13}-C_5)	1.079	∠ (N_{15}-C^1-C_2)	110.4	τ (H_{16}-N_{15}-C^1-C_2)	107.7
r (H_{14}-C_5)	1.087	∠ (H_{16}-N_{15}-C^1)	118.1	τ (C^{17}-N_{15}-C^1-C_2)	−61.1
r (N_{15}-C^1)	1.442	∠ (C^1-N_{15}-C^1)	122.2	τ (O_{18}-C^{17}-N_{15}-C^1)	−7.22
r (H_{16}-N_{15})	0.990	∠ (O_{18}-C^{17}-N_{15})	121.9	τ (C^{19}-C^{17}-N_{15}-C^1)	170.8
r (C^{17}-N_{15})	1.351	∠ (C^{19}-C^{17}-N_{15})	117.8	τ (C_{20}-C^{19}-C^{17}-N_{15})	18.8
r (O_{18}-C^{17})	1.225	∠ (C_{20}-C^{19}-C^{17})	116.7	τ (C_{21}-C_{20}-C^{19}-C^{17})	265.4
r (C^{19}-C^{17})	1.516	∠ (C_{21}-C_{20}-C^{19})	120.8	τ (C_{22}-C_{21}-C_{20}-C^{19})	179.6
r (C_{20}-C^{19})	1.508	∠ (C_{22}-C_{21}-C_{20})	120.7	τ (C_{23}-C_{22}-C_{21}-C_{20})	0.18
r (C_{21}-C_{20})	1.389	∠ (C_{23}-C_{22}-C_{21})	120.1	τ (C_{24}-C_{23}-C_{22}-C_{21})	−0.00
r (C_{22}-C_{21})	1.385	∠ (C_{24}-C_{23}-C_{22})	119.6	τ (C_{25}-C_{24}-C_{23}-C_{22})	−0.11
r (C_{23}-C_{22})	1.382	∠ (C_{25}-C_{24}-C_{23})	120.1	τ (H_{26}-C_{25}-C_{20}-C^{19})	0.60
r (C_{24}-C_{23})	1.384	∠ (H_{26}-C_{25}-C_{20})	119.5	τ (H_{27}-C_{24}-C_{25}-C_{20})	180.3
r (C_{25}-C_{24})	1.382	∠ (H_{27}-C_{24}-C_{25})	119.8	τ (H_{28}-C_{23}-C_{24}-C_{25})	180.2
r (H_{26}-C_{25})	1.073	∠ (H_{28}-C_{23}-C_{24})	120.2	τ (H_{29}-C_{22}-C_{23}-C_{24})	180.4
r (H_{27}-C_{24})	1.072	∠ (H_{29}-C_{22}-C_{23})	120.1	τ (H_{30}-C_{21}-C_{22}-C_{23})	180.7
r (H_{28}-C_{23})	1.072	∠ (H_{30}-C_{21}-C_{22})	119.7	τ (H_{31}-C^{19}-C^{17}-C_{20})	124.3
r (H_{29}-C_{22})	1.072	∠ (H_{31}-C^{19}-C^{17})	106.1	τ (H_{32}-C^{19}-C^{17}-C_{20})	−123.0
r (H_{30}-C_{21})	1.073	∠ (H_{32}-C^{19}-C^{17})	105.6	A	1284.3
r (H_{31}-C^{19})	1.081			B	197.0
r (H_{32}-C^{19})	1.084			C	193.9
				μ	7.23
				$-E$	832.768658

[a] Bond lengths in Å, bond angles in degrees, rotational constants (A, B, C) in MHz, dipole moment (μ) in Debyes and energy (E) in Hartrees. [b] For the definition of atom numbers, see Figure 3.

O_{18}, H_8, and H_{16} of PCNU and Antineoplaston A10 have enough electronic charges to form hydrogen bonds to the bases of DNA, and also that the piperidinedione ring is relatively flat and it is possible for this ring to be inserted between the DNA double helix as pointed out by Michalska in his MNDO study on the structure of 3-acetylamino-2,6-piperidinedione.[9] The piperidinedione ring shows a lot of similarity in its structural and electronic features to the pyrimidine bases, uracil, thymine, and cytosine.[12-15] Therefore, both PCNU and Antineoplaston A10 may easily interfere with the DNA replication and protein synthesis in tumor cells by hydrogen bonding and/or intercalation.

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Synthesis and Electrochemical Characteristics of Pitch Coke Carbon Material for Lithium Ion Battery

Chil-Hoon Doh, Seong-In Moon, Woo-Sik Kim†, and Mun-Soo Yun

Battery Technology Team, Korea Electrotechnology Research Institute, P. O. Box 20, Changwon 641-600, Korea
†Department of Polymer Science, Kyungpook National University, Taegu 702-701, Korea

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Carbon[1] is chemically very simple compound composed of only one element. But carbon has various structure, which lead versatile usage from structural material to advanced functional material. In the field of lithium ion battery, honeycomb-like layered stacking structure serves lithium ion intercalation site as the host. Guest lithium ion intercalates into the carbon host reversibly under electrochemical process by the following reaction[2]:

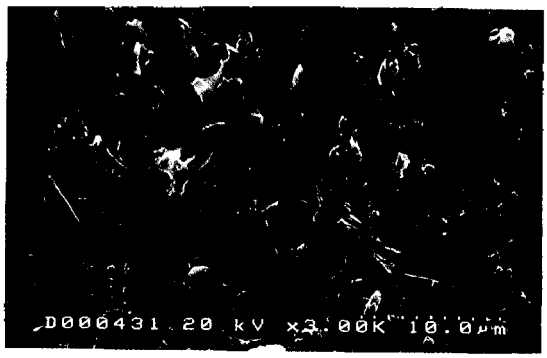
$$C_6 + Li^+ + e^- \rightleftarrows LiC_6$$

Intercalation characteristics closely depend on the particle size, surface area and stacking structure of carbon material. Fundamental requiring characteristics of carbon material for lithium ion battery are high specific capacity, high 1st Ah efficiency and stable cycling behavior.

Here, we discuss the synthesis and electrochemical properties of pitch coke derived from coal tar pitch by heat treatment under inert atmosphere on the purpose of the investigation of its applicability to lithium secondary battery.

Experimental

Pitch coke 1200 was synthesized by the heat-treatment of coal tar pitch. Coal tar pitch (softening point; 140 ℃) was carbonized at 500 ℃ for 1hour, and then heat-treated at 1200 ℃ for 2 hours under argon atmosphere. Heating rate was 10 ℃/min. Yield of synthesized pitch coke was 41 weight % based on loaded coal tar pitch. Coarse pitch coke was milled with zirconia ball to give pitch coke 1200, which is denoted as P.Coke12. X-ray diffractogram and SEM photographs of P.Coke12 were obtained by PW 1830 model of Phillips and S-2700 model of Hitachi, respectively.



(a) x 3000

(b) x 10000

Figure 1. SEM photograph of P.Coke12 electrode.

Anode was prepared as 75 μm sheet on one side of 50× 4.15 cm^2 area of copper foil (12 μm), coating of anode slurry, drying at 100 ℃ and then pressing. Anode slurry was the mixture of P.Coke12, super S. black, polyvinylidene fluoride and 1-methylpyrrolidone (weight ratio; 87 : 3 : 10 : 100). SEM morphology of P.Coke12 electrode in Figure 1 is shown. Particles having bended microstructure were observed in SEM photograph (a) and (b).

Cathode was prepared as 75 μm sheet on one side of 60× 4.2 cm^2 area of aluminum foil (25 μm) by similar process to anode process. Cathode slurry was the mixture of $LiCoO_2$ (FMC Ltd.), super S. black, polyvinylidene fluoride and 1-methylpyrrolidone (weight ratio; 92 : 3 : 5 : 100). Lithium metal was used as a reference electrode. Laminates of cathode, anode and separator (Cellgard 2500) were wound to make jelly roll by winding machine. Test cell was constructed on Pyrex glass tube using this jelly roll with lithium reference and electrolytic solution of 1 M $LiPF_6$ in ethylene carbonate and diethyl carbonate (1 : 1).

Assembled cell was tested by the galvanostatic charge-discharge by the Maccor series 2000 charge/discharge tester. Here, cut-off potential limits of P.Coke12 electrode were 0.02