sport rate is made very fast may reveal the detailed knowledge of this process. Measurements with a rotating disk electrode is in progress and will be reported in due course. We hope to distinguish contribution by kinetic or surface diffusion to overall current from mass transport rate. The arguments based on FePc mutilayer formation and thus the decrease in the effective number of FePc exposed to the solution dose not hold in this case since FePc is not likely to form a multilayer and this phenomenon was also observed when the coverage was far below monolayer. Although nitrite reduction was independent of surface coverage of FePc, reduction current at a constant amount of catalyst showed a linear dependence on a tested range of nitrite concentration (0.08 to 20 mM) as expected. Our experiments may imply important aspects in the practical applications. A minimum amount of electrocatalyst is needed to get full catalytic activity as long as one can be sure that electron transfer rate overrides diffusion or any other mass transport processes.

In this work, we showed FePc is a very efficient catalyst for the nitrite reduction in acidic solutions and Fe(II)Pc(-2)/Fe(II)Pc(-3) pair is responsible for such a high activity. Also we showed the reduction current is independent of the surface coverage within our experimental conditions and explained this effect in terms of kinetic *vs* diffusion control.

Acknowledgment. The author thanks Dr. I. T. Bae at Case Western Reserve University for the discussion. Financial support from Korea Research Foundation (04D0071) is gratefully acknowledged.

References

1. See, for example, Bockris, J. O'M.; Reddy, A. K. N. *Modern Electrochemistry*; Plenum Press: New York, U. S. A., 1970; Ch. 11.
2. Coleman, D. H.; White, R. E.; Hobbs, D. T. *J. Electrochem. Soc.* **1995**, *142*, 1152.
3. Leninger, A. L.; Nelson, D. L.; Cox, M. M. *Principles of Biochemistry*, 2nd Ed.; Worth Publishers: New York, U. S. A., 1993; Ch. 21.
4. Rhodes, M. R.; Barley, M. H.; Meyer, T. J. *Inorg. Chem.* **1991**, *30*, 629.
5. Barley, M. H.; Rhodes, M. R.; Meyer, T. J. *Inorg. Chem.* **1987**, *26*, 1746.
6. Barley, M. H.; Takeuchi, K. J.; Meyer, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 5876.
7. Younathan, J. N.; Wood, K. S.; Meyer, T. J. *Inorg. Chem.* **1992**, *31*, 3280.
8. Toth, J. E.; Anson, F. C. *J. Am. Chem. Soc.* **1989**, *111*, 2444.
9. Tanaka, A. A.; Fierro, C.; Scherson, D. A.; Yeager, E. B. *J. Phys. Chem.* **1987**, *91*, 3799.
10. Zecevic, S.; Simic-Glavaski, B.; Yeager, E.; Lever, A. B. P.; Minor, P. C. *J. Electroanal. Chem.* **1985**, *196*, 339.
11. Irvine, J. T. S.; Eggins, B. R.; Grimshaw, J. *J. Electroanal. Chem.* **1989**, *271*, 161.
12. Zagal, J.; Bindra, P.; Yeager, E. *J. Electrochem. Soc.* **1980**, *127*, 1506.
13. Nevin, W. A.; Liu, W.; Melnik, M.; Lever, A. B. P. *J. Electroanal. Chem.* **1986**, *213*, 217.
14. Elzing, A.; van der Putten, A.; Visscher, W.; Barendrecht, E. *J. Electroanal. Chem.* **1987**, *233*, 99.
15. Ercolani, C.; Paolett, A. M.; Pennesi, G.; Rossi, G. *J. Chem. Soc., Dalton Trans.* **1991**, 1371.
16. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 4th Ed.; Wiley: New York, 1980.
17. Randin, J. P.; Yeager, E. B. *J. Electrochem. Soc.* **1971**, *118*, 711.
18. Randin, J. P.; Yeager, E. B. *J. Electroanal. Chem.* **1972**, *36*, 257.

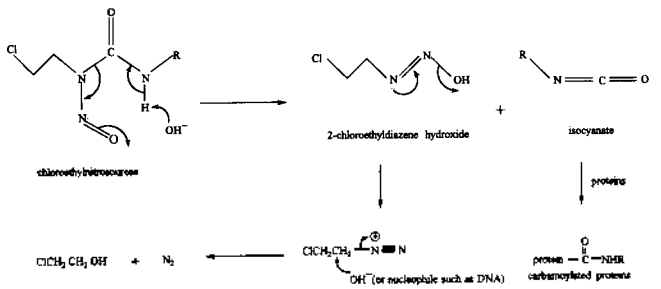
A Study on the Relationships between Molecular Structure and Antitumor Activity II: *Ab Initio* Study on 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)

Min Joo Lee*, Ji Ae Lee, and Yoo Hang Kim†

Department of Chemistry, Changwon National University, Changwon, Kyungnam 641-773, Korea
†Department of Chemistry and Center for Chemical Dynamics, Inha University, Inchon 402-751, Korea
Received February 25, 1998

The nitrosoureas form a class of compounds with tumor-inhibitory property and they derive their clinical usefulness from high lipophilicity together with low toxicity.[1] The chloroethylnitrosoureas which have been of clinical importance are 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine), 1-(2-chloroethyl)-3-(4-methylcycloethyl)-1-nitrosourea (MeCCNU), 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU).[2,3]

Especially, the CCNU displays therapeutic activity against brain tumors, colorectal tumors, Hodgkin's disease, multiple myeloma, gastrointestinal carcinoma, lung carcinoma, and prostate tumors.[4-6] The antitumor activity of nitrosoureas is closely related with their alkylation activity[7,8] and solubility.[9] Under physiological conditions, it was proposed that chloroethylnitrosoureas decompose to produce chloroethylcarbonium ions or diazonium hydroxides which function as the alkylating agents.[2] Because N-nitroso group in nitrosoureas



Scheme 1

labilizes the bond between the nitrosated nitrogen and the adjacent carbonyl group so that decomposition can occur under physiological conditions to give electrophiles. DNAs have been found to be the major targets of the electrophiles.[10] And organic isocyanates are formed that carbamoylate the lysine residues of proteins.[11] The mechanism by which chloroethylnitrosoureas effect their biological action was thought as in Scheme 1.[12,13] CCNU is highly lipid soluble and also has water solubility as well. In the previous structure-activity analysis, alkylation activities, carbamoylating activities, and the decomposition rates of chloroethylnitrosoureas were correlated with lethal toxicity, myelotoxicity, and L1210 leukemia antitumor activity in mice.[8]

Even though CCNU and BCNU possess wide ranging activities, PCNU and MeCCNU have been found to have a greater activity toward solid tumors than other nitrosoureas.[2,14] PCNU is an interesting compound which has 3- to 4-fold higher alkylating activity than CCNU. In a previous note published in this journal, we had carried out an *ab initio* theoretical structural study on PCNU and Antineoplaston A 10 molecules.[15] The optimized structures and atomic charges were obtained for both molecules. Interestingly, PCNU and CCNU have closely related structural features. The 2,6-dioxo-3-piperidyl group of PCNU is only at variance with cyclohexyl group of CCNU.

The purpose of this work is to extend our knowledge to CCNU molecule and to get basic data for elucidating the effect of geometrical structure and charge distributions on the alkylating activity, decomposition rate, and antitumor activity of CCNU 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 CCNU molecule. All of these results are discussed herein.

Ab Initio Calculations

The calculations were performed with the Gaussian-94 program[16] using the RHF/4-31G basis set to obtain the optimized geometries and atomic charge distributions of CCNU. Before the full geometry optimization of the whole molecule is attempted, the geometry optimization of two moieties-*i.e.*, amidoglutarimide and cyclohexyl fragments-has been carried out with our previous structural parameters[15] on the closely related molecules, *i.e.*, PCNU and Antineoplaston A10, as the starting values. In the next step the optimized amidoglutarimide and cyclohexyl fragments have been connected and completely optimized.

Results and Discussion

In Table 1 are presented structural parameters, rotational constants, dipole moment and total energy for CCNU, and in Figure 1 are given total atomic charges of it. The total atomic charges of some important atoms, which may affect the decomposition rate of CCNU, at the RHF/4-31G level are N_1= − 0.726, C_2=1.086, O_4=-0.396, O_{12}= − 0.595, N_{13}= − 0.894, and H_{14}=0.405. The dipole moment is 5.525 Debye at the RHF/4-31G level. From the comparison of these results with those obtained from our previous study[15] on PCNU, one can see that the atoms C_2, N_3, and H_{14} of CCNU are less positively charged by about 0.05, 0.01, and 0.02 unit of one electronic charge than those of PCNU, respectively. Therefore, it may be more difficult for CCNU to decompose to yield 2-chloroethyldiazene hydroxide and isocyanate in an aqueous solution than for PCNU. This may be one of the reasons why PCNU has a higher alkylating ac-

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

Parameter[b]	RHF/4-31G	Parameter[b]	RHF/4-31G	Parameter[b]	RHF/4-31G
$r(N_1\text{-}C_2)$	1.436	$\angle(N_1\text{-}C_2\text{-}O_{12})$	121.4	$\pi(C_2\text{-}N_1\text{-}N_3\text{-}O_4)$	15.8
$r(N_1\text{-}N_3)$	1.341	$\angle(N_1\text{-}C_2\text{-}N_{13})$	113.1	$\pi(C_2\text{-}N_3\text{-}N_1\text{-}C_5)$	164.9
$r(N_1\text{-}C_5)$	1.458	$\angle(N_1\text{-}N_3\text{-}O_4)$	117.5	$\pi(C_2\text{-}N_{13}\text{-}C_{15}\text{-}C_{16})$	− 84.4
$r(C_2\text{-}O_{12})$	1.213	$\angle(N_1\text{-}C_5\text{-}H_6)$	108.2	$\pi(C_2\text{-}N_{13}\text{-}C_{15}\text{-}C_{17})$	− 207.7
$r(C_2\text{-}N_{13})$	1.337	$\angle(N_1\text{-}C_5\text{-}C_7)$	113.2	$\pi(N_3\text{-}N_1\text{-}C_2\text{-}O_{12})$	48.4
$r(N_3\text{-}O_4)$	1.200	$\angle(N_1\text{-}C_5\text{-}H_8)$	108.7	$\pi(N_3\text{-}N_1\text{-}C_2\text{-}N_{13})$	− 134.6
$r(C_5\text{-}H_6)$	1.077	$\angle(C_2\text{-}N_1\text{-}N_3)$	122.5	$\pi(N_3\text{-}N_1\text{-}C_5\text{-}H_6)$	191.2
$r(C_5\text{-}C_7)$	1.510	$\angle(C_2\text{-}N_{13}\text{-}H_{14})$	118.6	$\pi(N_3\text{-}N_1\text{-}C_5\text{-}C_7)$	68.1
$r(C_5\text{-}H_8)$	1.083	$\angle(C_2\text{-}N_{13}\text{-}C_{15})$	122.3	$\pi(N_3\text{-}N_1\text{-}C_5\text{-}H_8)$	− 51.7
$r(C_7\text{-}H_9)$	1.074	$\angle(N_3\text{-}N_1\text{-}C_5)$	113.9	$\pi(N_3\text{-}N_1\text{-}C_5\text{-}H_9)$	63.6
$r(C_7\text{-}Cl_{10})$	1.898	$\angle(C_5\text{-}C_7\text{-}H_9)$	112.0	$\pi(H_6\text{-}C_5\text{-}C_7\text{-}H_9)$	63.6
$r(C_7\text{-}H_{11})$	1.073	$\angle(C_5\text{-}C_7\text{-}Cl_{10})$	110.9	$\pi(H_6\text{-}C_5\text{-}C_7\text{-}Cl_{10})$	− 52.7
$r(N_{13}\text{-}H_{14})$	0.994	$\angle(C_5\text{-}C_7\text{-}H_{11})$	112.8	$\pi(H_6\text{-}C_5\text{-}C_7\text{-}H_{11})$	190.2
$r(N_{13}\text{-}C_{15})$	1.463	$\angle(N_{13}\text{-}C_{15}\text{-}C_{16})$	111.3	$\pi(O_{12}\text{-}C_2\text{-}N_{13}\text{-}H_{14})$	189.2
$r(C_{15}\text{-}C_{16})$	1.533	$\angle(N_{13}\text{-}C_{15}\text{-}C_{17})$	109.4	$\pi(O_{12}\text{-}C_2\text{-}N_{13}\text{-}C_{15})$	0.7
$r(C_{15}\text{-}C_{17})$	1.531	$\angle(C_{15}\text{-}C_{16}\text{-}C_{18})$	111.1	$\pi(C_{15}\text{-}C_{16}\text{-}C_{18}\text{-}C_{19})$	55.7
$r(C_{15}\text{-}H_{21})$	1.082	$\angle(C_{15}\text{-}C_{16}\text{-}H_{22})$	108.7	$\pi(C_{17}\text{-}C_{15}\text{-}C_{16}\text{-}C_{18})$	− 55.8
$r(C_{16}\text{-}C_{18})$	1.533	$\angle(C_{15}\text{-}C_{16}\text{-}H_{23})$	109.2	$\pi(C_{17}\text{-}C_{15}\text{-}C_{16}\text{-}H_{22})$	65.0
$r(C_{16}\text{-}H_{22})$	1.087	$\angle(C_{16}\text{-}C_{18}\text{-}C_{19})$	111.3	$\pi(C_{17}\text{-}C_{15}\text{-}C_{16}\text{-}H_{23})$	181.9
$r(C_{16}\text{-}H_{23})$	1.082	$\angle(C_{17}\text{-}C_{15}\text{-}H_{21})$	109.3	$\pi(C_{17}\text{-}C_{18}\text{-}C_{19}\text{-}C_{20})$	− 27.5
$r(C_{17}\text{-}H_{24})$	1.088	$\angle(C_{18}\text{-}C_{19}\text{-}C_{20})$	111.1	$\pi(C_{17}\text{-}C_{19}\text{-}C_{20}\text{-}H_{30})$	122.1
$r(C_{17}\text{-}H_{25})$	1.084	$\angle(C_{19}\text{-}C_{18}\text{-}H_{26})$	109.4	$\pi(C_{17}\text{-}C_{19}\text{-}C_{20}\text{-}H_{31})$	− 120.9
$r(C_{18}\text{-}C_{19})$	1.533	$\angle(C_{19}\text{-}C_{18}\text{-}H_{27})$	110.3	$\pi(C_{17}\text{-}C_{20}\text{-}C_{19}\text{-}H_{28})$	117.4
$r(C_{18}\text{-}H_{26})$	1.087	$\angle(C_{19}\text{-}C_{20}\text{-}H_{30})$	110.3	$\pi(C_{17}\text{-}C_{20}\text{-}C_{19}\text{-}H_{29})$	− 65.7
$r(C_{18}\text{-}H_{27})$	1.084	$\angle(C_{19}\text{-}C_{20}\text{-}H_{31})$	109.3	$\pi(C_{19}\text{-}C_{20}\text{-}C_{17}\text{-}H_{24})$	65.2
$r(C_{19}\text{-}C_{20})$	1.533	$\angle(C_{20}\text{-}C_{17}\text{-}H_{24})$	109.3	$\pi(C_{19}\text{-}C_{20}\text{-}C_{17}\text{-}H_{25})$	− 117.1
$r(C_{19}\text{-}H_{28})$	1.084	$\angle(C_{20}\text{-}C_{17}\text{-}H_{25})$	110.4	$\pi(C_{20}\text{-}C_{17}\text{-}C_{15}\text{-}H_{21})$	− 64.5
$r(C_{19}\text{-}H_{29})$	1.087	$\angle(C_{20}\text{-}C_{19}\text{-}H_{28})$	110.0	$\pi(C_{20}\text{-}C_{19}\text{-}C_{18}\text{-}H_{26})$	65.8
$r(C_{20}\text{-}H_{30})$	1.084	$\angle(C_{20}\text{-}C_{19}\text{-}H_{29})$	109.3	$\pi(C_{20}\text{-}C_{19}\text{-}C_{18}\text{-}H_{27})$	177.3
$r(C_{20}\text{-}H_{31})$	1.074			A	726.78
				B	298.54
				C	239.36
				μ	5.525
				− E	1121.1271067

[a] Bond lengths in Å, bond angles in degrees, rotational constants (A, B, C) in MHz, dipole moment (μ) in Debye and energy (E) in Hartree. [b] For the definition of atom numbers, see Figure 1.

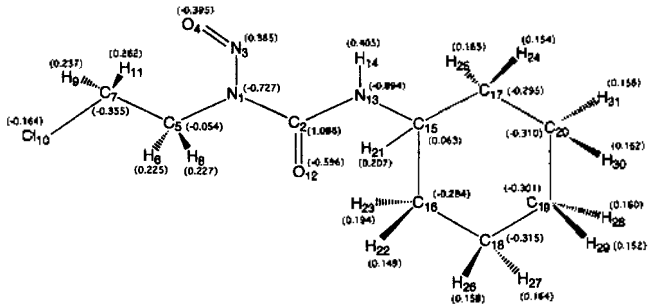


Figure 1. Structural model and atom numbering of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU). The numbers in parentheses are the atomic electronic charges calculated in this work.

tivity than CCNU. Thus the charge distribution state on the atoms of antitumor agents may contribute to the antitumor activity of molecules. Therefore, studying the antitumor activity not only on the aspect of structure but also on the aspect of charge distribution will give more comprehensive and profound understanding about the activity of antitumor agents.

Acknowledgment. The authors wish to express their gratitude to Inha University for financial support to YHK and to Institute of Basic Science of Changwon National University for partial support to MJL.

References

1. Ludlum, D. B. *Cancer*; Becker, F. F. ed.; Plenum, New York, U. S. A., **1977**, *5*, 295.
2. Carter, S. K. *Cancer Chemother. Rep.* **1973**, part 3, *4*, 35.
3. Lewis, J. G. *Therapheutics*; Hodder and Stoughton, London, U. K., 1978, 65.
4. Carter, S. K.; Slavik, M. *Ann. Rev. Pharmacol.* **1974**, *14*, 157.
5. Hansen, H. H.; Selawry, D. S.; Pajak, T. F.; Spurr, C. L.; Folkson, G.; Bruner, K.; Cuttner, J.; Nissen, N. I.; Holland, J. K. *Cancer* **1981**, *47*, 14.
6. Carter, S. K.; Bakowski, M. T.; Hellmann, K. *Chemotherapy of Cancer*; John Wiley & Sons: New York, U. S. A., 1977, 70.
7. Panasci, L. C.; Fox, P. A.; Schein, P. S. *Cancer Res.* **1977**, *37*, 3321.
8. Panasci, L. C.; Green, D.; Nagourney, R.; Fox, P. A.; Schein, P. S. *Cancer Res.* **1977**, *37*, 2615.
9. Hansch, C.; Smith, N.; Engle, R.; Wood, H. *Cancer Chemother. Rep.* **1972**, part 1, *56*, 443.
10. Elliott, R. D. In *Cancer Chemotherapeutic Agents*; Foye W. O. Ed.; ACS Professional Reference Book: Washington DC, U. S. A., 1995; p 133.
11. Schmall, B.; Cheng, C. J.; Fujimara, S.; Gersten, N.; Grunberger, D.; Weinstein, I. B. *Cancer Res.* **1973**, *33*, 1921.
12. Montgomery, J. A.; James, R.; McCaleb, G. S.; Kirk, M. C.; Johnston, T. B. *J. Med. Chem.* **1975**, *18*, 568.
13. Montgomery, J. A. *Cancer Treatment Rep.* **1976**, *60*, 651.
14. Carter, S. K.; Wasserman, T. D. *Cancer Treatment Rep.* **1976**, *60*, 807.
15. Lee, M. J.; Lee, S. K.; Kim, S. H.; Kim, Y. H. *Bull. Korean Chem. Soc.* **1996**, *17*, 858.
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Rev. B. 2*, Gaussian Inc., Pittsburgh PA, 1995.

Dynamics of Polar Solvation for the Electronic Excited State of Coumarin 481 with Excess Vibrational Energy

Gukhee Park and Tai Jong Kang*

Department of Chemistry, Taegu University, Kyoungsan 712-714, Korea
Received March 9, 1998

The dipolar interaction between the electronically excited solute molecule and the surrounding solvents is expected to be important in determining the kinetics of chemical reaction such as the excited state charge transfer. Over the past decade the dynamic nature of solute-solvent interaction has been the focus of many solution dynamics studies[1-5] and widely investigated using various kinds of ultrafast spectroscopic techniques.[6]

Time-resolved Stokes shift experiments have provided fairly detailed picture of the polar solvation dynamics. The underlying concept of the dynamic Stokes shift experiment relies on the presumption that there is significant change in the magnitude and/or direction of dipole moment upon electronic excitation. The electronic charge distribution of the probe is strongly perturbed upon excitation with a ultrashort laser pulse and noneqilibrium configuration between the probe and solvents is instantaneously formed. Subsequently the solvent molecules start to reorganize in order to lower the free energy of solvation. The process of lowering the free energy of solvation results in the red shift of emission