Journal of Physical and Theoretical Chemistry
of Islamic Azad University of Iran, 7 (1) 53-59: Spring 2010
(J. Phys. Theor. Chem. IAU Iran)
ISSN: 1735-2126

Drug Delivery study of Tamoxifen with Single Walled Carbon Nanotubes

K. Shahanipour[1], A.H. Esmailian[2], F. Mollaamin[3,*], B. Khalili Hadad[5] and K. Shahanipour[4]

[1] M Sc. Student, Qom Branch, Islamic Azad University, Qom, Iran
[2] Department of Physics, Qom Branch, Islamic Azad University, Qom, Iran
[3] Department of Chemistry, Qom Branch, Islamic Azad University, Qom, Iran
[4] Department of Biochemistry, Falavarjan Branch, Islamic Azad University, Falavarjan, Iran
[5] Department of Biology, Roudhen Branch, Islamic Azad University, Roudhen, Iran
Received May 2010; Accepted June 2010

ABSTRACT

As drug delivery systems Nanoparticulate widely investigated because of many advantages such as smaller size, controlled drug release potential, targeting ability, enhancement of therapeutic efficacy and reduction of toxicity. So, carbon nanotubes have recently received considerable attention as alternative drug delivery carrier. In this study we investigate interaction of tamoxifen with open-end of single-walled carbon nanotubes (SWNTs) using the Gaussian 98 program. We have computed NMR shielding tensors at B1LYP and HF levels by using 3-21G and STO-3G basis sets in the water. Our results reveal that NMR chemical shielding parameters are strongly affected by inducing solvent media. Regarding to our plotted graphs of σ_{iso} , σ_{aniso}, $\Delta\sigma$, η , δ in different methods and basis sets, the largest σ_{iso} values obtained for O_{43} atom at the HF in STO-3G whereas the smallest one belonged to C_{34}. It is interesting to note that the apposite trend have been observed for asymmetry parameters(η).

Keywords: Tamoxifen; NMR parameters; SWNT; Water

INTRODUCTION

The development of new and efficient drug delivery systems is of fundamental importance to improve the pharmacological profiles of many classes of therapeutic molecules. Many different types of drug delivery systems are currently available. Within the family of nanomaterials, carbon nanotubes (CNT) have emerged as a new alternative and efficient tool for transporting and translocating therapeutic molecules. CNT can be functionalised with bioactive peptides, proteins, nucleic acids and drugs, and used to deliver their cargos to cells and organs. Because functionalised CNT display low toxicity and are not immunogenic, such systems hold great potential in the field of nanobiotechnology and nanomedicine.

The structure of a SWNT can be conceptualized by wrapping a one-atom-thick layer of graphite called graphene into a seamless cylinder. The way the graphene sheet is wrapped is represented by a pair of indices (n,m) called the chiral vector. The integers n and m denote the number of unit vectors along two directions in the honeycomb crystal lattice of graphene. If m = 0, the nanotubes are called "zigzag". If n = m, the nanotubes are called "armchair". Otherwise, they are called "chiral". These numerous characteristics make them very desirable in many fields nanotechnology, electronics, optics, architecture and the medical field. Combining carbon nanotubes with biological systems can

*Corresponding author: smollaamin@gmail.com

significantly improve medical science especially diagnostics and disease treatment. Nothing has been fully developed and finalized yet, but we see progress every day. Scientists have discovered that nanotubes, when exposed to infrared light, tend to heat up to 160°F (70°C) in just 120 seconds. If they are placed inside the cancer cells, they simply destroy them. Testings also showed that infrared has no effects on cell where no nanotubes are placed. This could lead to development of a cancer-killer.

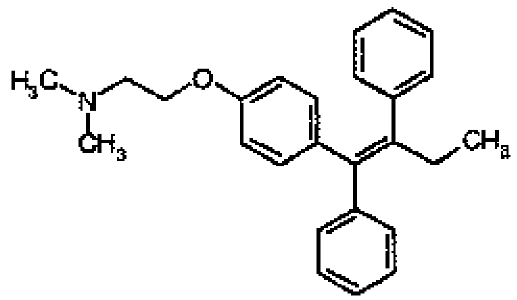

Fig. 1. The schematic diagram of Tamoxifen structure that interacted to SWNT.

Carbon nanotubes can also be used as blood vessels in order to deliver drugs to their target. When the drug delivery is done that way, the drug dosage can be lowered. There are two methods, both equally effective, a) the drug can be attached to the side or behind, b) or the drug can actually be placed inside the nanotube.

Tamoxifen, a member of the Selective Estrogen Receptor Mod- ulator (SERM) family(see fig 1), has been widely used in the treatment of estrogen receptor (ER) - expressing breast cancer [2–4].

Because antitumour effects have been predominantly observed in patients with ER-positive tumours, it is generally accepted that the primary action of hydroxytamoxifen, its active metabolite, is mediated through inhibition of the ER pathway. But, it has previously been shown that some ER-negative cancers also respond to tamoxifen, [5,6] which means that the molecule can be active because of an ER-independent antitumour mechanism that has not yet been clearly identified [7].

Tamoxifen works against the effects of estrogen on these cells (an "anti-estrogen") slows the growth of cancer cells and prevents original breast cancer from returning. It also has beneficial effects of menopausal estrogen replacement therapy such as lowering of blood cholesterol and slowing of osteoporosis.

The combination of SWNTs with drug important structures, such as tamoxifen or polypeptides, is particularly intriguing since it opens the door to novel biotechnology and nanotechnology applications [9]. SWNTs can be bind to the polymers and biological system such as DNA, carbohydrates and drugs[12]. Recently literatures have shown that tamoxifen binds to SWNTs with covalent and non-covalent conjugations [14-16], but the details of these interactions have yet many questions.

In this paper, the tamoxifen interaction with open-end of SWNT and water effects on this intersection have been investigated.

Nuclear magnetic resonance (NMR) spectroscopy is a valuable technique for obtaining chemical information. This is because the spectra are very sensitive to changes in the molecular structure. This same sensitivity makes NMR a difficult case for molecular modeling [10-12]. NMR spectroscopy is a powerful tool for study the structure dynamics and interaction of biological malecule such as protein and nucleic acids in solution [13-16].

As we know the effect of water on proteins plays an important role in the chemical behavior of them and the effects span a considerable range and are governed primarily by solvent polarity. So in our current research, we have theoretically studied the effects of water and gas phase on the chemical shielding parameters of ^{13}C, ^{15}N , ^{17}O, ^{1}H, nuclei involving in complex and its structural stability.

COMPUTATIONAL DETAILES

In the present work, we modeled structure of tamoxifen and coupled with SWNT by selected atoms with chem. office package and then optimized at the Hartree-Fock and B1LYP levels of theory with 3-21G and STO-3G basis sets.

Density functional theory (DFT) implemented in Gaussian 98 [29] for the vacuum and solvent effects which provided logical accuracy and are particularly suitable for the study of defects in a wide range of materials [30]. DFT is based on a theorem due to Hohenberg and Kohn, which states that all ground state properties are functions of the total electronic charge density ρ(r) [31-32].

To account for the solvent effects, the self-consistent reaction field (SCRF) method is most commonly used [35]. Hence, SCRF based on Onsager model used to include the effects of the solvents on tamoxifen interaction with open-end of SWNT.

After fully optimization of tamoxifen interaction with open-end of SWNT, we have calculated NMR parameters using the density functional B1LYP and HF method by Gauge Including Atomic Orbitals (GIAO) and have been reported in tables 1-3. For more investigation of levels and basis sets effect, the graphs of obtained NMR parameters versus selected atoms have been evaluated.

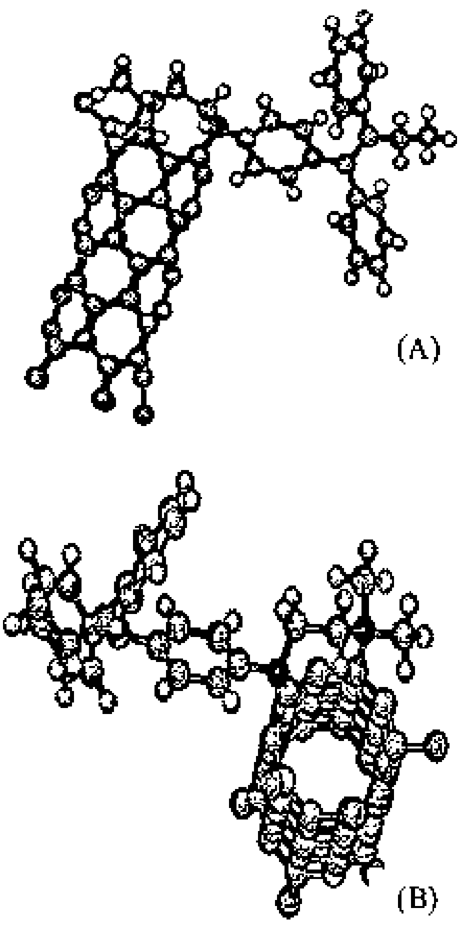

Fig. 2. A and B are schematic diagrams of tamoxifen interaction with open-end of SWNT.

RESULTS AND DISCUSSION

Many investigations have been done on tamoxifen interaction with SWNTs whereas interaction quality for practical area is important. In this work, we carried out theoretical study about this interaction and explored the interaction between tamoxifen with open-end of SWNT (Fig.2) to develop practical application of tamoxifen interaction with SWNTs.

In Fig.1 the interaction between tamoxifen atoms has been displayed with open-end of SWNT atoms. To demonstrate of this application of this interaction, the calculated physical properties have been investigated in vacuum and solvents which are important in molecular properties. According to Fig.1, the nitrogen, oxygen, carbon and hydrogen atoms of tamoxifen interacted to carbon atoms of SWNT, under influence of circularly interaction a dense region created in interaction site. We have investigated the structural and electrical reasons for this fact.

In table 1-3, chemical shift anisotropy asymmetry (η), isotropy (σ iso), anisotropy (σ aniso), and Δσ and chemical shift tensor (δ) are observed for ^{13}C, ^{15}N, ^{17}O, ^{1}H nuclei in interaction site of tamoxifen interacted with SWNTs with respect to HF and B1LYP levels of theory and 3-21G and STO-3G basis sets. The diagram of NMR parameter has been drawn at the levels in different basis sets for atoms of tamoxifen interacted with SWNTs (Fig.2).

As expected, the NMR shielding tensors of ^{13}C, ^{15}N, ^{17}O, ^{1}H nuclei are drastically affected by what it is bonded to and the type of bond to its neighbor. Our obtained results yielded strong evidence that intermolecular effects such as tamoxifen interaction with open-end of SWNT play very important role in determining the ^{13}C, ^{15}N, ^{17}O, ^{1}H -NMR chemical shielding tensors of active site of tamoxifen.

For O_{43} atom which interacted with SWNTs, the σiso component showed the largest intermolecular effects and it shows positive shielding values at the HF in STO-3G basis set whereas the smallest η belongs to it at the HF in STO-3G basis set. After O_{43}, N_{38} shows positive shielding values at the HF in STO-3G basis set and the smallest η belongs to it at the HF in 3-21G basis set.

Fig. 3 b. shows that, at three methods σ aniso value of C_{39} is increased.

Table 1. NMR parameters (ppm)of C ,N,O, H nuclei involving in active site tamoxifen interacted with open-end of SWNT, in water at the level of RHF/STO-3G theory

Atom	σ iso	σ aniso	Δσ	η	δ
C27	167.7629	65.2363	-72.9663	-0.78812	48.6442
C34	81.4765	185.2129	185.2129	0.561389	123.4752
N38	276.1111	7.5775	-11.5334	-0.31401	7.689
C39	55.2370	134.6094	-221.7233	-0.21421	147.8155
C42	192.3122	67.6476	67.6476	0.211635	45.0984
O43	373.2649	78.0386	-88.36205	-0.76634	58.908
C44	180.1912	70.0900	70.09005	0.355709	46.7267
H50	30.7114	12.5187	12.5187	0.139375	8.3458
H54	29.1089	5.7506	-7.79395	-0.47566	5.1959

Table 2. NMR parameters (ppm) of C ,N,O, H nuclei involving in active site tamoxifen interaction with open-end of SWNT in water at the levels of RHF/3-21G theory

Atom	σ iso	σ aniso	Δσ	η	δ
C27	93.1051	254.2409	-333.808	-0.52328	222.5387
C34	28.2099	197.8119	197.812	0.251894	131.8747
N38	236.9963	22.6763	-24.4018	-0.85857	16.2679
C39	214.0322	194.4644	194.4644	0.741971	129.643
C42	173.2326	53.5668	53.5668	0.115342	35.7112
O43	304.9508	64.2407	-84.7266	-0.51642	56.4844
C44	146.5885	67.4331	67.43315	0.430456	44.9554
H50	30.1777	12.4295	12.42955	8.259691	8.2864
H54	27.9090	8.7129	-14.3769	-0.21207	9.5846

Table 3. NMR parameters (ppm) of C, N, O, H nuclei involving in active site tamoxifen interaction with open-end of SWNT in water at the level of B1LYP/3-21G theory in GIAO method

Atom	σ iso	σ aniso	Δσ	η	δ
C27	73.9307	158.5845	-192.868	-0.64449	128.5788
C34	71.1281	150.9085	-190.996	0.580228	127.3306
N38	201.0071	19.8262	-36.1905	-0.09565	24.127
C39	193.0047	332.4962	293.0327	0.134673	195.3552
C42	148.4710	75.3014	75.30145	0.150497	50.201
O43	248.7010	72.6701	-83.7014	-0.73641	55.8009
C44	121.3629	80.7539	80.75395	0.417184	53.836
H50	28.7609	8.7130	-9.18935	0.896331	6.1262
H54	24.2619	7.9377	7.93765	-0.79759	5.2918

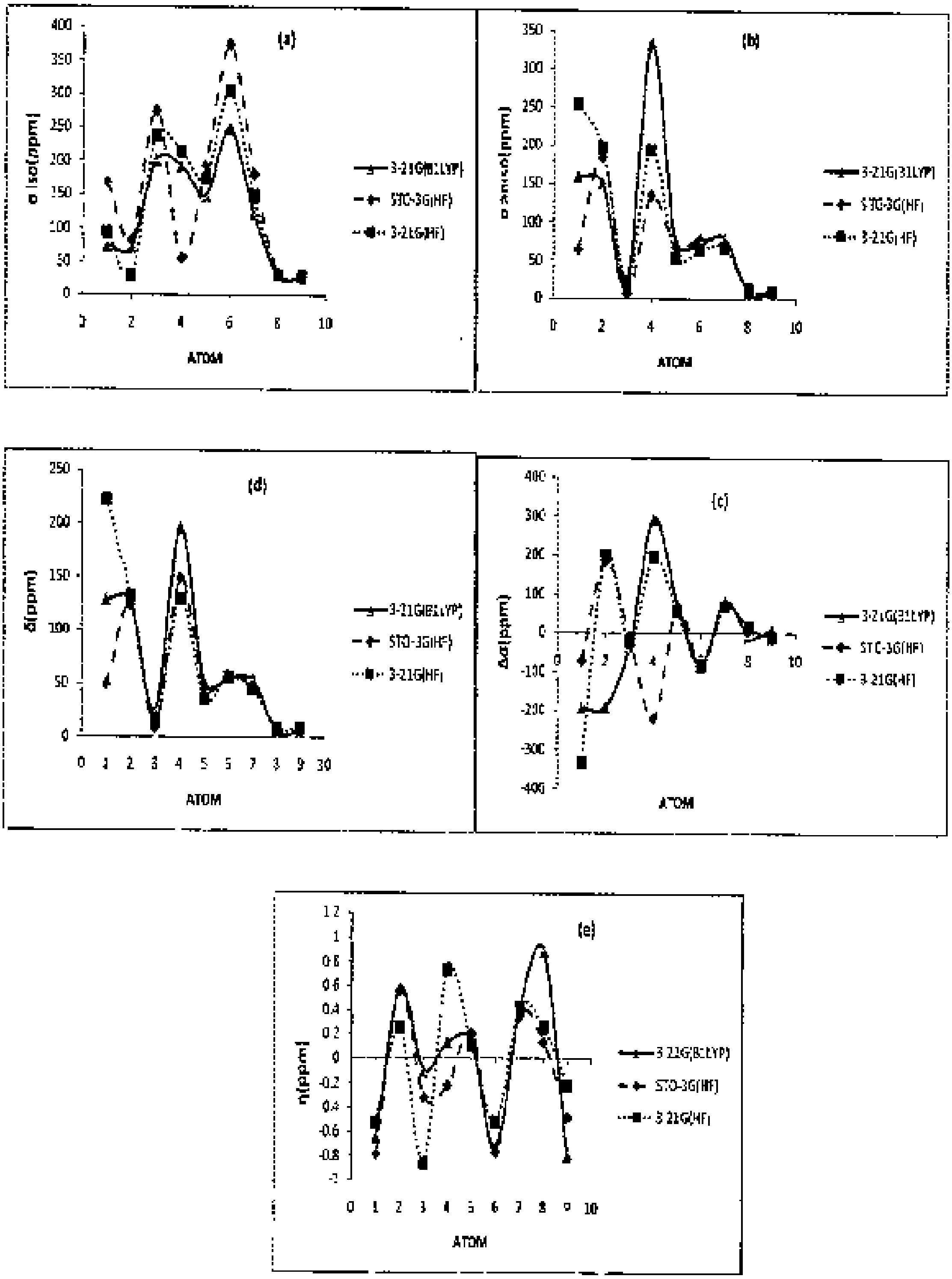

Fig. 3. The graphs of a) isotropic shielding values (σiso) , b) anisotropic shielding value(σaniso) , c) indirect shielding (Δσ), d) chemical shift tensor (δ), e) asymmetry parameters(η) , of propose atoms of active site tamoxifen interaction with open-end of SWNT , in water at the levels of HF/STO-3G, HF/3-21G and B3LYP/3-21G theories in GIAO method.

CONCLUSION

The results reported in this paper indicates that it is possible to measure NMR tensors of various nuclei involving in biological compounds in the presence water theoretically. As expected, the NMR shielding tensors of ^{13}C, ^{15}N , ^{17}O, ^{1}H ouclei are drastically affected hy what it is booded to and the type of hond to its aeighbor.

we have showed the interaction hetween tamoxifen and SWNT to increased the practical applicatiaos of tamoxifen/SWNT system. tamoxifen interacts with open-end of SWNT circularly. According to the results, in interaction place there is a optimum level of shielding values. Dense region that created in interactioo place has effective role on tamoxifen/SWNT system. Our results from DFT calculatioos show that the dense regioa has unique electrical and structural oature .Therefore, it can be seen this type of interaction with unique properties which is effective on practical applications of tamoxifen/SWNT system like drug delivery.

In conclusion, we have shown that theoretical calculatians can be used to successfully solve chemical and physical prohlems. In similarly with experimental methods, they involve assumptions and interpretation, and they have their limitations, but there are many problems that are best studied hy theory. Thus, theoretical methods have become a campetitive alternative to experiments for chemical aod physical investigatians.

REFERENCES

[1] B.J.A. Furr, V.C. Jordan, The pharmacolagy and clinical uses of tamaxifen, Pharmacol. Ther. 25 (2) (1984) 127–205.

[2] V.C. Jordan, Tamoxifen (ICl46,474) as a targeted therapy to treat and prevent breast cancer, Br. J. Pharmacol. 147 (Suppl. 1) (2006).

[3] L. Wickerham, Tamoxifen — an update ao curreot data and where it can now be used, Breast Cancer Res. Treat. 75 (Suppl. 1) (2002).

[4] G.J. Goldenberg, E.K. Froese, Drug and harmone seositivity of estragen receptorpositive and -negative human breast cancer cells in vitro, Cancer Res. 42 (12) (1982) 5147–5151.

[5] E.P. Gelmann, Tamoxifen for the treatment of malignancies other than breast and endometrial carcinoma, Semin. Oncol. 24 (1 . suppl. 1) (1997).

[6] P. De Medina, G. Favre, M. Poirot, Multiple targetiog by the antitumor drug tamoxifen: a structure-activity study, Curr. Med. Chem. Anti. Canc. Agents 4 (6) (2004) 491–508.

[7] G. Lu, P. Maragakis, E. Kaxiras. Nano Lett.5.5 (2005) 897.

[8] T. Ramanathan, F. T. Fisher, R. S. Ruoff, L. C. Brinson. Chem. Mater. 17 (2005) 1290.

[9] A. Star, E. Tu, J. Niemann, J.Christophe, P. Gabriel, C. S. Jniner, C. Valcke. PNAS. 41, 03 (2006) 921.

[10] C. Hu, Y. Zhang, G. Bao, Y. Zhang, M. Liu. Z. L. Wang. J. Phys. Chem B. 43, 109 (2005) 20072.

[11] M. E. Hughes, E. Brandin, J. A. Golovchenko. Nano. Lett. 5, 7 (2007) 1191.

[12] M Muhl.Encycl Camput Chem.3. 1998. 1835.

[13] C J Jameson , H J Osten.Annual Reports on NMR spectroscopy ..17. 1986. 1.

[14] C J Jameson. Annual Reports on NMR spectroscopy.21.1989.51.

[15] B Furtm. C Richter. J H Schwalbe. Chem Biochem.2003.10-36.

[16] S. E. Bucher. J M Burke. Biochemistry. 33. 1994. 992-999.

[17] T J Warren. P B Moore. J Biomol NMR. 20. 2001.311-323.

[18] S A Mc Callum. A J Pardi J Mol Biol..325. 2003.843-856.

[19] Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Zakrzewski, V.G.; Montgomery, J.A. Jr.; Stratmann, R.E.; Burant, J.C.; Dapprich, S.; Millam,

J.M.; Daniels, A.D.; Kudin, K.N.; Strain, M.C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterssoo, G.A.; Ayala, P.Y.; Cui, Q.; Morokuma, K.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Cioslowski, J.; Ortiz, J.V.; Baboul, A.G.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.: Gomperts, R.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Andres, J.L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E.S.; Pople, J.A. Gaussian 98, Revision A.7, Gaussian, Inc.: Pittsburgh PA; 1998.

[20] M. Monajjemi, , M. H Razavian, F. Mollaamin F. Naderi, and B.Honarparvar, Russian J.Phys.Chem A, 13, (2008) 113.

[21] F. Mollaamin, M. T Baei, M. Monajjemi, R.Zhiani, and B. Honarparvar, Russian J. Phys. Chem A 80, 13(2008) 190.

[22] A. Maiti, Microelectronics 39 (2008) 208.

[23] C. Lee, W. Yang, R. G. Parr, Phys. Rev (1998) 785.