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Computational prediction of the absolute configuration of stereogenic carbon center

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Abstract

It is suggested that the sign of the optical rotation of a chiral molecule can be deduced by calculation (RHF/6-31G(d, p) level of theory) of the relative weight of the HOMO (or HOMO-1 and so on) coefficients of the atoms attached to the stereogenic carbon atom. **To cite this article:** M. Santelli, *C. R. Chimie 8 (2005)*.

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Résumé

Il est montré que le signe de rotation d'une molécule chirale peut être déduit par le calcul (méthode RHF/6-31G(d, p)) de la contribution dans les plus hautes orbitales moléculaires occupées de chaque atome relié au centre stéréogénique. **Pour citer cet article :** M. Santelli, *C. R. Chimie 8 (2005)*.

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Keywords: Absolute configuration; Sign of the optical rotation; Stereogenic carbon center

Mots clés : Configurations absolues ; Signe du pouvoir rotatoire ; Atome de carbone stéréogénique

The phenomenon of optical activity of molecules is of major importance in organic chemistry. From its discovery by Biot in 1813 and the observations of Pasteur (1848–1860), this one is the cause of the concept of tetrahedral carbon described by Le Bel and van't Hoff [1,2]. However, some stereochemical problems are present such as the prediction of the sign of the optical rotatory power.

Some efforts have been devoted to elaborate theories to relate optical rotatory power, and particularly optical rotatory dispersion and circular dichroism spectra, to molecular structure [3]. From a theoretical point of view, the calculation of the optical rotatory power of a molecule is well established by the Rosenfeld equation which involve the gyration polarizability tensor of the molecule [4–7]. But as reported by Eyring, “since the eigenfunctions of the complex molecules are not known to any high degree of accuracy, it has not as yet

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proved possible to determine the absolute configuration of any molecules by actual calculation” [8].

The correlation between the sign of rotation of the plane of the polarized light and the structure of the molecules has been tentatively described as “an asymmetric screw pattern of polarizability” (Brewster’s rules) [9,10]. The polarizability of each four groups are derived from the atomic refraction of the atoms attached to the asymmetric center.

In 1960, Julg applied the molecular orbitals (MO) method to the optical rotatory power theory and shown that the expression for the molecular rotation is explicitly given as a function of the atomic orbitals [11]. Recently, ab initio methods have been used to study the lower electronic states and, the oscillator and optical rotatory strengths of the lower electronic transitions of oxirane and aziridine derivatives [12].

Our approach is based on the assumption that for the long wavelength radiation, changes in the direction of polarization could be correlated with the asymmetric distribution of electrons in the high occupied MO. It may be stated that in a system $C^1R^2R^3R^4R^5$, the sign of the optical rotation could be deduced by calculation of the relative weight of the HOMO (or HOMO-1 and so on) coefficients of the atoms attached to the asymmetric carbon C^1 and comparison of these values. For carbon, oxygen and nitrogen atoms, the sum of the absolute values of the molecular coefficients $2s$, $2p_x$, $2p_y$, $2p_z$ has been calculated and for hydrogen, only the absolute value of the molecular coefficient $1s$ has been considered¹. In the relative ranking of these values, if the decreasing order obtained is clockwise, the contribution of the MO is dextrarotatory and levorotatory in the

other case. To illustrate this hypothesis, the geometry of various molecules having one or two stereogenic centers was optimized at the RHF/6-31G(d, p) level of theory (Gaussian 98 program, revision A.11.4) [13].

Table 1 summarizes results concerning usual compounds 1–6. In each case, the sign of the optical rotatory power was obtained by calculation with a very good prediction and matched perfectly with the measured one.

With carboxylic derivatives 7–11 (Table 2), the prediction are quite fair but in contradiction for the lactic acid and the alanine methyl ester. Calculations shown that the coefficients of the MO are greatly modified by the conformation of the molecule and the atom order can be reversed.

Compounds bearing a phenyl group as substituent are well described by the atom order resulting from the calculation of the MO coefficients. For diol 15, the relatively small rotation can be the result of the opposed prediction from the MO coefficients of various conformations (Table 3).

Interesting results are observed with cyclohexane derivatives, in particular with the two compounds 21 and 22 with a twofold (C_2) axis (Table 4).

Further studies with other compounds and various conformations of the present compounds are ongoing and will be reported in due course.

Acknowledgments

I wish to thank Drs C. Ollivier, J.-L. Parrain and M. Rajzmann for their aid during the course of this work.

¹ It is more correct to compare the sum of the squares of the coefficients but, as we are only interested by the comparative ranking of these values, the result should be the same.

Table 1

Calculated total energies, MO energies, sum of the MO coefficients, atom decreasing order and predicted sign of the optical rotatory power for compounds **1–6**

Compound	Abs. conf.	$[\alpha]_D$	Energy (au)	MO num. ^a	MO energy (au) ^b	MO coeff. ^c 2	MO coeff. ^c 3	MO coeff. ^c 4	MO coeff. ^c 5	Atom decreasing order	Pred. sign ^d
1 	S	+13	-232.17666	21	-0.43352	0.48084	0.20340	0.75866	0.17654	O ⁴ > C ² > C ³ > H ⁵	(+)
				20	-0.45555	0.29482	0.54957	0.36246	0.11048	C ³ > O ⁴ > C ² > H ⁵	(+)
				19	-0.48200	0.06096	0.48618	0.17721	0.02920	C ³ > O ⁴ > C ² > H ⁵	(+)
				18	-0.49554	0.16350	0.61613	0.35727	0.00567	C ³ > O ⁴ > C ² > H ⁵	(+)
				17	-0.51187	0.42170	0.13186	0.65530	0.09796	O ⁴ > C ² > C ³ > H ⁵	(+)
2 	R	-21.9	-267.99730	21	-0.42779	0.51671	0.19575	0.43797	0.07444	C ² > O ⁴ > C ³ > H ⁵	(-)
				20	-0.46748	0.48628	0.25726	0.44534	0.02615	C ² > O ⁴ > C ³ > H ⁵	(-)
				19	-0.49231	0.18955	0.52183	0.65352	0.17218	O ⁴ > C ³ > C ² > H ⁵	(-)
3 	R	+13.9	-191.92440	16	-0.43450	0.55390	0.18392	0.61561	0.09316	O ⁴ > C ² > C ³ > H ⁵	(+)
				15	-0.44420	0.24889	0.27900	0.73787	0.09004	O ⁴ > C ³ > C ² > H ⁵	(-)
				14	-0.52153	0.33154	0.35677	0.36718	0.18203	O ⁴ ~ C ³	
				13	-0.52884	0.46121	0.44334	0.51336	0.05056	O ⁴ > C ² > C ³ > H ⁵	(+)
4 	R	-18	-248.17192	21	-0.39985	0.32948	0.07590	0.31700	0.06957	C ² > O ⁴ > C ³ > H ⁵	(-)
				20	-0.43314	0.28890	0.22253	0.60607	0.19119	O ⁴ > C ² > C ³ > H ⁵	(+)
				19	-0.47474	0.40064	0.42238	0.57076	0.06103	O ⁴ > C ³ > C ² > H ⁵	(-)
5 	R	-22	-248.169357	21	-0.40007	0.30536	0.37215	0.72395	0.01560	N ⁴ > C ³ > C ² > H ⁵	(-)
				20	-0.43275	0.30342	0.13049	0.33472	0.08459	N ⁴ > C ² > C ³ > H ⁵	(+)
				19	-0.47646	0.52248	0.22450	0.22160	0.00147	C ³ ~ N ⁴	
				18	-0.50162	0.17987	0.37704	0.28099	0.22764	C ³ > N ⁴ > H ⁵ > C ²	(-)
6 	R	+12	-341.684752	24	-0.43151	0.30108	0.23277	0.20385	0.07892	C ² > C ³ > O ⁴ > H ⁵	(+)
				23	-0.45752	0.05262	0.42360	0.62422	0.16245	O ⁴ > C ³ > H ⁵ > C ²	(+)
				22	-0.47895	0.06138	0.38242	0.24703	0.02184	C ³ > O ⁴ > C ² > H ⁵	(+)

Calculated total energies, MO energies, sum of the MO coefficients, atom order and predicted sign of the rotatory power for compounds **1–6**.^a MO number beginning by the HOMO, HOMO-1, and so forth.^b Energy of the occupied MO.^c Sum of the MO coefficients (absolute values) (for C, O, N: 2s, 2p_x, 2p_y, 2p_z; for H: 1s) at the atom 2–5.^d Predicted sign of the optical rotatory power.

Table 2

Calculated total energies, MO energies, sum of the MO coefficients, atom decreasing order and predicted sign of the optical rotatory power for compounds 7–11

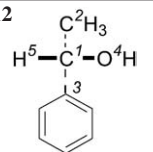
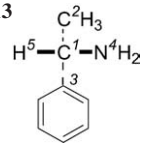
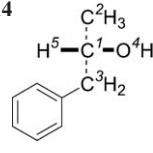
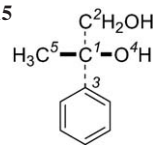
Compound	Abs. conf.	$[\alpha]_D$	Energy (au)	MO num. ^a	MO energy (au) ^b	MO coeff. ^c 2	MO coeff. ^c 3	MO coeff. ^c 4	MO coeff. ^c 5	Atom decreasing order	Pred. sign ^d
$ \begin{array}{c} \text{7 MeO}-\text{C}^{2^-}-\text{O} \\ \\ \text{H}^5-\text{C}^1-\text{O}^4\text{H} \\ \\ \text{C}^3\text{H}_3 \end{array} $	R	+8.5	-380.75207	28	-0.44787	0.08745	0.34772	0.68689	0.17651	O ⁴ > C ³ > H ⁵ > C ²	(+)
				27	-0.45912	0.33659	0.28563	0.26864	0.03645	C ² > C ³ > O ⁴ > H ⁵	(+)
				26	-0.48036	0.11763	0.08329	0.04304	0.01530	C ² > C ³ > O ⁴ > H ⁵	(+)
				25	-0.52132	0.40553	0.23309	0.48408	0.0664	O ⁴ > C ² > C ³ > H ⁵	(+)
$ \begin{array}{c} \text{8 HO}-\text{C}^{2^-}-\text{O} \\ \\ \text{H}^5-\text{C}^1-\text{O}^4\text{H} \\ \\ \text{C}^3\text{H}_3 \end{array} $	R	-3.9	-341.72722	24	-0.45378	0.13864	0.32453	0.64580	0.18401	O ⁴ > C ³ > H ⁵ > C ⁵	(+)
				23	-0.46836	0.27801	0.33143	0.32168	0.00823	C ³ ~ O ⁴	(-)
				22	-0.50688	0.23478	0.06632	0.11251	0.01433	C ² > O ⁴ > C ³ > H ⁵	(-)
				21	-0.53533	0.38979	0.32610	0.51956	0.06579	O ⁴ > C ² > C ³ > H ⁵	(+)
$ \begin{array}{c} \text{9(-)}-\text{O}-\text{C}^{2^-}-\text{O} \\ \\ \text{H}^5-\text{C}^1-\text{O}^4\text{H} \\ \\ \text{C}^3\text{H}_3 \end{array} $	R	+13.5	-341.17218	24	-0.20870	0.25296	0.13289	0.21438	0.04723	C ² > O ⁴ > C ³ > H ⁵	(-)
				23	-0.21351	0.02364	0.06576	0.12166	0.02858	O ⁴ > C ³ > H ⁵ > C ²	(+)
				22	-0.23171	0.11245	0.07324	0.12994	0.03777	O ⁴ > C ² > C ³ > H ⁵	(+)
$ \begin{array}{c} \text{10 MeO}-\text{C}^{2^-}-\text{O} \\ \\ \text{H}^5-\text{C}^1-\text{N}^{4(+)}\text{H}_3 \\ \\ \text{C}^3\text{H}_3 \end{array} $	R	-7.0	-361.28906	28	-0.62341	0.09739	0.06839	0.03512	0.01383	C ² > C ³ > N ⁴ > H ⁵	(+)
				27	-0.62531	0.20858	0.19360	0.03704	0.05872	C ² > C ³ > H ⁵ > N ⁴	(-)
				26	-0.67575	0.26132	0.12204	0.03405	0.02782	C ² > C ³ > N ⁴ > H ⁵	(+)
				25	-0.69736	0.27036	0.35535	0.04685	0.12717	C ³ > C ² > H ⁵ > N ⁴	(+)
$ \begin{array}{c} \text{11 MeO}-\text{C}^{2^-}-\text{O} \\ \\ \text{H}^5-\text{C}^1-\text{N}^4\text{H}_2 \\ \\ \text{C}^3\text{H}_3 \end{array} $	R	+1.7	-360.92254	28	-0.40007	0.39014	0.18136	0.86594	0.06312	N ⁴ > C ² > C ³ > H ⁵	(+)
				27	-0.45467	0.10387	0.17898	0.39810	0.05408	N ⁴ > C ³ > C ² > H ⁵	(-)
				26	-0.46741	0.12143	0.08237	0.06573	0.00079	C ² > C ³ > N ⁴ > H ⁵	(-)
				25	-0.50205	0.11113	0.52603	0.17905	0.18777	C ³ > H ⁵ > N ⁴ > C ²	(+)

Calculated total energies, MO energies, sum of the MO coefficients, atom order and predicted sign of the rotatory power for compounds 7–11.

^a MO number.^b Energy of the occupied MO beginning by the HOMO, HOMO-1, and so forth.^c Sum of the MO coefficients (absolute values) (for C, O, N: 2s, 2p_x, 2p_y, 2p_z; for H: 1s) at the atom 2–5.^d Predicted sign of the optical rotatory power.

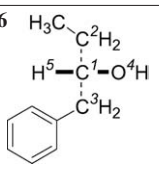
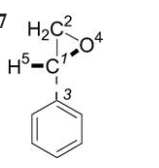
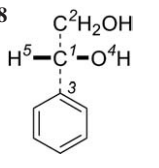
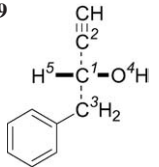
Table 3

Calculated total energies, MO energies, sum of the MO coefficients, atom decreasing order and predicted sign of the optical rotatory power for compounds 12–19

Compound	Abs. conf.	$[\alpha]_D$	Energy (au)	MO num. ^a	MO energy (au) ^b	MO coeff. ^c 2	MO coeff. ^c 3	MO coeff. ^c 4	MO coeff. ^c 5	Atom decreasing order	Pred. sign ^d
12 	S	-45	-383.65780	33	-0.33272	0.1928	0.3997	0.0745	0.0538	C ³ > C ² > O ⁴ > H ⁵	(-)
				32	-0.33946	0.0428	0.0214	0.0330	0.0096	C ² > O ⁴ > C ³ > H ⁵	(-)
				31	-0.44522	0.3715	0.0796	0.6197	0.1699	O ⁴ > C ² > H ⁵ > C ³	(-)
				30	-0.47427	0.3260	0.4230	0.3536	0.0972	C ³ > C ² > O ⁴ > H ⁵	(-)
13 	S	-40	-363.82840	33	-0.32783	0.14071	0.35153	0.21958	0.02734	C ³ > N ⁴ > C ² > H ⁵	
				32	-0.33833	0.03564	0.04885	0.03583	0.00187	C ² ~ N ⁴	(+)
				31	-0.39405	0.16247	0.34020	0.72739	0.07314	N ⁴ > C ³ > C ² > H ⁵	(-)
				30	-0.48059	0.43123	0.28444	0.18936	0.14991	C ² > C ³ > N ⁴ > H ⁵	(+)
14 	S	+38.7	-422.70064	37	-0.33317	0.05365	0.14555	0.05506	0.00954	C ² ~ C ⁴	
				36	-0.34192	0.01633	0.01414	0.03242	0.01037	O ⁴ > C ² > C ³ > H ⁵	(+)
				35	-0.43602	0.13547	0.40624	0.72884	0.17495	O ⁴ > C ³ > H ⁵ > C ²	(+)
				34	-0.46763	0.36764	0.29559	0.37960	0.12108	O ⁴ > C ² > C ³ > H ⁵	(+)
15 	R	-4.2	-497.55761	41	-0.33527	0.16912	0.34794	0.17332	0.15828	O ⁴ ~ C ²	
				40	-0.34096	0.02966	0.00205	0.02143	0.02286	O ⁴ ~ C ⁵	
				39	-0.43586	0.35140	0.19695	0.18304	0.10774	C ² > C ³ > O ⁴ > C ⁵	(-)
				38	-0.45074	0.17831	0.33312	0.60463	0.43986	O ⁴ > C ⁵ > C ³ > C ²	(+)
				37	-0.48607	0.35775	0.20036	0.43573	0.27865	O ⁴ > C ² > C ⁵ > C ³	(+)

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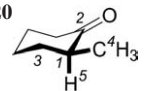
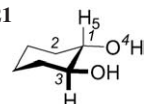
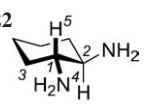
Table 3
(continued)

Compound	Abs. conf.	$[\alpha]_D$	Energy (au)	MO num. ^a	MO energy (au) ^b	MO coeff. ^c 2	MO coeff. ^c 3	MO coeff. ^c 4	MO coeff. ^c 5	Atom decreasing	Pred. sign ^d
16 	S	+25.5	-461.73379	41	-0.32401	0.06695	0.13660	0.06693	0.00256	C ² = C ⁴	
				40	-0.33295	0.02001	0.01506	0.03399	0.01001	O ⁴ > C ² > C ³ > H ⁵	(+)
				39	-0.43223	0.41864	0.37436	0.50678	0.01450	O ⁴ > C ² > C ³ > H ⁵	(+)
				38	-0.46385	0.32924	0.32193	0.34983	0.17951	O ⁴ > C ² > C ³ > H ⁵	(+)
17 	R	-24	-382.44645	32	-0.33012	0.24913	0.33260	0.18688	0.04658	C ³ > C ² > O ⁴ > H ⁵	(-)
				31	-0.34069	0.02403	0.00505	0.02021	0.00368	C ² > O ⁴ > C ³ > H ⁵	(-)
				30	-0.45416	0.23238	0.26407	0.91486	0.10815	O ⁴ > C ³ > C ² > H ⁵	(-)
				29	-0.45799	0.45971	0.11714	0.57504	0.04603	O ⁴ > C ² > C ³ > H ⁵	(+)
18 	R	-39	-458.51891	37	-0.33016	0.19438	0.43562	0.08836	0.05702	C ³ > C ² > O ⁴ > H ⁵	(-)
				36	-0.33547	0.05214	0.03592	0.03434	0.01191	C ² > C ³ > O ⁴ > H ⁵	(+)
				35	-0.44368	0.40604	0.08685	0.58847	0.16359	O ⁴ > C ² > H ⁵ > C ³	(-)
				34	-0.46296	0.31874	0.13293	0.19028	0.0635	C ² > O ⁴ > C ³ > H ⁵	(-)
19 	R	+11.1	-459.32962	39	-0.33935	0.08259	0.14049	0.06067	0.01338	C ³ > C ² > O ⁴ > H ⁵	(-)
				38	-0.34694	0.02061	0.01239	0.03371	0.01026	O ⁴ > C ² > C ³ > H ⁵	(+)
				37	-0.39134	0.54368	0.22084	0.17086	0.10374	C ² > C ³ > O ⁴ > H ⁵	(+)
				36	-0.40094	0.60821	0.009972	0.15804	0.03227	C ² > O ⁴ > H ⁵ > C ³	(+)

^a MO number beginning by the HOMO, HOMO-1, and so forth.^b Energy of the occupied MO.^c Sum of the MO coefficients (absolute values) (for C, O, N: 2s, 2p_x, 2p_y, 2p_z; for H: 1s) at the atom 2–5.^d Predicted sign of the optical rotatory power.

Table 4

Calculated total energies, MO energies, sum of the MO coefficients, atom decreasing order and predicted sign of the optical rotatory power for compounds **20–22**

Compound	Abs. conf.	$[\alpha]_D$	Energy (au)	MO num. ^a	MO energy (au) ^b	MO coeff. ^c 2	MO coeff. ^c 3	MO coeff. ^c 4	MO coeff. ^c 5	Atom decreasing order	Pred. sign ^d
20 	<i>S</i>	−45.6	−346.96634	31	−0.39176	0.35623	0.15439	0.11760	0.04393	C ² > C ³ > C ⁴ > H ⁵	(−)
				30	−0.45487	0.19147	0.45046	0.27032	0.03982	C ³ > C ⁴ > C ² > H ⁵	(−)
				29	−0.47123	0.11267	0.43907	0.31381	0.14363	C ³ > C ⁴ > H ⁵ > C ²	(+)
21 	<i>SS</i>	+42	−383.95393	32	−0.41276	0.26437	0.44308	0.42099	0.05827	C ³ > O ⁴ > C ² > H ⁵	(+)
				31	−0.44843	0.21524	0.53460	0.24956	0.00933	C ³ > O ⁴ > C ² > H ⁵	(+)
				30	−0.45862	0.33298	0.19465	0.44169	0.08852	O ⁴ > C ² > C ³ > H ⁵	(+)
22 	<i>RR</i>	+12.5	−344.29275	32	−0.36777	0.26430	0.21872	0.44403	0.00526	N ⁴ > C ² > C ³ > H ⁵	(+)
				31	−0.38690	0.21467	0.30285	0.68586	0.04486	N ⁴ > C ³ > C ² > H ⁵	(−)
				30	−0.43287	0.39921	0.34502	0.19948	0.05090	C ² > C ³ > N ⁴ > H ⁵	(+)

^a MO number beginning by the HOMO, HOMO-1, and so forth.^b Energy of the occupied MO.^c Sum of the MO coefficients (absolute values) (for C, O, N: 2s, 2p_x, 2p_y, 2p_z; for H: 1s) at the atom 2–5.^d Predicted sign of the optical rotatory power.

References

- [1] E.L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962.
- [2] E.L. Eliel, S.H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
- [3] A.D. Buckingham, P.J. Stiles, *Acc. Chem. Res.* 7 (1974) 258.
- [4] L. Rosenfeld, *Z. Phys.* 52 (1929) 161.
- [5] M.A. Osipov, B.T. Pickup, D.A. Dunmur, *Mol. Phys.* 84 (1995) 1193.
- [6] W.R. Salzman, *Chem. Phys. Lett.* 134 (1987) 622.
- [7] K.R. Sundberg, *J. Chem. Phys.* 68 (1978) 5271–5276.
- [8] H. Eyring, J. Walter, G.E. Kimball, in: *Quantum Chemistry*, Wiley, New York, 1963, p. 342.
- [9] J.H. Brewster, *J. Am. Chem. Soc.* 81 (1959) 5475; 5483; 5493.
- [10] J.H. Brewster, *Topics in Stereochemistry*, Interscience Publishers, New York Vol. 2, 1967, p. 1.
- [11] A. Julg, *Tetrahedron* 12 (1961) 146.
- [12] A. Rauk, *J. Am. Chem. Soc.* 103 (1981) 1023.
- [13] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J.J. Dannenberg, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, Gaussian, Inc, Pittsburgh, PA, USA, 1998.