Asian Journal of Chemistry Vol. 15, No. 1 (2003), 25–32

Reaction of Methyl Thioacetate with Nitrilimines: An Experimental, Local Ionization Energy and Electrostatic Potential Investigation

FAKHR ABU-AWWAD* and BASSAM ABU THAHER
Chemistry Department, Islamic University of Gaza, Box 108, Gaza, Palestinian Authority
E.mail: fmacm@mail.iugaza.edu

The reaction of hydrazonoyl chloride [1] precursor of nitrilimines [2] with methyl thioacetate [3] proceeds away from the expected cycloaddition that aimed at obtaining 1,3,4-thiadiazine-5-one [4]. Unexpectedly, the final product was acyclic adduct. The reaction was computationally verified and compared with the reaction of nitrilimines [2] with α-aminoester [5] to give 4,5-dihydro-1,2,4-triazine-6-ones [6]. For both reactions, the reactants, transition states and sought products were fully optimized using the HF/6-311G (d,p). Transition structures were tested in the existence of one imaginary vibrational frequency. Calculated minima of local ionization energy ($\bar{I}_{S,\min}$) and the extrema of electrostatic potential ($V_{S,\min}$, $V_{S,\max}$) of the reactants predicted and verified similar trends in both reactions which indicate an analogous reactivity and thus cyclic products [4, 6] are equally expected.

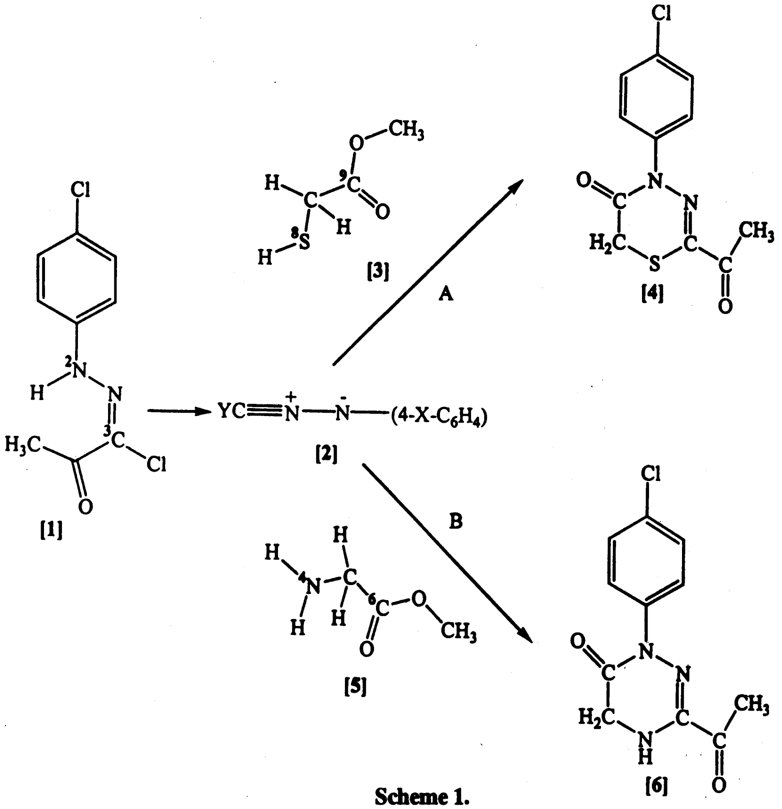
Key Words: Reaction, Methyl thioacetate, Nirilimines.

INTRODUCTION

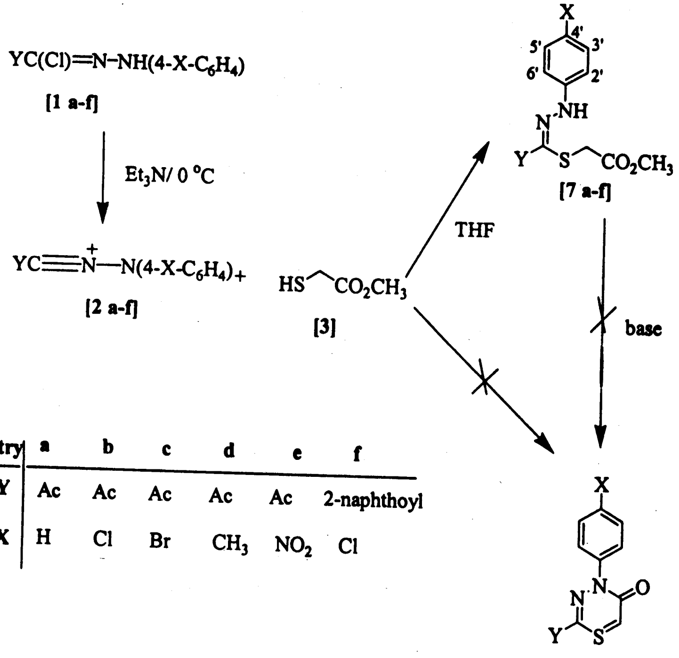
Nitrilimines such as 1,3-dipole are well known for their three different types of reactions[1]: cycloaddition, cyclocondensation and normal addition reactions.[2] The one-pot reaction of nitrilimines [2] with α-aminoester [5] to give 4,5-dihydro-1,2,4-triazine-6-ones [6] has been thoroughly studied.[3] Analogously, we allowed nitrilimines [2] to react with methyl thioacetate [3] to produce 1,3,4-thiadiazine-5-one [4]. **Scheme-I** illustrates both reactions. Few studies have tackled the targeted product in the literature[4–7], though it is known for its biological activity.[8–14]

EXPERIMENTAL

The reaction of nitrilimines [2] generated *in situ* from the respective hydrazonoyl chloride [1], by addition of triethylamine (NEt_3) with methyl thioacetate gives the corresponding acyclic thiohydrazone ester **[7a–f] (Scheme-II).** For the first few trials of experimental work, the separated product was acyclic adduct, but not the aimed at [4]. Several attempts of cyclization employing reflux with charcoal or using a weak base of triethyl amine or a strong base of sodium hydroxide were not successful.



Scheme 1.



Entry	a	b	c	d	e	f
Y	Ac	Ac	Ac	Ac	Ac	2-naphthoyl
X	H	Cl	Br	CH_3	NO_2	Cl

Scheme-2

Structural assignment of **[7a–f]** is based on elemental analysis and spectral data. IR spectra of these compounds show the existence of the bands of these characteristic functional groups. While NH band appears at about 3200 cm^{-1}, the bands of carbonyl groups of ketone and ester appear about 1720 cm^{-1}. The ^1H NMR spectra of these compounds show a singlet for the NH in the range of 9.80–10.0 ppm, while the signal of methoxy group of esters appears at about 3.7 ppm. ^{13}C NMR spectra display all peaks of carbons, especially methyl ester carbon (COOMe) in the range of 52.81–52.97 as well as the carbonyl carbon of the ester group in the range of 170.67–170.88 ppm.

Melting points were determined on electrothermal melting temperature apparatus and were uncorrected. Elemental analysis was carried out by Perkin-Elmer elemental analyzer 2400 CHN. The IR spectrum was obtained by Perkin-Elmer 273 in KBr disc. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX 200 (200 MHz) instrument for solutions of **[7a–e]** in $CDCl_3$ at 21°C, using TMS as an internal reference. Chemical shifts were expressed downfield from TMS.

Synthesis of [7a–f]: Triethylamine (5.0 g, 0.05 mol) in THF (10 mL) was dropwise added to a stirred solution of hydrazonoyl chloride (0.01 mol) and methyl thioacetate (Merck, 5.3 g, 0.05 mol) in THF (40 mL) at room temperature and the stirring was continued for 3–4 days until the reaction was completed. The solvent was then evaporated *in vacuo*. The crude solid was washed with water and then filtered. The obtained product was recrystallized from hot ethanol. The following compounds were prepared by this procedure:

Methyl-S-(1-phenylhydrazonopropan-2-one)thioacetate [7a]:

Yellow crystals from ethanol, m.f. $C_{12}H_{14}N_2O_3S$, yield 55%, m.p. 110–111°C

IR (KBr) (cm^{-1}): 3221 ν(NH), 3050, 2961, 2914 ν(CH), 1730, 1726 (CO of ester and ketone), 1665 ν(C=N), 1603, 1529, 1467 (Ph), 1217 ν(C—S), 1140 ν(C—O).

^1H NMR ($CDCl_3$): δ/ppm = 2.53 (s, 3H, CH_3CO), 3.60 (s, 2H, CH_2S), 3.67 (s, 3H, OCH_3), 7.41–7.05 (m, 5H, aromatic protons), 9.82 (s, 1H, ArNH).

^{13}C NMR: δ/ppm = 25.37 (CH_3CO), 34.52 (CH_2CO_2Me), 52.81 (CH_3O), 114.77 (C-2′/C-6′), 123.52 (C-4′), 129.54 (C-3′/C-5′), 132.31 (C=N), 141.82 (C-1′), 170.67 (COOMe), 193.39 ($COCH_3$).

% Analysis, Found (Calcd.) $C_{12}H_{14}N_2O_3S$ (m.w. = 266.32), C, 54.17 (54.12), H, 5.11 (5.30), N, 10.50 (10.52).

Methyl-S-[1-(4-chlorophenyl) hydrazonopropan-2-one]thioacetate [7b]:

Yellow crystals from ethanol, m.f. $C_{12}H_{13}N_2O_3SCl$, yield 67%, m.p. 106–107°C.

IR (KBr) (cm^{-1}): 3228 ν(NH), 3019, 2965, 2924 ν(CH), 1723 ν(CO, ester), 1679 ν(CO, ketone), 1598, 1518, 1467, 819 (*p*-subt. Ph), 1231 ν(C—S), 1163 ν(C—O).

^1H NMR ($CDCl_3$): δ/ppm = 2.54 (s, 3H, CH_3CO), 3.62 (s, 2H, CH_2S), 3.68 (s, 3H, CH_3O), 7.35–7.21 (m, 4H, aromatic protons), 9.84 (s, 1H, NH).

^{13}C NMR: δ/ppm = 25.41 (CH_3CO), 35.04 (S-CH_2CO_2Me), 52.94 (CH_3O—C=O), 115.89 (C-2′/C-6′), 128.43 (C-4′), 129.57 (C-3′/C-5′), 133.12 (C=N), 140.47 (C-1′), 170.77 (COOMe), 193.36 ($COCH_3$).

% Analysis, Found (Calcd.) $C_{12}H_{13}N_2O_3SCl$ (m.w. = 300.77) C, 47.50 (47.92), H, 4.29 (4.36), N, 9.18 (9.31).

Methyl-S-[1-(4-bromophenyl) hydrazonopropan-2-one]thioacetate [7c]:

Yellow crystals from ethanol, m.f. $C_{12}H_{13}N_2O_3SBr$ yield 58%, m.p. 98–99°C.

IR (KBr) (cm^{-1}): 3200 ν(NH), 3030, 2960, 2920 ν(CH), 1727 (CO ester), 1672 (CO, ketone), 1595, 1518, 1463, 820 (*p*-subst. Ph), 1220 ν(C—S), 1160 ν(C—O).

^{1}H NMR ($CDCl_3$): δ/ppm = 2.52 (s, 3H, CH_3CO), 3.62 (s, 2H, SCH_2 CO_2Me), 3.68 (s, 3H, OCH_3), 7.49–7.16 (m, 4H, aromatic protons), 9.83 (s, 1H, NH).

^{13}C NMR: δ/ppm = 25.42 (CH_3CO), 35.04 (SCH_2CO_2Me), 52.93 (OCH_3), 115.90 (C-4′), 116.29 (C-2′/C-6′), 132.48 (C-3′/C-5′), 133.28 (C=N), 140.96 (C-1′), 170.77 (CO_2Me), 193.37 ($COCH_3$).

% Analysis, Found (Calcd.) $C_{12}H_{13}N_2O_3SBr$ (m.w. = 345.22) C, 41.61 (41.75), H, 3.36 (3.50), N, 7.88 (8.11).

Methyl-S-[1-(4-methylphenyl)hydrazonopropan-2-one]thioacetate [7d]:

Yellow crystals from ethanol, m.f. $C_{13}H_{16}N_2O_3S$, yield 40%, m.p. 90–91°C.

IR (KBr) (cm^{-1}): 3224 ν(NH), 3055, 2960, 2916 ν(CH), 1732, 1724 (CO of ester and ketone), 1667 ν(C=N), 1600, 1530, 1465 (Ph), 1220 ν(C—S), 1140 ν(C—O).

^{1}H NMR ($CDCl_3$): δ/ppm = 2.34 (s, 3H, CH_3Ph), 2.52 (s, 3H, CH_2CO), 3.58 (s, 2H, $SCH_2CO_2CH_3$), 3.67 (s, 3H, OCH_3), 7.26–7.10 (m, 4H, aromatic protons), 9.80 (s, 1H, NH).

^{13}C NMR: δ/ppm = 20.81 (CH_3Ph), 25.35 (CH_3CO), 34.98 (SCH_2CO_2Me), 52.83 (OCH_3), 114.74 (C-2′/C-6′), 130.06 (C-3′/C-5′), 131.56 (C-4′), 133.22 (C=N), 139.50 (C-1), 170.72 (CO_2Me), 193.43 ($COCH_3$).

% Analysis, Found (Calcd.) $C_{13}H_{16}N_2O_3S$ (m.w. = 280.35) C 55.31 (55.70), H 5.36 (5.70), N 9.79 (9.99).

Methyl-S-[1-(4-nitrophenyl)hydrazonopropan-2-one]thioacetate [7e]:

Yellow crystals from ethanol, m.f. $C_{12}H_{13}N_3O_3S$ yield 65%, m.p. 150–151°C.

IR (KBr) (cm^{-1}): 3206 ν(NH), 3040, 2960, 2920 ν(CH), 1727 (CO, ester), 1671 (CO, ketone), 1595, 1520 (Ph) 1540, 1350 ν(NO_2), 1220 ν(C—S), 1167 ν(C—O).

^{1}H NMR ($CDCl_3$): δ/ppm = 2.55 (s, 3H, CH_3CO), 3.69 (s, 3H, OCH_3), 3.70 (s, 2H, $SCH_2CO_2CH_3$), 8.28–7.26 (m, 4H, aromatic protons), 10.02 (s, 1H, NH).

^{13}C NMR: δ/ppm = 25.63 (CH_3CO), 35.05 (S-CH_2CO_2Me), 52.15 (OCH_3), 114.29 (C-2′/C-6′), 125.96 (C-3′/C-5′), 136.94 (C=N), 142.96 (C-1′), 146.99 (C-4′), 170.71 (CO_2Me) 193.36 ($COCH_3$).

% Analysis, Found (Calcd.) $C_{12}H_{13}N_3O_3S$ (m.w. = 311.32), C 46.06 (46.30), H 3.93 (4.21), N 13.58 (13.50).

Methyl-S-[1-(4-chlorophenyl)hydrazono-2-naphthyl ethan-2-one]thioacetate [7f]:

Yellow crystals from ethanol, m.f. $C_{21}H_{17}N_2O_3SCl$, yield 62%, m.p. 96–97°C.

IR (KBr) (cm^{-1}): 3188 ν(NH), 3040, 2950, 2910 ν(CH), 1713 ν(CO, ester), 1621 (conj. CO, ketone), 1600, 1507 (Naphth. and Ph), 1221 ν(C—S), 1160 ν(C—O).

^{1}H NMR ($CDCl_3$): δ/ppm = 3.70 (s, 3H, OCH_3), 3.77 (s, 2H, SCH_2 CO_2CH_3), 7.28–7.08 (m, 4H, aromatic protons), 8.49–7.39 (m, 7H, Naphth.), 9.91 (s, 1H, NH).

^{13}C NMR: δ/ppm = 35.06 (SCH_2CO_2Me), 52.97 (CH_3O), 115.95 (C-2′/C-6′), 125.69 (C-4′), 127.49, 127.79, 128.10, 128.39, 129.45 (1C naphth.), 129.66 (C-3′/C-5′), 132.14, 132.49, 133.05, 134.90 (1C naphth)., 135.10 (C═N), 140.74 (C-1′), 170.88 (CO_2Me), 188.17 (CO naphth.).

% Analysis, Found (Calcd.) $C_{21}H_{17}N_2O_3SCl$ (m.w. = 412.90), C 61.44 (61.09) H 4.10 (4.15), N 8.49 (8.59).

Computational Procedures

Initial starting guess geometries were generated using PC Spartan[15] software where the preliminary semiempirical-AM1 and HF/3-21G optimizations and vibrational frequency calculations were conducted. Gaussian 94 package[16] was used to fully optimize the geometries of the studied structures without any symmetry constraints at the restricted Hartree-Fock (RHF) level with the standard basis set, 6–311G(d,p). All HF/6–311G(d,p) equilibrium and transition structures were subjected to vibrational analysis to verify their natures and to acquire zero point vibrational data. We first examined **[3]** and **[5]** since they are the only uncommon starting structures in both reactions. The transition structures are characterized by having one imaginary calculated vibrational frequency while the ground states structures had no imaginary vibrations.

The generated wave functions of reactants were used to calculate the average local ionization energy $\bar{I}(\mathbf{r})$ on the molecular surfaces defined by 0.001 e bohr^{-3} contour of the electronic density *via* eq. (1). $\bar{I}(\mathbf{r})$ is defined within the framework of self-consistent field molecular orbital (SCF-MO) theory. It is interpreted as the average energy required to remove an electron from any point **r** in the space of a molecule.[17] Consequently, $\bar{I}(\mathbf{r})$ has proved to be a good criterion of chemical reactivity.[18–20]

$$\bar{I}(r) = \sum_i \frac{\rho_i(r)|\varepsilon_i|}{\rho(r)} \qquad (1)$$

The positions at which the surface has the lowest values ($\bar{I}_{S,\,min}$) are indicative of sites that are most reactive toward electrophiles.[21] $\rho_i(\mathbf{r})$ is the electronic density of the ith molecular orbital at the point **r**, ε_i is the orbital energy of the ith molecular orbital and $\rho(\mathbf{r})$ is the total electronic density function.

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\,dr'}{|r' - r|} \qquad (2)$$

On the other side, the electrostatic potential $V(\mathbf{r})$ has proved to be a useful tool for studying the electrophilic and nucleophilic molecular reactivity.[22–25] $V(\mathbf{r})$ is expressed rigorously by eq. (2). Z_A is the charge on nucleus A, located at R_A and $\rho(\mathbf{r})$ is the electronic density function. The overall sign of $V(\mathbf{r})$ in any particular region of molecular vicinity depends upon the competing terms on the right side of eq. (2) that corresponds to the effects of the nuclei and the electrons, respectively. An approaching electrophile will be mostly attracted to the regions where V(r) has the lowest negative value ($V_{S,\min}$) where the effects of the electrons are dominant.[25–27] However, the maxima of V(**r**) on the molecular surface ($V_{S,\max}$) serve the analogous purpose for nucleophilic attack.[24, 28]

In this work, we employ these indicative calculated $I_{S,\min}$, $V_{S,\min}$ and $V_{S,\max}$ at specific molecular sites (atoms) where bond-breaking and/or bond-forming is likely to form the cyclic products. We assigned a specific number for each atom of any indicative interest such that ^3C and ^1N in **[1]**, ^9C and ^8S in **[3]**, and ^6C, ^4N in **[5]**. The calculated values of $\bar{I}_{S,\min}$, $V_{S,\min}$ and $V_{S,\max}$ are sought to verify the already reported cyclization reaction between **[1]** and **[5]**. Hence, the mapped values on the molecular surface of **[3]** are compared with that on the molecular surface of **[5]** to prove their expected analogousness. Also, the energy gaps between the highest occupied orbitals of both reactants **[3, 5]** and the lowest unoccupied orbital of **[1]**, $\varepsilon_{(HOMO-LUMO)}$, are calculated and followed as a criterion of chemical reactivity.[18] Lastly, we compare the stabilities of both products **[4, 6]** in terms of their calculated energies.

RESULTS AND DISCUSSION

Table-1 gives the frontier orbitals energies and the calculated $\bar{I}_{S,\min}$, $V_{\min}$ and $V_{S,\min}$ of the systems. The calculated total energies for both products favour the aimed at product **[4]** with a higher stability attributed to 8256 eV lowering compared to **[6]**. The calculated vibrational frequencies showed no imaginary value associated with the optimized structure **[4]** with S—C bond lengths of 1.773 and 1.803 Å and C—S—C angle of 94.88. Another supporting evidence is the $\varepsilon_{(HOMO\,[3,5]-LUMO\,[1])}$, which is –12.01 and –12.75 eV for reactants **[3,1]** and **[5,1]** respectively with a net favour of –0.74 eV of reaction of **[1]** with **[3]**. Table-1 shows comparable charge distributions on the molecular surfaces of **[1]** and **[3]**, primarily close to the atomic sites of concern. Calculated $\bar{I}_{S,\min}$ on the surfaces of **[3]** and **[5]** are found at ^8S and ^4N with 11.09 and 11.90 eV respectively. Similarly calculated $V_{S,\min}$ are found at ^8S and ^4N with –20.3 and –39.5 kcal/mol respectively. These values point to the most appropriate atomic sites to be attacked by ^3C of **[1]** as an electrophile with a potential of +35.4 kcal/mol. On the other side, having a second highest potential of +44.2 kcal/mol after removal of proton, ^2N of **[1]** would approach ^9C of **[3]** or ^6C of **[5]** with similar priority depending on their analogous potentials.

Consequently, an overall conclusion out of the computational work is that there is analogous chemical reactivity for both **[3]** and **[5]** toward the incoming reactant **[1]** whether it works as an electrophile at ^3C or as a nucleophile at ^2N where a cyclization is completed at both atoms. The reaction of methyl thioacetate with hydrazonoyl chloride would yield 1,3,4-thiadiazine-5-one analogous to reaction of α-aminoester with hydrazonoyl chloride which already yielded 1,2,4-triazine-6-one. This conclusion has motivated us to seek the appropriate experimental requirements to close the acyclic adduct that has just been synthesized.

TABLE-1

CALCULATED ε_{HOMO}, ε_{LUMO}, $\bar{I}_{S,min}$ (eV) AND $V_{S,max}$ (kcal/mol) AT HF/6-311G(d,p)

Structure	HOMO	LUMO	Atom	I_{min}	$V_{S,min}$	$V_{S,max}$
[1]	–8.29	1.94	^{2}N	15.34	+3.3	+44.2
			^{3}C	14.32	–7.2	+35.4
			^{1}H	17.38	+41.6	+61.0
[3]	–10.07	4.10	^{8}S	11.09	–20.3	+18.1
			^{9}C	12.38	–0.66	+25.0
[5]	–10.81	5.18	^{4}N	11.90	–39.5	+21.0
			^{6}C	15.37	–0.70	+22.9
			^{5}H	15.80	–5.70	+26.1

ACKNOWLEDGEMENTS

Authors would like to thank Prof. Dr. H.H. Otto at the Institute of Pharmaacy, Germany, and Prof. Peter Politzer at the University of New Orleans, USA for their contribution to this work.

REFERENCES

1. H. Barrtsch and T. Esker, *Heterocycles*, 1461 (1988); H.M. Hassaneen, H.A.H. Mousa and K.A.M. Nosrat, *Heterocycles*, **27**, 695 (1988).
2. M.R. El-Haddad, A.R.S. Ferwanah and A.M. Awadallah, *J. Prakt. Chem.*, **340**, 623 (1998).
3. M.M. El-Abadelah, A.Q. Hussein and B.A. Abu Thaher, *Heterocycles*, **32**, 1887 1991).
4. W. Hanefeld and M. Schilitzer, *Arch. Pharm.*, **326**, 249 (1993).
5. Bose, *Chem. Zentralbl.*, **11**, 1651 (1926).
6. R. Soliman, M. Gabr, M.S. Abouzeit-Har and F.M. Sharabi, *J. Pharm. Sci.*, **70I**, 94 (1980).
7. Y. Matsubara, M. Yoshihara, T. Nakanura, S. Yamada and T. Maeshima, *Phosphorus Sulfur*, **16**, 89 (1983); Y. Matsubara, S. Yamada, M. Yoshihara and T. Maeshima, *Chem. Pharm. Bull.*, **32**, 1590 (1984).
8. R.A. Mekheimer and R.M. Shaker, *J. Chem. Res. Miniprint, EN*, **2**, 449 (1999).
9. M.I. Al-Ashmawy, Z.K.A. El-Samii, S.A. El-Feky and N.A. Osman, *Boll. Chim. Farm.*, **4**, 110 (1998).
10. Th. Jira, Stelzer, W.-D. Pfeiffer, C.H. Schopplich, S. Siegert and M. Kindermann, *Pharmazie*, **52-II**, 831 (1997).
11. W.D. Pfeiffer, E. Bulka and R. Fermum, DD209196; *Chem. Abstr.*, **101**, 19197g (1984).
12. W.D. Pfeiffer, E. Bulka and R. Fermum, DD2040331; *Chem. Abstr.*, **104**, 68891n (1986).
13. W.D. Pfeiffer, E. Dilk, E. Bulka and R. Fermum, DD204092; *Chem. Abstr.*, **101**, 7216 (1984).
14. I. Demiloge, M. Morvan, G. Nadler and R.G. Zimmermann, *J. Heterocycl. Chem.*, **28**, 1525 (1991).
15. P.C. Spartan, Wavefunction, Inc., Irvine, CA, USA (1995).
16. M.J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.A. Robb, J.R. Cheeseman, T.A. Keith, G.A. Petersson, J.a. Montgomery, K. Raghavachari, M.A. Al-Laham, V.C. Zakrezewski, J.V. Ortiz, J.B. Foresman, J. Cioslowski, B.B. Stefanov, A. Nanayakkara, M. Challacombe, C.Y. Peng, P.Y. Ayala, W. Chen, M.W. Wong, J.L. Andres, E.S. Replogle, R. Gomperts, R.L. Martin, D.J. Fox, J.S. Binkley, D.J. Defrees, J. Baker, J.P.

Stewart, M. Head-Gordon, C. Gonzalez and J.A. Pople, Gaussian 94, Gaussian, Inc., Pittsburgh, PA, USA (1995).
17. P. Sjoberg and P. Politzer, *J. Phys. Chem.*, **94**, 3959 (1990).
18. M.M. Hania and F. Abu-Awwad, *Asian J. Chem.*, **12**, 1159 (2000).
19. M. Su and S. Chu, *Chem. Phys. Lett.*, **308**, 283 (1999).
20. G. Ghigo, G. Tonachini and J. Fossey, *J. Phys. Org. Chem.*, **10**, 885 (1997).
21. P. Politzer, F. Abu-Awwad and J.S. Murray, *Int. J. Quant. Chem.*, **69**, 607 (1998).
22. P. Politzer and D.G. Truhlar (Eds.), Chemical Applications of Atomic and Molecular Electrostatic Potentials, Plenum, New York (1981).
23. B. Balabov and P. Bohadova-Parvanova, *J. Phys. Chem. A*, **103**, 6793 (1999).
24. J.S. Murray and P. Politzer, *J. Org. Chem.*, **56**, 6715 (1991).
25. J. Murray and P. Politzer, *J. Chem. Res. (S)*, 110 (1992).
26. J.S. Murray, S. Ranganathan and P. Politzer, *J. Org. Chem.*, **56**, 3734 (1991).
27. J.S. Murray, F. Abu-Awwad, P. Politzer, L.C. Wilson, A.S. Troupin and R.E. Wall, *Int. J. Quant. Chem.*, **70**, 1137 (1998).
28. J.S. Murray and P. Politzer, *J. Chem. Res. S.*, 110 (1992).

(*Received:* 19 March 2002; *Accepted:* 28 June 2002) AJC-2787