Pergamon

Tetrahedron Letters 43 (2002) 1709–1712

TETRAHEDRON LETTERS

Remarkable discrepancy in the predominant structures of acyl(or thioacyl)aminothiadiazoles, acyl(or thioacyl)aminooxadiazoles and related compounds having the potential for rotational, geometrical and tautomeric isomerism

Yoshimitsu Nagao,[a,*] Hitoshi Iimori,[a] Satoru Goto,[a] Terukage Hirata,[a] Shigeki Sano,[a] Hiroshi Chuman[a] and Motoo Shiro[b]

[a]*Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan*
[b]*Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8666, Japan*

Received 30 November 2001; revised 4 January 2002; accepted 7 January 2002

Abstract—X-Ray crystallographic structures of 5-ethyl-2-trifluorothioacetylamino-1,3,4-thiadiazole **2**, 5-ethyl-3-*p*-nitrobenzyl-2-trifluorothioacetylimino-1,3,4-thiadiazoline **4** and 5-*n*-propyl-2-trifluoroacetylamino-1,3,4-thiadiazole **7** proved to be monomeric or dimeric bearing intermolecular hydrogen bondings and/or an intramolecular nonbonded 1,5-type S···S or S···O interactions. In contrast, the X-ray crystallographic structure of 5-ethyl-2-trifluoroacetylamino-1,3,4-oxadiazole **5** was shown to be dimeric involving ordinal intra- and intermolecular hydrogen bondings without any close contact. The ab initio computational studies (HF/6-311G*) of the four monomeric formylamino- and thioformylaminothiadiazoles(or -oxadiazoles) and formylimino- and thioformyliminothiadiazolines(or -oxadiazolines) structures **8**–**11** clarified the relative structure–stability order and a remarkable discrepancy in the predominant structures of the acylamino- and thioacylaminothiadiazoles and -oxadiazoles having the potential for rotational, geometrical and tautomeric isomerism.

Although the biological implications, or the lack thereof, of intramolecular nonbonded S···X (X = O, S, N, etc.) interactions have been recently discussed,[1] a large number of sulfur atom-containing heterocyclic natural products[2] and heterocyclic drugs[1,3] with or without a design involving such a specific nonbonded interaction have been reported. Various nonbonded S···O interactions have recently been observed to be essential factors in regulating the conformation and geometry of organosulfur compounds, and these interactions have been discussed in terms of X-ray crystallographic and spectroscopic analyses as well as theoretical calculations.[4] There have been several papers that have discussed the nonbonded S···S interaction, e.g. the transannular S···S interaction in geometrically constrained 1,5-dithiocane derivatives,[5] 1-tosylimino-1,5-dithiacyclooctane,[6] bis(phenylthio)-dibenzothiophenes,[7] thiathiophthenes ('bond switching'),[8] etc.[9] Recently, we have demonstrated intramolecular nonbonded 1,5-type S···O interactions (S···O close contact) in the free rotatory molecules of acyliminothiadiazoline derivatives exhibiting extensive angiotensin II (AII) receptor antagonistic activity and their related compounds based on X-ray crystallographic analyses and ab initio MO calculations.[10] However, the binding affinity of an acyliminooxadiazoline derivative to the AII receptor proved to be lower than that of an acyliminothiadiazoline derivative.[10] Thus, such difference of the affinity to the AII receptor between thiadiazoline and oxadiazoline derivatives prompted us to investigate the molecular structure characteristics of the acyl and thioacyl derivatives of aminothiadiazole, aminooxadiazole and their related compounds. We describe here intramolecular nonbonded 1,5-type S···S and S···O interactions and a remarkable discrepancy in the predominant structures of acyl(or thioacyl)aminothiadiazole and acyl(or thioacyl)aminooxadiazole derivatives.

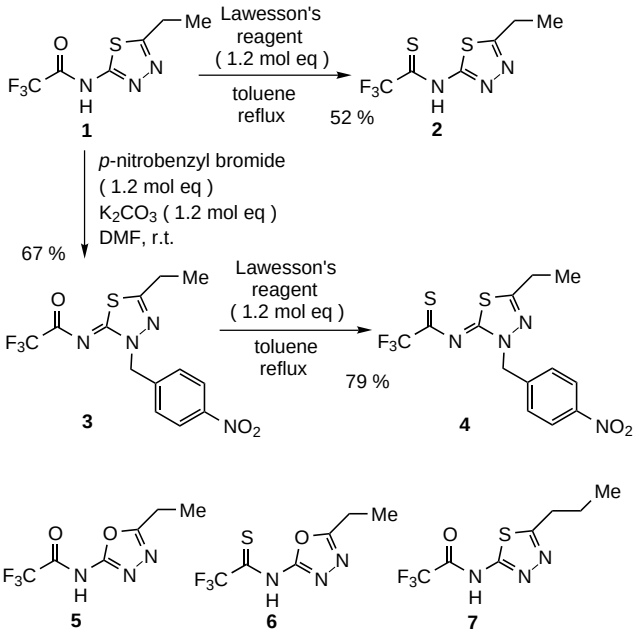
Treatment of 5-ethyl-2-trifluoroacetylamino-1,3,4-thiadiazole **1** with the Lawesson's reagent[11] in toluene under reflux afforded the desired trifluorothioacylamide

Keywords: intramolecular nonbonded interaction; thiadiazoles; oxadiazoles; X-ray crystallographic structures; ab initio MO calculation; hydrogen bonding.

* Corresponding author. Tel.: +81-88-633-7271; fax: +81-88-633-9503; e-mail: ynagao@ph2.tokushima-u.ac.jp

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00080-1

2 [yellow prisms, mp 134–136°C ($CHCl_3$–hexane)] in a 52% yield. The reaction of **1** with *p*-nitrobenzyl bromide in the presence of K_2CO_3 in DMF gave *N*-nitrobenzyl derivative **3** [67% yield, pale yellow prisms, mp 103–104°C (ethanol)], which was similarly treated with the Lawesson's regent[11] to give trifluorothioacetylimide **4** [79% yield, yellow prisms, mp 116–117°C ($CHCl_3$–hexane)], as shown in Scheme 1. A similar reaction of 5-ethyl-2-trifluoroacetylimino-1,3,4-oxadiazoline **5**[10] with the Lawesson's reagent[11] under reflux or at room temperature, however, resulted in the



Scheme 1.

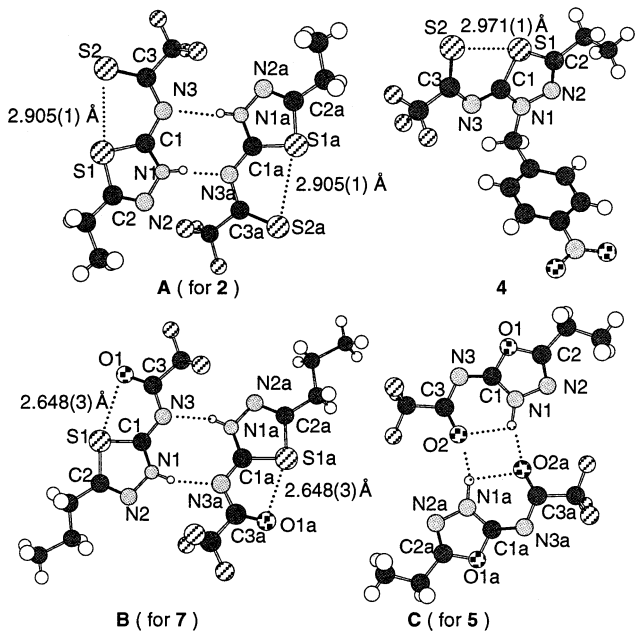


Figure 1. Computer-generated drawing of compounds **A** (for **2**), **4**, **B** (for **7**) and **C** (for **5**) derived from the X-ray coordinates.

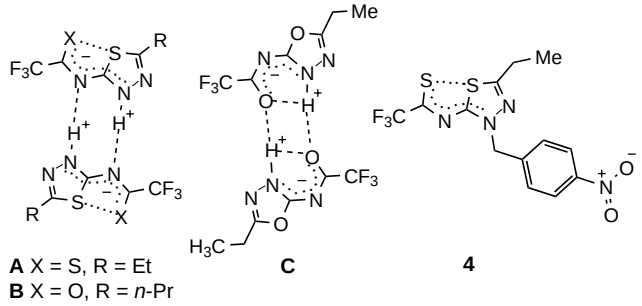


Figure 2. Rational chemical structures of **A**–**C** and **4**.

decomposition of **5** without yielding the desired product **6**.

The crystallographic structures of **2**, **4** and **5** were determined by X-ray analyses,[12] as shown in Fig. 1. Extremely close contact [2.971(1) Å, cf. the sum (3.60 Å) of van der Waals radii (S and S)] between sulfur (S1) and sulfur (S2) atoms and the planarity of the S1–C1–N3–C3–S2 moiety (see torsion angles)[12] can be seen in compound **4** as we anticipated. Similar close contact [2.905(1) Å] between the thiocarbonyl sulfur and the thiadiazole sulfur atoms can also be seen in the crystal structure of **2**. However, the analyzed crystallographic structure unexpectedly proved to be dimeric **A**[13] involving characteristic intermolecular hydrogen bondings, as represented in Fig. 1. Therefore, the X-ray crystallographic analysis of the earlier reported compound **7**[10] was carefully reexamined. As a result, a similar dimeric structure **B** with the close contact of 1,5-type S1···O1 [2.648(3) Å, cf. the sum (3.32 Å) of van der Waals radii (S and O)] and intermolecular hydrogen bondings was revealed. In contrast, the structure of trifluoroaminooxadiazole **5** based on the X-ray crystallographic analysis (Fig. 1), was shown to be dimeric **C** involving ordinal intra- and intermolecular hydrogen bondings and without signs of any close contact.[13] Hence, the unusual dimeric structures **A** and **B** must be understood in terms of the intramolecular 1,5-type nonbonded S···S and S···O interactions, respectively, in comparison with structure **C**. The rational crystallographic structures of **A**, **B**, **C** and **4** can be represented as a characteristic anion- or electron-delocalized formula (Fig. 2) due to the almost similar bond lengths[13] of C1–N1, C1–N3, and C3–N3.

In order to understand the structural discrepancy between trifluoroacetyl(or trifluorothioacetyl)aminothiadiazole and trifluoroacetyl(or trifluorothioacetyl)-aminooxadiazole described above, the corresponding eight possible kinds of monomeric rotational and geometrical isomers and tautomers, **8**–**15** (Fig. 3) were evaluated in terms of the ab initio MO calculations at some HF levels by using simplified monomeric formylamino(or -imino) and thioformylamino(or -imino) structures.[14,15] In our computational studies of **8**–**15** ($R^1=R^2=H$; X=O, Y=O or S; X=S, Y=O or S), the sterically unstable structures **12**–**15** were neglected on the basis of the earlier calculation outcome.[10,15] Thus, the relative energy values obtained

from the ab initio geometry optimization of structures **8**–**11** at the HF/6-311G* level are listed in Table 1.[14]

In structures **8**–**11** of the formyl(or thioformyl)oxadiazole-related compounds (X = O, Y = O or S), the plausible main structure–stability factors can be speculated from an inspection of the molecular structures as follows. Factor 1: intramolecular hydrogen bonding between N3-hydrogen and carbonyl oxygen (or thiocarbonyl sulfur) atoms; Factor 2: *endo*-olefinic stabilization of the heterocyclic moiety (vide infra); and Factor 3: weak carbonyl O···O1 or thiocarbonyl S···O1 close contact.[10] Thus, the relative structure–stability order in the oxadiazole-related compounds can be rationalized as follow: **9** (Factor 1)>**11** (Factors 2 and 3)>**10** (Factor 2)>**8** (Factor 3).

In structures **8**–**11** of the formyl(or thioformyl)-thiadiazole-related compounds (X = S, Y = O or S), the plausible main structure–stability factors may be considered to be as follows. Factor 4: remarkable carbonyl O···S1 or thiocarbonyl S···S1 close contact, Factor 1 and Factor 2. Eventually, the relative structure–stability order in the thiadiazole-related compounds is regarded to be as the follows. **11** (Factors 4 and 2)>**9** (Factor 1)>**8** (Factor 4)>**10** (Factor 2). With regard to the tautomeric energy gaps [**8** versus **11**: ΔE (X = O) = 5.485, 4.643 kcal/mol or ΔE (X = S) = 2.627, 2.116 kcal/mol], Factor 2 is fairly differential depending on whether there is formyl(or thioformyl)amino-oxadiazole–formyl(or thioformyl)iminooxadiazoline tautomerism or formyl(or thioformyl)aminothiadiazole–formyl(or thioformyl)iminothiadiazoline tautomerism. The participation of the former as Factor 2 in the structure–stability should be larger than that of the latter, which can also be supported by the ab initio MO calculation outcome of 2-amino-1,3,4-oxa(or thia)diazole and 2-imino-1,3,4-oxa(or thia)diazoline, as shown in Table 2.[14]

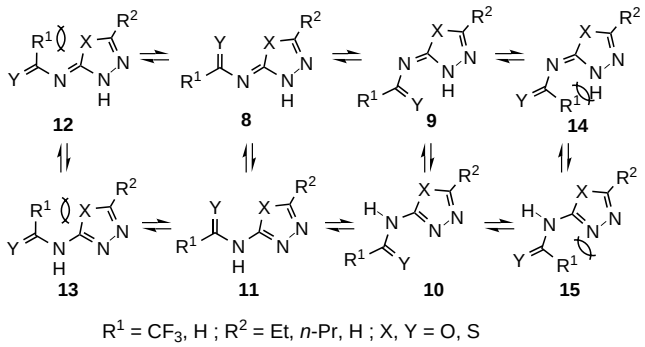


Figure 3. Possible rotational and geometrical isomers and acylamino–acylimino tautomers.

Table 1. Ab initio MO calculation of selected rotational and geometrical isomers and acylamino–acylimino tautomers (**8**–**11**, R¹ = R² = H) at the HF/6-311G* level

	Relative energy (kcal/mol)			
X, Y	**8**	**9**	**10**	**11**
O, O	6.698	0.000	4.118	1.213
O, S	6.816	0.000	4.814	2.173
S, O	2.627	2.175	9.183	0.000
S, S	2.116	1.597	9.304	0.000

Table 2. Ab initio MO calculation of *endo*/*exo*-olefinic tautomers

	Relative energy (kcal/mol)			
	AO[a]	IO[b]	AT[c]	IT[d]
HF/6-311G*	0.000	5.831	0.000	3.760
HF/6-31G*	0.000	5.833	0.000	4.037

[a] AO: 2-amino-1,3,4-oxadiazole
[b] IO: 2-imino-1,3,4-oxadiazoline
[c] AT: 2-amino-1,3,4-thiadiazole
[d] IT: 2-imino-1,3,4-thiadiazoline

In conclusion, the ab initio computation has determined that structure **11** (R¹ = R² = H; X = S, Y = O or S) involving the intramolecular nonbonded S···S or S···O interaction and structure **9** (R¹ = R² = H; X = O, Y = O or S) involving intramolecular hydrogen bonding, are the most stable among the four related isomeric structures, respectively. The ab initio-computational outcomes are sufficiently consistent with the X-ray crystallographic analyses giving structures **A** (for **2**), **B** (for **7**), and **C** (for **5**), except for their unexpected dimeric formulas. The molecular structure characteristics described herein may provide new insights into the molecular design of drugs and a new type of pharmacophore.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research (B) (2) (No. 12470482) from the Japan Society for the Promotion of Science.

References

1. (a) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Barzi, A.; Nocentini, G.; Yang, H.; O'Connor, A.; Jayaram, H. N.; Carrell, C.; Goldstein, B. M. *J. Med. Chem.* **1995**, *38*, 3829–3837 and references cited therein; (b) Mokara, G. M.; Keserû, G. M. *J. Med. Chem.* **1997**, *40*, 4154–4159; (c) Tanaka, R.; Oyama, Y.; Imajo, S.; Matsuki, S.; Ishiguro, M. *Bioorg. Med. Chem.* **1997**, *5*, 1389–1399; (d) Kumagai, T.; Tamai, S.; Abe, T.; Matsunaga, H.; Hayashi, K.; Kishi, I.; Shiro, M.; Nagao, Y. *J. Org. Chem.* **1998**, *63*, 8145–8149; (e) Yamada, S.; Misono, T. *Tetrahedron Lett.* **2001**, *42*, 5459–5500.
2. (a) Ireland, C.; Scheuer, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5688–5691; (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195–8197; (c) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243–1245; (d) Shiozawa, H.;

Kagasaki, T.; Torikata, A.; Tanaka, N.; Fujimoto, K.; Hata, T.; Furukawa, Y.; Takahashi, S. *J. Antibiot*. **1995**, *48*, 907–909; (e) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1–10 and references cited therein; (f) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc*. **1997**, *119*, 103–111 and references cited therein; (g) Wu, S.; Greer, A. *J. Org. Chem*. **2000**, *65*, 4883–4887.

3. (a) Metzger, J. V. *Comprehensive Heterocyclic Chemistry: Thiazoles and Their Benzo Derivatives*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 6, Part 4B (Potts, K. T., Ed.), pp. 235–331 and references cited therein; (b) Abstracts of the 5th Annual Meeting of Division of Medicinal Chemistry in Japan (Toyama), 1996; (c) Fujita, T. *Biosci. Biotech. Biochem*. **1996**, *60*, 557–566 and references cited therein; (d) Hirata, T.; Goto, S.; Tamura, K.; Okuhira, M.; Nagao, Y. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 385–388; (e) Martínez, A.; Castro, A.; Cardelús, I.; Llenas, J.; Palacios, J. M. *Bioorg. Med. Chem*. **1997**, *5*, 1275–1283.
4. (a) Kucsman, A.; Kapovits, I. In *Organic Sulfur Chemistry*: *Theoretical and Experimental Advances*; Bernardi, F.; Csizmadia, I. G.; Mangini, A., Eds.; Elsevier Scientific Publishing Co.: Amsterdam, 1985; pp. 191–245; (b) Burling, F. T.; Goldstein, B. M. *J. Am. Chem. Soc*. **1992**, *114*, 2313–2320; (c) Lábbe, G.; Meervelt, L. V.; Emmers, S.; Dehaen, W.; Toppet, S. *J. Heterocycl. Chem*. **1992**, *29*, 1765–1768; (d) Pandya, N.; Basile, A. J.; Gupta, A. K.; Hand, P.; MacLaurin, C. L.; Mohammad, T.; Ratemi, E. S.; Gibson, M. S.; Richardson, M. F. *Can. J. Chem*. **1993**, *71*, 561–571; (e) Minyaev, R. M.; Minkin, V. I. *Can. J. Chem*. **1998**, *76*, 776–788.
5. Glass, R. S.; Adamowicz, L.; Broeker, J. L. *J. Am. Chem. Soc*. **1991**, *113*, 1065–1072.
6. Iwasaki, F.; Furukawa, N. *Acta Crystallogr*. **1987**, *C43*, 80–83.
7. Yasui, M.; Murata, S.; Iwasaki, F.; Furukawa, N. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 744–751.
8. (a) Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc*. **1980**, *102*, 7753–7759; (b) Ohkata, K.; Ohsugi, M.; Yamamoto, K.; Ohsawa, M.; Akiba, K.-y. *J. Am. Chem. Soc*. **1996**, *118*, 6355–6369 and references cited therein.
9. (a) Johnson, S. M.; Maier, C. A.; Paul, I. C. *J. Chem. Soc. (B)* **1970**, 1603–1608; (b) Olmstead, M. M.; Williams, K. A.; Musker, W. K. *J. Am. Chem. Soc*. **1982**, *104*, 5567–5568; (c) Doi, J. T.; Kessler, R. M.; deLeeuw, D. L.; Olmstead, M. M.; Musker, W. K. *J. Org. Chem*. **1983**, *48*, 3707–3712; (d) Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron* **1998**, *54*, 5353–5362; (e) Kobayashi, K.; Koyama, E.; Namatame, K.; Kitaura, T.; Kono, C.; Goto, M.; Obinata, T.; Furukawa, N. *J. Org. Chem*. **1999**, *64*, 3190–3195; (f) Nagao, Y.; Nishijima, H.; Iimori, H.; Ushirogochi, H.; Sano, H.; Shiro, H. *J. Organomet. Chem*. **2000**, *611*, 172–177.
10. Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc*. **1998**, *120*, 3104–3110.
11. Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg*. **1978**, *87*, 223–228.
12. The crystal data of compound **2**: monoclinic, $P2_1/c$ (#14), $a=5.044(2)$, $b=18.340(6)$, $c=10.632(2)$ Å, $\beta=101.44(1)°$, $V=963.5(5)$ Å^3, $z=4$, $D_{calcd}=1.662$ g/cm^3, $R=0.058$, $R_w=0.113$. **4**: monoclinic, $P2_1/c$ (#14), $a=8.204(2)$, $b=18.0448(2)$, $c=11.081(1)$ Å, $\beta=101.52(1)°$, $V=1607.3(4)$ Å^3, $z=4$, $D_{calcd}=1.555$ g/cm^3, $R=0.040$, $R_w=0.071$. **5**: monoclinic, $C2/c$ (#15), $a=23.566(6)$, $b=4.691(7)$, $c=17.331(7)$ Å, $\beta=116.87(2)°$, $V=1709(2)$ Å^3, $z=8$, $D_{calcd}=1.625$ g/cm^3, $R=0.084$, $R_w=0.105$.
13. Selected torsion angles and bond lengths, **A**: S1–C1–N3–C3 = −1.4(3)°, S2–C3–N3–C1 = 0.4(3)°, C2–N2 = 1.283(3) Å, C1–N1 = 1.327(3) Å, C1–N3 = 1.338(3) Å, C3–N3 = 1.338(3) Å; **4**: S1–C1–N3–C3 = 3.5(4)°, S2–C3–N3–C1 = 0.6(4)°, C2–N2 = 1.285(3) Å, C1–N1 = 1.338(3) Å, C1–N3 = 1.322(3) Å, C3–N3 = 1.332(3) Å; **B**: S1–C1–N3–C3 = 0.9(4)°, O1–C3–N3–C1 = −3.5(5)°, C2–N2 = 1.286(4) Å, C1–N1 = 1.322(4) Å, C1–N3 = 1.337(3) Å, C3–N3 = 1.343(4) Å; **C**: N1–C1–N3–C3 = 10.4(10)°, O2–C3–N3–C1 = 5.3(9)°, C2–N2 = 1.279(8) Å, C1–N1 = 1.324(7) Å, C1–N3 = 1.306(7) Å, C3–N3 = 1.356(8) Å.
14. All calculations were carried out using the inter Pentium-III/500 MHz microprocessor. The ab initio MO calculations were performed on the basis of the GAMESS program at the Hatree–Fock (HF) levels.[16] The starting monomeric structure, obtained from each corresponding X-ray crystallographic structure, was used for the optimization at the 3-21G*, 6-31G*, and 6-311G* levels. The global energy minimum for each structure was normalized to 0 kcal/mol.
15. Relative energy of structures **10** and **11** based on the ab initio MO calculation at the HF/3-21G* level: 2-trifluoroacetyl-amino-5-propyl-1,3,4-thiadiazole ($R^1=CF_3$, $R^2=n$-Pr, X = S, Y = O): **10** $E=8.16$ kcal/mol, **11** $E=0.000$ kcal/mol; 2-formylamino-1,3,4-thiadiazole: **10** $E=9.323$ kcal/mol, **11** $E=0.000$ kcal/mol. ΔE value ($R^1=CF_3$, $R^2=n$-Pr versus $R^1=R^2=H$) = 1.16 kcal/mol.
16. (a) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. T. *QCPE Bull*. **1990**, *10*, 52–54; (b) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem*. **1993**, *14*, 1347–1363.