Acridin-9-yl Isothiocyanate: Comparison of Structural Parameters from Quantum-Chemical Calculations with Corresponding X-Ray Data

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Dedicated to Professor Pavol Kristian in honour of his 70th birthday

X-Ray structural parameters of acridin-9-yl isothiocyanate were confirmed and compared with those obtained by AM1, PM3, and *ab initio* calculations. For *ab initio* results, the angle C-9—N—C-10 is critical from the viewpoint of this comparison. Experimental structural parameters for representative isothiocyanates (acridin-9-yl isothiocyanate, 9-isothiocyanato-10-methylacridinium cation, HNCS, CH_3NCS, vinyl isothiocyanate, PhNCS, $4\text{-BrC}_6\text{H}_4\text{NCS}$) are in good agreement with those obtained by *ab initio* calculations if electron correlation effects were involved using the 6-31G and 6-311G basis set, respectively, with polarization functions on nitrogen atom. AM1 and PM3 calculated parameters are in good agreement with all structural experimental data under consideration.

For acridine derivatives, two characteristics are typical: great biological efficiency and specific physico-chemical properties. The most interesting are cyto-static efficiency, ascribed to intercalating effect [1], cholinergic effect in connection with Alzheimer's disease [2] and intesive fluorescence, used in biomolecule markers [3]. Attention was paid to these derivatives also from the theoretical point of view [4, 5] using quantum-chemical calculations (AM1, PM3).

For the synthesis of starting acridin-9-yl compounds, we used derivatization of the acridine skeleton with very reactive —NCS group, which enters into addition, cycloaddition, and cyclocondensation reactions, giving various types of organic compounds [6, 7]. Thus, acridin-9-yl isothiocyanates [8—10] and $O(S)$-methyl $S(O)$-allyl N-(2/4-R-acridin-9-yl)thiocarbonimidates as their reaction products as well as configuration and conformation structures occurring in sigmatropic rearrangement, were studied both experimentally and theoretically (NMR spectra, dipole moments, and quantum-chemical calculations MNDO, AM1, PM3) [11, 12].

To obtain further information on structure and reactivity of acridin-9-yl isothiocyanate, we focused in this contribution on semiempirical (AM1, PM3) and *ab initio* quantum-chemical calculations. For this purpose, X-ray structural data for acridin-9-yl isothiocyanate were established. In addition it was possible to make some general conclusions on structure of other types of isothiocyanates (Scheme 1), resulting from comparison of structural data taken from literature with corresponding data obtained by quantum-chemical calculations.

EXPERIMENTAL

The synthesis of the title compound was described elsewhere [15]. Recrystallization from various solvents usually yields fine cotton-like yellow needles.

For X-ray structural analysis, single crystals obtained by recrystallization from diethyl ether were used. These were studied using Siemens AED diffractometer and Ni-filtered CuKα radiation ($\lambda = 1.54178$ Å). Crystal data are: monoclinic, space group P21/n, $a = 3.797(3)$, $b = 33.925(5)$, $c = 8.493(3)$, $\beta = 100.86(2)°$, $V = 1126(1)$ Å^3, $Z = 4$. The structure was solved by the direct method using the program SIR92 [16] and anisotropically refined by full-matrix least-squares refinement against all data on F2 using the program SHELXL93 [17].

Using the MOPAC [18, 19], Gaussian 90 [20], Gaussian 94 [21], and Gamess [21] programs, molecular geometries of all molecules under study (Scheme 1) were totally optimized by appropriate MO methods. 3-21G,

Table 1. Selected Bond Lengths and Valence Angles for Acridin-9-yl Isothiocyanate

Bond lengths/Å			
S—C	1.554(5)	C-9a—C-9	1.402(6)
N—C-5a	1.346(6)	C-9a—C-4a	1.432(6)
N—C-4a	1.351(6)	C-5a—C-8a	1.430(6)
N—C-10	1.169(6)	C-8—C-8a	1.416(6)
N—C-9	1.382(6)		

Valence angles/°			
C-5a—N—C-4a	118.2(4)	N—C-9—C-8a	118.9(4)
C-9—N—C-10	163.6(5)	N—C—S	176.8(5)
N—C-9—C-9a	119.9(5)		
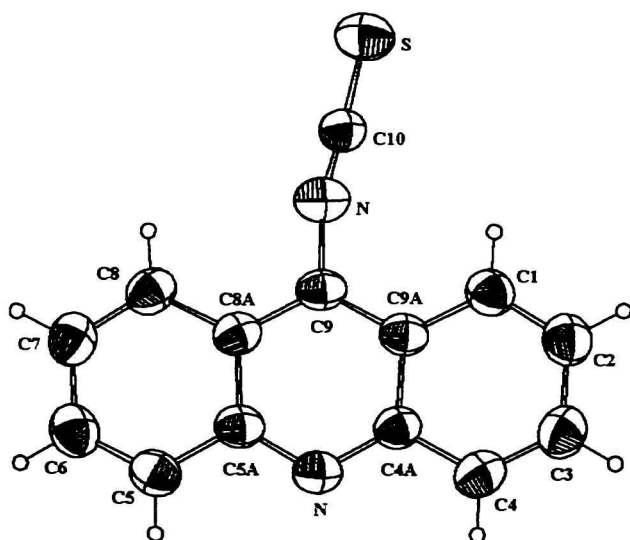
Fig. 1. ZORTEP [27] view of the acridin-9-yl isothiocyanate molecule.

3-21G*, 3-21G**, 6-31G, 6-31G*, 6-31G**, 6-311G**, and 6-311G(2d, 3p) basis sets were used [22, 23]. The electron correlation effects were involved using the second-order Møller—Plesset perturbation theory [24] as well as Becke's three-parameter hybrid method [25].

Some important structural parameters from X-ray analysis are selected in Table 1. The thermal ellipsoids in ZORTEP [27] view of the acridin-9-yl isothiocyanate molecule (Fig. 1) are drawn at the 30 % probability level.

RESULTS AND DISCUSSION

Preliminary results of structure analysis (Table 1, Fig. 1) confirmed the molecular structure of acridin-9-yl isothiocyanate. The —NCS group is out of the mean plane formed by the acridine skeleton, the dihedral angle around N—C-9 bond (C-10—N—C-9—C-8a) exhibiting a value of $-152(1)°$. X-Ray analy-

sis also confirmed the nonlinearity $(176.8(5)°)$ of the —NCS group (Table 1). The obtained value for this angle as well as the bond distances in this group are in line with those found in 4-bromophenyl isothiocyanate [13]. The bond distances and angles in the acridine skeleton agree with data published for analogous compounds [14]. The whole acridine skeleton is not exactly planar. Whereas the ring containing the C-8 atom is planar within experimental errors, the middle and the other terminal rings are not. The angle between the mean planes of the terminal rings is $2.0(1)°$. This value is smaller than the value $6.2°$ found in the acridine skeleton of N-acridinium-9-yl-N'-propylidenehydrazine thiocyanate [14].

Quantum-chemical calculations of optimized structures of the compounds under study (Scheme 1) were carried out by both semiempirical (AM1, PM3) and nonempirical (RHF, MP2, B3LYP with 3-21G, 6-31G, 6-311G basis sets and polarization and diffuse functions) methods. The bond distances for C-9—N, C═N, and C═S calculated by semiempirical as well as nonempirical methods are comparable and are in good agreement with corresponding values established by experimental methods: for acridin-9-yl isothiocyanate, the values calculated by B3LYP/6-31G** are (d/pm): 137.30; 119.51; 158.76 (for experimental values see Table 1). We have obtained similar results in calculation of the optimized angle N═C═S; for acridin-9-yl isothiocyanate, the nonlinearity of the —NCS group (B3LYP/6-31G**) is $176.26°$ vs. experimental $176.8(5)°$ – see Table 2. The calculations also predict deviation of the —NCS group out of plane formed by the acridine skeleton. Dihedral angles calculated by B3LYP/6-31G** compared with corresponding X-ray data for acridin-9-yl isothiocyanate (this paper) are: C-9—N—C-10—S ($177.52°$ vs. $178.29°$), C-1a—C-9—N—C-10 ($28.04°$ vs. $29.26°$), and C-1—C-1a—C-9—N ($1.72°$ vs. $1.98°$).

A critical structural parameter from the viewpoint of comparison of quantum-chemical calculations and experimental values is the valence angle C-9—N—C. The experimentally established values of this angle for the compounds under study are in the range $130.25°$—$153.63°$ and the values calculated by semiempirical methods AM1 and PM3 (range $136.25°$—$144.96°$) correspond well with them. The experimental value $163.6(5)°$ for the valence angle C-9—N—C of acridin-9-yl isothiocyanate in this paper is a little greater. We assume that the value for this angle may be affected by crystal packing forces, hence the values for the solid state (X-ray) may significantly differ from those in the solution or gas phase.

The packing is controlled by the planarity of the title molecule and the attractive forces within the layers may contribute to a short contact C-3—H-3...N-1i (i: $x + 1/2, 1/2 - y, z - 1/2$). The distance H-3—N-1$i$ 2.693(6) Å is shorter than the sum of van der Waals radii for these atoms [26], 2.75 Å; the other

Table 2. Quantum-Chemical Calculations of the C—N—C, resp. H—N—C Valence Angle/° in Isothiocyanato Group of Some Isothiocyanates

Method	I^a	II	III^b	$IV^{c,d}$	$VII^{e,f}$	$VIII^g$
AM1	143.87	138.08	137.12	138.24	140.58	136.52
PM3	144.96	139.32	138.80	140.32	139.43	136.25
RHF/6-31G*	179.98	179.70	180.00	179.98	180.00	142.07
RHF/6-31++G**	–	–	179.90	179.79	179.53	143.11
RHF/6-311+G**	–	–	179.42	180.00	179.46	144.25
RHF/6-311G**	–	–	179.68	179.84	179.60	143.58
RHF/6-311G(2d, 3p)	–	–	180.00	179.69	180.00	135.06
RHF/6-311++G(2d, 3p)	–	–	179.51	179.92	179.67	135.22
MP2/3-21G	179.93	–	–	–	179.82	154.65
MP2/6-31G**	–	144.79	–	147.30	146.91	132.60
B3LYP/6-31G**	158.05	150.38	151.47	153.08	153.65	131.42
B3LYP/6-311+G**	–	–	151.56	153.21	153.91	133.09
B3LYP/6-311G(2d, 3p)	–	–	151.32	153.07	151.21	131.57
B3LYP/6-311++G(2d, 3p)	–	–	151.13	152.76	149.31	131.54

a) X-Ray: ∠CNC 163.6(5)° – this paper; b) X-Ray: ∠CNC 153.63° [13]; c) Microwave spectrum: ∠CNC 145° [28]; d) Microwave spectrum: ∠CNC 148° [29]; e) Electron diffraction: ∠CNC 141.6° [30]; f) Microwave spectrum: ∠CNC 147° [31]; g) Microwave spectrum: ∠HNC 130.25° [33].
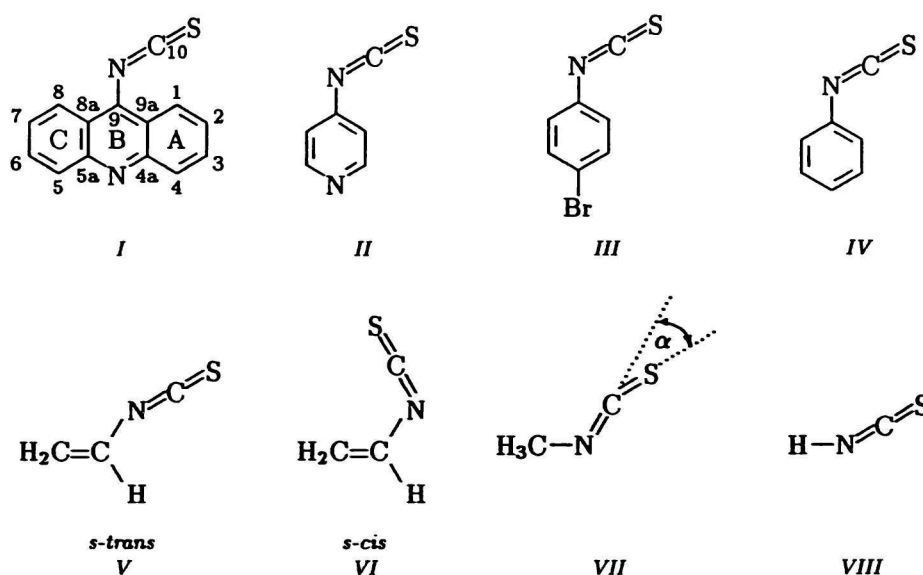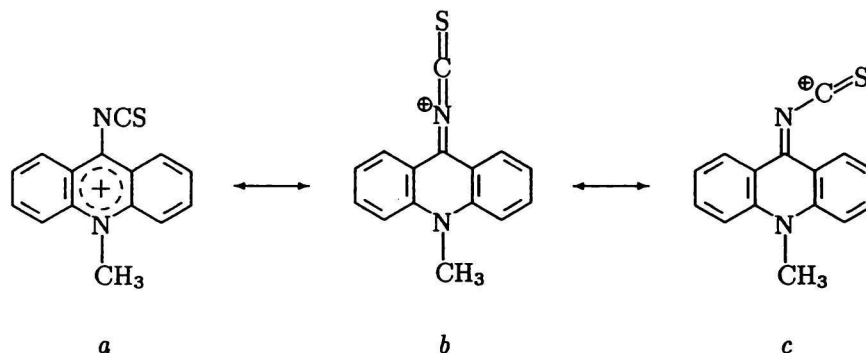

Scheme 1

relevant values are: C-3...N-1i 3.613(6) Å, angle C-3—H-3...N-1i 170.0(5)°.

If nonempirical quantum-chemical methods are used for such comparison, the choice of the 6-31G or 6-311G basis set with polarization functions on nitrogen atom and electron correlation effects are important. For all the compounds under study (Scheme 1), only calculations involving electron correlation effects using the above-mentioned basis sets afforded values for this angle (131.42°—158.05°) well comparable with the experimental values (except HNCS molecule, RHF/6-31G* calculation – Table 2).

For 9-isothiocyanato-10-methylacridinium cation several structures with different localization of positive charge may be taken into account (Scheme 2). Hydrolysis of the above-mentioned cation afforded 9-aminoacridinium salt and hence the structure b had been excluded [34]. AM1, PM3 calculations and *ab initio* calculation involving electron correlation effects (B3LYP/6-31G**) give for angle C-9—N—C values 141.36°—152.25°, but the value obtained from RHF/6-31G** is 179.94° (structure b). Electron charges as well as the structural parameters given by these *ab initio* calculations are comparable with AM1 and PM3 calculations and positive charge is partially localized on the carbon of the —NCS group. 9-Isothiocyanato-10-methylacridinium triflate increases the reactivity of 9-NCS group so that nucleophilic addition reactions with various types of alcohols take place at room temperature, whereas analogous reactions of phenyl isothiocyanate require increased temperature and longer reaction

Scheme 2

time. Acridin-9-yl isothiocyanate reacts two orders of magnitude faster than phenyl isothiocyanate and two orders of magnitude slower than benzoyl isothiocyanate [35]. This can be explained by means of calculations of energies of the frontier orbitals LUMO (isothiocyanates) and HOMO (alcohols). AM1 calculations for reactions of phenyl isothiocyanate, acridin-9-yl isothiocyanate, and 9-isothiocyanato-10-methylacridinium cation with methanol give $\Delta\varepsilon$ [$\Delta\varepsilon = \varepsilon_{LUMO}$(isothiocyanate) $- \varepsilon_{HOMO}$(methanol)]: 10.6176 eV, 9.0572 eV, and 5.0010 eV.

To make the comparison of theoretical and experimental data for isothiocyanato compounds more general, we have calculated and compared the data for selected, representative types of isothiocyanates.

Experimental and theoretical studies show that although vinyl isothiocyanate is a relatively flexible molecule, definite *s-trans* and *s-cis* rotamers exist [36] (Scheme 1). The experimental works (MW-spectra) show the *s-trans* rotamer to be more stable by 2.6 kJ mol^{-1} [37] and at least 2 kJ mol^{-1} [36]. We have found the *s-trans* rotamer stable about 4.15 kJ mol^{-1} (B3LYP/6-31G**).

The CNC valence angle of methyl isothiocyanate was found to be about 147°—151° (microwave spectra [31, 32]) and 141.6° (electron diffraction study [30]). Barrier to linearity of the CNCS skeleton of height 1.91—2.59 kJ mol^{-1} for the molecule was determined [32]. In this paper we have calculated (B3LYP/6-31G**) this barrier to linearity to be about 1 kJ mol^{-1}. Analogically, barrier to linearity of the NCS group about 0.66 kJ mol^{-1} was determined from energy dependence *vs.* α (Scheme 1). For the HNCS molecule the energy at linear conformation was calculated (*ab initio*) 1.03 kJ mol^{-1} higher than for the bent molecule [38]. B3LYP/6-31G** calculation gives for the barrier to linearity value 0.87 kJ mol^{-1}.

CONCLUSION

Optimized structural parameters (bond lengths, valence angles) obtained by semiempirical quantum-chemical calculations (AM1, PM3) are in good agreement with corresponding experimental data. From this point of view for *ab initio* calculations it is necessary to involve electron correlation effects and use 6-31G or 6-311G basis set with polarization functions on nitrogen atom. Supplementation of the basis sets by diffuse functions has influenced calculated structural parameters only slightly.

REFERENCES

1. Sugaya, T., Matsukuma, I., Shun-ichi, I., Nimura, S., Skida, Y., and Osawa, Y., *J. Med. Chem. 37*, 1028 (1994).
2. Moos, W. H. and Hershenson, F. M., *Drug News Prospect 2*, 397 (1989).
3. Sato, H., Mochizuki, H., Tomila, Y., Yzako, T., Sato, N., and Kanamori, T., *J. Biolumin. Chemilumin. 11*, 23 (1996).
4. Rak, J., Blazheyowski, J., and Zauhar, R. J., *Can. J. Chem. 71*, 1106 (1993).
5. Smith, D. A., Gilbert, M. J., Ulmer, Ch. W. II, and Cheatham, S. F., *J. Mol. Struct. (Theochem.) 251*, 283 (1991).
6. Drobnica, Ľ., Kristian, P., and Augustín, J., in *The Chemistry of Cyanates and Their Thio Derivatives.* (S. Patai, Editor.) Part 2, Chap. 22, p. 1003. Wiley, New York 1977.
7. Kristian, P., Bernát, J., Imrich, J., Danihel, I., Suchár, G., Chomča, I., Hočová, S., Bušová, T., Guspanová, J., and Linden, A., *Molecules 1*, 181 (1996).
8. Danihel, I., Kristian, P., and Imrich, J., *Org. React. 29*, 41 (1995).
9. Danihel, I., Suchár, G., Kristian, P., and Böhm, S., *Collect. Czech. Chem. Commun. 61*, 1615 (1996).
10. Danihel, I., Imrich, J., Kristian, P., Liptaj, T., and Mazagová, D., *Collect. Czech. Chem. Commun. 59*, 1833 (1994).

11. Danihel, I., Pihlaja, K., Suchár, G., Imrich, J., Kristian, P., Böhm, S., and Hočová, S., *Collect. Czech. Chem. Commun. 63*, 387 (1998).
12. Imrich, J., Danihel, I., Pihlaja, K., Böhm, S., and Kristian, P., to be published.
13. Ulický, L. and Soldánová, J., *Chem. Pap. 39*, 473 (1985).
14. Linden, A., Guspanová, J., Bernát, J., and Kristian, P., *Acta Crystallogr., Sect. C*, in press.
15. Kristian, P., *Chem. Zvesti 15*, 641 (1961).
16. Altomare, A. M., Cascarano, G., Giacovazzo, C., Burla, M. C., Polidori, G., and Camalli, M., *J. Appl. Crystallogr. 27*, 435 (1994).
17. Sheldrick, G. M., SHELX93 – Program for the refinement of crystal structure. University of Goettingen, Germany, 1993.
18. Dewar, M. J. S., Zoebish, E. G., Healy, E. F., and Stewart, J. J. P., *J. Am. Chem. Soc. 107*, 3902 (1985).
19. Stewart, J. J. P., *J. Comput. Chem. 10*, 209 (1989).
20. Frisch, M. J., Head-Gordon, M., Trucks, G. W., Foresman, J. B., Schlegel, H. B., Raghavachari, K., Robb, M. A., Binkley, J. S., Gonzales, C., Defrees, D. J., Fox, D. J., Whiteside, R. A., Seeger, R., Melius, C. F., Baker, J., Martin, R. L., Kahn, L. R., Stewart, J. J. P., Topiol, S., and Pople, J. A., *Gaussian 90*. Gaussian Inc., Pittsburgh, Pa., 1990.
21. 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., Cioslowski, J., Stefanov, B. B., Nanayakkara, A., Challacombe, M., Peng, C. Y., Ayala, P. Y., Chen, W., Wong, M. W., Andres, J. L., Replogle, E. S., Gomperts, R., Martin, R. L., Fox, D. J., Binkley, J. S., Defrees, D. J., Baker, J., Stewart, J. J. P., Head-Gordon, M., Gonzales, C., and Pople, J. A., *Gaussian 94*. Gaussian Inc., Pittsburgh, Pa., 1995.
22. Hehre, W. J., Ditchfield, R., and Pople, J. A., *J. Chem. Phys. 56*, 2257 (1972).
23. Francl, M. M., Pietro, W. J., Hehre, W. J., Binkley, J. S., Pople, J. A., Gordon, M. S., and Defrees, D. J., *J. Chem. Phys. 77*, 3654 (1982).
24. Krishnan, R. and Pople, J. A., *Int. J. Quantum Chem. 14*, 91 (1976).
25. Becke, A. D., *J. Chem. Phys. 98*, 5648 (1993).
26. Taylord, R. and Kennard, O., *J. Am. Chem. Soc. 104*, 5063 (1993).
27. Zsolnai, L. and Pritzkow, H., ZORTEP (modified ORTEP program). University of Heidelberg, Germany, 1995.
28. Higgins, R. J., Combs, L. L., Malloy, T. B., Jr., and Cook, R. L., *J. Mol. Struct. 28*, 121 (1975).
29. Onda, M., Kambayashi, S., Sakaizumi, T., and Yamaguchi, I., *J. Mol. Struct. 34*, 299 (1976).
30. Anderson, D. W. W., Rankin, D. W. H., and Robertson, A., *J. Mol. Struct. 14*, 385 (1972).
31. Cradock, S., *J. Mol. Spectrosc. 92*, 170 (1982).
32. Koput, J., *J. Mol. Spectrosc. 118*, 189 (1986).
33. Yamada, K., Winnewisser, M., Winnewisser, G., Szalanski, L. B., and Gerry, M. C. L., *J. Mol. Spectrosc. 7*, 295 (1980).
34. Singer, B. and Maas, G., *Z. Naturforsch., B 39*, 1399 (1984).
35. Mazagová, D., Kristian, P., Suchár, G., Imrich, J., and Antalík, M., *Collect. Czech. Chem. Commun. 59*, 2632 (1994).
36. Caminati, W., *J. Mol. Struct. 190*, 227 (1988).
37. Kirby, C. and Kroto, H., *J. Mol. Spectrosc. 70*, 216 (1978).
38. Bak, B., Christiansen, J. J., Nielsen, O. J., and Svanholt, H., *Acta Chem. Scand., Ser. A 31*, 666 (1977).