Theoretical Approach and First Examples of *N*-Acyl-Thioformamides as Dienophiles in the Diels–Alder Reaction

Roger Arnaud, Pierre Y. Chavant, Karine Molvinger and Yannick Vallée*

L.E.D.S.S., laboratoire associé au CNRS, Université Joseph Fourier, B.P. 53X, 38041 Grenoble, France.

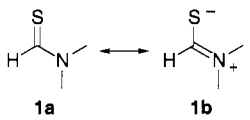
ab initio Calculations as well as experimental results show that the C = S bond of a thioamide can act as a dienophile in the Diels–Alder reaction provided that the nitrogen atom is substituted by π-acceptor groups.

Thioaldehydes, especially those bearing an electron-withdrawing group, make good dienophiles in the Diels–Alder reaction.[1] This is not the case however, for thiocarbonyl compounds bearing strong electron-donating groups. Dithioesters and thionoesters[2] are poorly reactive, and thioamides, generally, completely unreactive.[3] Thioformamides have the advantages against thioaldehydes of being stable and relatively easily obtained compounds. Furthermore, their [4π + 2π] cycloadditions would allow rapid access to nitrogen-substituted sulfur heterocycles. Here we present the first normal electronic demand Diels–Alder reaction of *N*-substituted thioformamides. The proper choice of the nitrogen substituents has been rationalized by an *ab initio* study.

From a theoretical point of view, two basic models have been proposed to explain reactivity differences in concerted cycloadditions: (i) a PMO model;[4] for us the key point is the shape and the energy of the LUMO of the thiocarbonyl compound, (ii) the state correlation diagram (SCD) model[5] which has been successfully applied to cycloaddition reactions.[6] In this diagram, the magnitude of the ππ* type singlet-to-triplet vertical excitation energy of the reactants is the key element of the barrier height (in our case, for a given diene, the key element is reduced to the ππ* S → T vertical excitation energy of the substituted thioformamide). In addition, for both models, the exothermicity of the cycloaddition should be considered. The role played by the heats of reaction is clear in the SCD diagram: When the exothermicity of the reaction increases, the curve crossing appears early on the reaction coordinate and thus a lower energy barrier is expected (in accordance with Hammond's postulate). *Ab initio* calculations[7,8] predict a planar C_s equilibrium geometry for *N,N*-dimethyl thioformamide **1**.[9] This suggests a strong conjugation in compound **1** and thus an important participation of the Lewis structure **1b** in the conventional resonance formalism (Fig. 1).

This assumption is confirmed by a NBO analysis of compounds **1a** and **1b**: The former structure is most certainly the principal resonance structure with 0.5718 non-Lewis electrons, but **1b** is only slightly inferior with 0.6953 non-Lewis electrons (for comparison, the corresponding values for vinylamine are respectively 0.3349 and 1.0819). As expected, NBO deletion procedure reveals a strong stabilizing interaction between the nitrogen p lone pair n_N and the antibonding π^*_{CS} orbital. The $n_N \rightarrow \pi^*_{CS}$ stabilization is calculated to be 75.8 kcal mol^{-1} (1 cal = 4.184 J). The structural consequence of this intramolecular charge transfer partially filling up to π^*_{CS} orbital, is a lengthening of the C=S bond and a shortening of the C–N bond. In addition, it is expected that the cycloadditions with **1** which is strongly stabilized by the $n_N \rightarrow \pi^*_{CS}$ interaction, will be less exothermic than the reactions with the non-stabilized methanethial.[10]

So, our goal was to reduce as far as possible the π donor property of the amino group by putting π acceptor groups in place of the methyl substituents in **1**, guided by the theoretical quantities mentioned. The results of the calculations for the hypothetic molecules **1–7** are presented in Table 1.

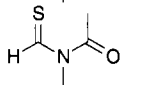
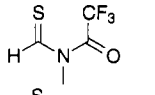
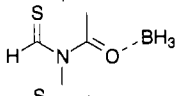
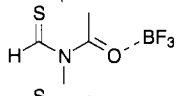
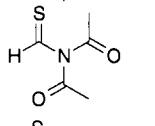
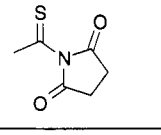


1a **1b**

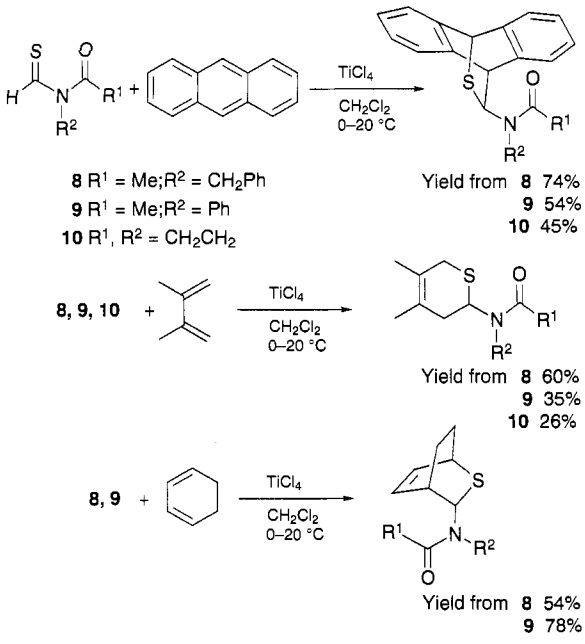
Fig. 1

Calculations shows that the substitution of NMe_2 for H lengthens the C–S bond by 0.056 Å, increases the excitation gap by 22.6 kcal mol^{-1} and raises the LUMO by 0.65 eV. The strong $n_N \rightarrow \pi^*_{CS}$ interaction certainly leads to a significant lowering of the exothermicity of the cycloaddition reaction.† Thus, all reactivity indexes clearly traduce the lower reactivity of **1** as compared to methanethial. As expected, the substitution of a methyl group by a π acceptor group, as in compound **2**, restores in part the electrophilic property of the C=S bond. However, two points deserve comments. The first concerns the diacetylated derivative **6**. The various calculated indexes predict a relatively poor reactivity of this compound in hetero-Diels–Alder reaction. The explanation could be the loss of conjugation resulting from a non-planar equilibrium structure. When the two carbonyl groups are maintained in the molecular plane, as in compound **7**, the effect of the two acceptor groups is almost additive. The second refers to the frontier orbital energies. It is well known that a π donor group such as dimethylamino raises the π_{CS} orbital to a larger extent than the π^*_{CS} one.[11] Effectively, changes of the substituent little affect the LUMO level (substitution of NMe_2 for H raises the π_{CS} level by 2.68 eV). However, BH_3 or BF_3 complexation rises relatively more substantially the LUMO of the thioformamide derivative.‡

Table 1

Compound	d_{CS} (d_{CN})/Å	$n_N \rightarrow \pi^*_{CS}{}^b$ [$\rho(\pi^*_{CS})$]^a	$\Delta E_{ST}{}^b$	E_{LUMO}/eV
	1.598	0 (0)	58.7	0.957
1 	1.654 (1.319)	−75.8 (0.3235)	81.3	1.607
2 	1.632 (1.350)	−50.5 (0.2256)	72.2	1.497
3 	1.623 (1.364)	−42.5 (0.1889)	69.6	1.193
4 	1.620 (1.365)	−41.4 (0.1860)		0.884
5 	1.617 (1.370)	−38.6 (0.1714)	67.2	0.618
6 	1.624 (1.366)	−39.3 (0.1745)	69.9	1.254
7 	1.608 (1.385)	−29.3 (0.1164)	63.8	1.158

^{a} Occupancy of π*. ^{b} In kcal mol^{-1}.



Scheme 1

The feasability of [4 + 2] cycloadditions with thioformamide moieties was then checked with the *N*-acyl thioformamides **8**, **9** and **10**, closely related to the parent compound **2**, and easily prepared§ from *O*-ethyl thioformate.[12] Compounds **8** and **9** were inert in the presence of anthracene at 150 °C for 4 h but reacted readily with various dienes in the presence of a Lewis acid (BCl_3, $TiCl_4$) in CH_2Cl_2 at temperatures above −20 °C. Some examples are shown in Scheme 1.¶

When cyclohexadiene was used, only one diastereoisomer was obtained.‖ These examples show that hetero-Diels–Alder reaction can be obtained from thioformamides. However, the need to use a Lewis acid is a severe drawback in the case of readily polymerisable dienes. Calculations indicate that such problems could be overcome by using trifluoroacetyl- or diacyl-derivatives analogous to **3** or **6**.[13]

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Footnotes

* E-mail: Yannick.Vallee@ujf-grenoble.fr

† We are currently performing a theoretical study of the Diels–Alder reactions of model deactivated thiocarbonyl compounds [HC(S)-X] with *cis*-butadiene. HF/6-31G* preliminary results effectively indicate a strong dependence of the energy of the cycloaddition to the π donor ability of the substituent X, *e.g.* X = H, −43.6 kcal mol^{-1}; X = NH_2, −18.0; X = NH(CHO), −26.3; X = NH(CHO)BH_3, −32.0; X = $N(CHO)_2$, −38.2. This latter compound possesses a C_s equilibrium geometry and perfectly mimics compound **7**.

‡ In these cases, the participation of the charge transfer configuration D ± (diene)-A-(dienophile) should be considered in addition to the D-A and ^{3}D*-^{3}A* configurations (^{3}A* signifies excitation of the dienophile to its π triplet state), in the Valence Bond mixing.

§ Compounds **8** and **9**: thioformylation of benzylamine or aniline with *O*-ethyl thioformate according to ref. 12, then excess acetic anhydride, neat, 100 °C, 1 h. **10**: *N*-trimethylsilyl-pyrollidinone, ethyl thioformate, 10% TMSOTf, neat, 70 °C, 4 h.

¶ Typical procedure: To a solution of **9** (2.5 mmol, 446 mg) and 1,3-cyclohexadiene (4 mmol, 380 μl) in 1 ml of dry CH_2Cl_2 was added at 0 °C. $TiCl_4$ (2.5 mmol, 1 mol dm^{-3} solution in CH_2Cl_2). After 1 h at room temperature, hydrolysis with a few drops of a saturated Na_2CO_3 solution, followed by chromatography (Silica Gel, pentane–ethyl acetate, 70:30), yielded 489 mg (76%) of adduct. ^{1}H NMR: (300 MHz, $CDCl_3$, 25 °C, TMS): δ 1.25–1.60 (m, 2 H), 1.70 (s, 3 H), 1.70–2.15 (m, 2 H), 3.05–3.15 (m, 1 H), 3.30–3.40 (m, 1 H), 4.91 (dd, 1 H, *J* = 7.5 Hz), 6.06 (dd, 1 H, *J* = 7.5 Hz), 6.43 (s, 1 H), 7.20–7.50 (m, 5 H). ^{13}C NMR: δ 22.54, 23.71, 28.15, 34.02, 63.08, 77.50, 127.80, 128.57, 129.16, 131.07, 132.67, 138.78 and 169.94. IR (film)/ν 1660 cm^{-1}.

‖ ^{1}H NMR evidence (250 MHz, C_6D_6, 50 °C).

References

1 G. W. Kirby, *Phosphorus Sulfur*, 1993, **74**, 17; E. Vedejs, T. H. Eberlein, D. J. Mazur, C. K. McClure, D. A. Perry, R. Ruggeri, E. Schwartz, J. S. Stults, D. L. Varie, R. G. Wilde and S. Wittenberger, *J. Org. Chem.*, 1986, **51**, 1556; C. M. Bladon, I. E. G. Ferguson, G. W. Kirby, A. W. Lochead and D. C. McDougall, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1541.

2 P. Beslin and P. Metzner, *Tetrahedron Lett.*, 1980, **21**, 4657; P. Herczegh, M. Szély and R. Bognar, *Tetrahedron Lett.*, 1986, **27**, 1509.

3 Inverse electronic demand Diels–Alder reactions have been reported with $HC(S)NMe_2$: G. Seitz, R. Mohr, W. Overheu, R. Allmann and M. Nagel, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 890; A. Padwa, B. Harrison, S. S. Murphree and P. E. Yeske, *J. Org. Chem.*, 1989, **54**, 4233. Other papers dealing with Diels–Alder reaction of electron-deficient thioamides have appeared: J. D. Friedrich, *J. Org. Chem.*, 1987, **52**, 2442; Y. Tamaru, H. Sakata, M. Kimura, H. Harayama, H. Konishi, K. Fugami and S. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1994, 2365. See also I. T. Barnish, C. W. G. Fishwick and D. R. Hill, *Tetrahedron Lett.*, 1991, **32**, 405.

4 R. Sustmann, *Tetrahedron Lett.*, 1971, **12**, 2717; R. Sustmann and W. Sicking, *Chem. Ber.*, 1987, **120**, 1323.

5 A. Pross and S. S. Shaik, *J. Am. Chem. Soc.*, 1981, **103**, 3702; S. S. Shaik and A. Pross, *J. Am. Chem. Soc.*, 1982, **104**, 2708.

6 A. Ioffe and S. S. Shaik, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2101.

7 Geometry optimisations were carried out at the HF/6-31 + G(d,p) level of theory, using the GAUSSIAN 92 systems of program: M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Reploge, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, *GAUSSIAN 92*, revision A, Gaussian Inc., Pittsburg, 1992. Diffuse functions were included in order to treat the lone pair properly: T. Clark, J. Chandrasekhar, G. W. Spitznagel and P. V. R. Schleyer, *J. Comput. Chem.*, 1983, **4**, 294.

8 NBO analyses were performed with the program NBO Version 3.1: E. D. Glendening, A. E. Reed, J. E. Carpenter and F. Weinhold. Quantitative analyses of hyperconjugation interactions between NBOs were obtained using the NBO Fock matrix deletion procedure: L. A. Curtiss, D. J. Pochatko, A. E. Read and F. Weinhold, *J. Phys. Chem.*, 1983, **82**, 2679. The ππ* S → T vertical excitation energies were computed using the Cl-Singles (CIS) method. This method, which is not always highly quantitatively predictive, is sufficient for our purpose insofar as relative excitation energies are researched: J. B. Foresman, M. Head-Gordon, J. A. Pople and M. J. Frisch, *J. Phys. Chem.*, 1992, **96**, 135.

9 The same is true for $HCSNH_2$: M. C. Ou and S. Y. Chu, *J. Phys. Chem.*, 1995, **99**, 556; K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1995, **117**, 2201. Interestingly, in the case of vinylamine the planar structure has been characterized as a transition structure for nitrogen inversion: K. Lammersta and B. V. Prasad, *J. Am. Chem. Soc.*, 1994, **116**, 642.

10 Diels–Alder reactions are exothermic processes; for recent calculations see: M. A. McCarrick, Y. D. Wu and K. N. Houk, *J. Org. Chem.*, 1993, **58**, 3330.

11 G. Pfister-Guillouzo, A. Senio, F. Gracian, M. Khalid, J.-L. Ripoll and Y. Vallée, *New J. Chem.*, 1995, in the press.

12 J. C. Stowell, B. M. Ham, M. A. Esslinger and A. J. Duplantier, *J. Org. Chem.*, 1989, **54**, 1212.

13 Activation of cyanothioformamides by *N*-acylation has been already pointed out: K. Friedrich and M. Zamkanei, *Tetrahedron Lett.*, 1977, **18**, 2139; K. Friedrich and M. Zankanei, *Chem. Ber.*, 1979, **112**, 1867.