

Structural Conformers of (1,3-Dithiol-2-ylidene)ethanethioamides: The Balance Between Thioamide Rotation and Preservation of Classical Sulfur-Sulfur Hypervalent Bonds

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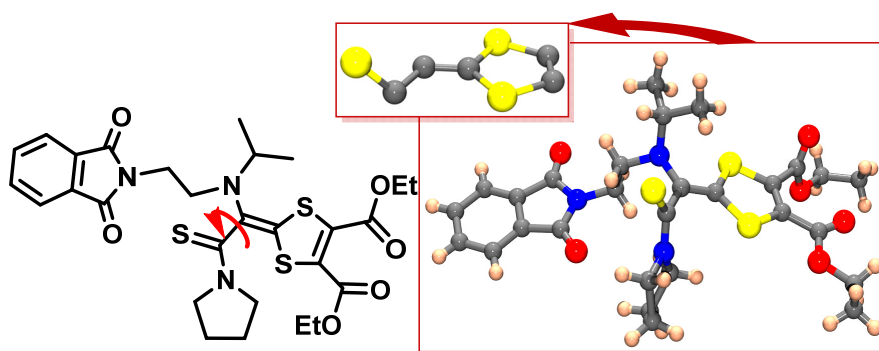
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34 **ABSTRACT:** The reaction of *N*-(2-phthalimidoethyl)-*N*-alkylisopropylamines and S₂Cl₂ gave 4-
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36 *N*-(2-phthalimidoethyl)-*N*-alkylamino-5-chloro-1,2-dithiol-3-thiones that quantitatively
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38 cycloadded to dimethyl or diethyl acetylenedicarboxylate to give stable thioacid chlorides, which
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40 in turn reacted with one equivalent of aniline or a thiole to give thioanilides or a dithioester.
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42 Several compounds of this series showed atropisomers that were studied by a combination of
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44 dynamic NMR, simulation of the signals, conformational analysis by DFT methods, and single
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46 crystal X-ray diffraction, showing a good correlation between the theoretical calculations, the
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48 experimental values of energies and the preferred conformations in the solid state. The steric
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50 hindering of the crowded substitution at the central amine group was found to be the reason of the
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52 presence of permanent atropisomers in this series of compounds, and the cause of a unique
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54 disposition of the thioxo group at close-to-right angles with respect to the plane defined by the 1,3-
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6 dithiole ring in the dithiafulvene derivatives, thus breaking the sulfur-sulfur hypervalent bond that
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8 is always found in this kind of compounds.
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10 11 12 13 **INTRODUCTION:**

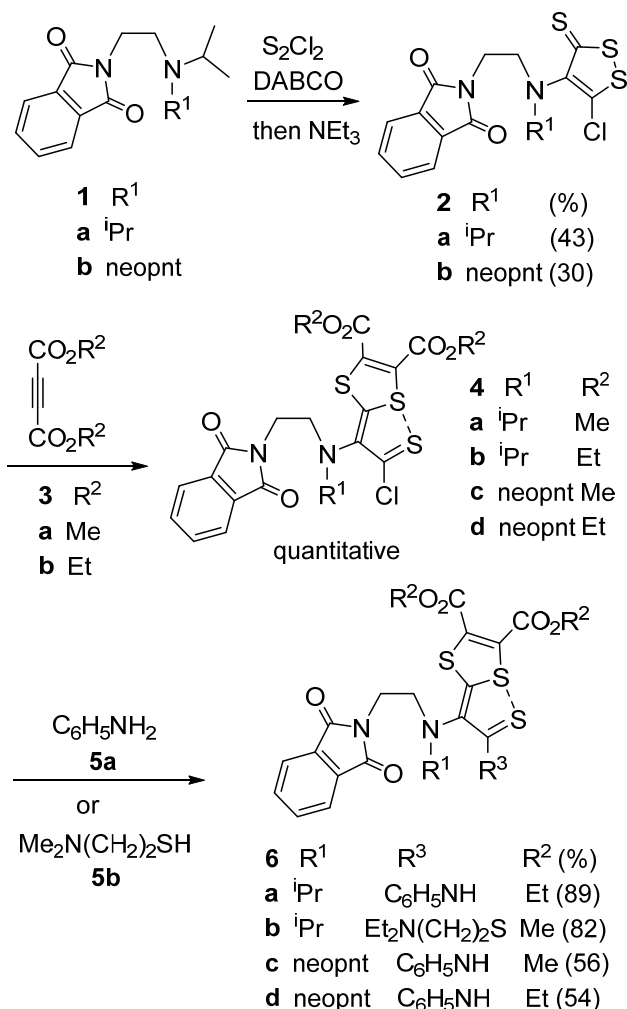
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15 3*H*-1,2-Dithiole-3-thione and its derivatives (dithiolethiones)¹ have been the subject of intense
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17 research due to their physiological effects as potent cancer-preventive and anticancer agents,
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19 because they are inducers of cytoprotective phase 2 enzymes,² and are currently used as
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21 hepatoprotective agents in clinical trials.³ Most recently they have been studied as hydrogen
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23 sulfide-releasing drugs with high therapeutic potential in the H₂S signaling system for relevant
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25 research areas such as cardiovascular and gastrointestinal systems, immunology and cancer
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27 biology,⁴ and in the control of oxidative posttranslational cysteine modifications with medical
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29 applications.⁵ Instead the 1,3-dithiol-2-ylidene derivatives (dithiafulvenes)⁶ are important donor
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31 units in electronic materials and molecular devices such as organic superconductors,⁷ push-pull
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33 chromophores,⁸ switchable organic materials,⁹ and receptors.¹⁰ Apart from classical methods¹¹ for
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35 the preparation of 1,3-dithiole derivatives, the 1,3-dipolar cycloadditions of 1,2-dithiole-3-thiones
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37 and activated triple bonds permits multiple cycloadditions in one pot, therefore giving rise to
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39 complex derivatives by very short reaction pathways.¹² With the aim to prepare new derivatives for
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41 anticancer screening schemes,¹³ we revisited an old reaction that was useful for that purpose. As in
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43 the previous case, some starting materials and some reaction products obtained from the reported
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45 sequence showed an intriguing dynamical behavior by either ¹H or ¹³C NMR that, despite the
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47 increasing complexity, could be studied by a combination of experimental and computational
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49 methods. Dynamic NMR studies are common tools for the elucidation of inversion-rotation
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51 barriers in stereodynamics of hindered heterocyclic systems,¹⁴ rotation barriers in *ortho*-
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53 disubstituted biaryls¹⁵ and molecular rotors.¹⁶ Studies involving polysulfur heterocyclic
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6 compounds are much more scarce,¹⁷ therefore new findings in this field are of great interest. In this
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8 paper we now report the synthesis and the dynamic NMR study of some new 1,4-dithiafulvene 2-
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10 (*N,N*-dialkylamino)thioacetanilides and their starting materials, supported by DFT calculations and
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12 X-ray diffraction analysis of structures of key compounds.
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18 RESULTS AND DISCUSSION:

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20 The synthesis of the new compounds **6a-d** was accomplished in two steps from amines **1a-b** by the
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22 selective sulfuration of a tertiary isopropylamine group.^{6,12a,13} The mechanism of the
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24 transformation of **1a-b** to **2a-b** is complicated and involve several steps explained in earlier
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26 publications.¹⁸ This process was performed by the reaction of S₂Cl₂ (5 equiv) with *N*-(2-
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28 phthalimidoethyl)-*N*-alkylisopropylamines [alkyl = isopropyl, 2,2-dimethylpropyl (neopentyl)] **1a-**
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30 **b** (1 equiv) in the presence of DABCO (4 equiv) in CHCl₃ at room temperature for 3 days,
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32 followed by reaction of the mixture with triethylamine (6.5 equiv) for additional two hours at room
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34 temperature, all in a one-pot process. Reaction work-up and column chromatography of the residue
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36 gave **2a** (45%) or **2b** (30%). Cycloaddition of **2a-b** with dimethyl or diethyl
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38 acetylenedicarboxylate (**3a-b**, 1 equiv) quantitatively afforded the thioacid chlorides **4a-d** as red
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40 solids, which were sufficiently stable to be characterized by spectroscopy. Thioacid chlorides **4a-d**
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42 reacted with one equivalent of aniline **5a** or 2-(*N,N*-dimethylamino)ethylmercaptane **5b** to give
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44 products **6a-d** (54-89%). Isolation of **4a-d** was not necessary for the preparation of products **6a-d**
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46 which, in fact, were obtained in one-pot reactions from **2a-b** by the sequential addition of reagents
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48 at room temperature (Scheme 1). The obtained compounds were fully characterized by
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50 spectroscopy and gave satisfactory microanalyses (see Experimental Section and Supporting
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52 Information).
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Scheme 1. New (1,3-dithiol-2-ylidene)ethanethioamides and dithioesters



From the large collection of compounds that could be obtained by this series of reactions, the selected compounds **6a-d** were ideally suited for the study of their dynamic NMR behavior as new molecular atropisomeric probes because all of them showed diastereomeric preferred conformations, studied by dynamic NMR, of the isopropyl or neopentyl signals. In this way, compounds **6a-b** showed diastereomeric preferred conformations of the isopropyl signals in dynamic NMR. The ¹H NMR spectrum of **6a** showed a broad signal at δ 1.1 in deuterated chloroform at room temperature, corresponding to slowly interchanging methyl groups of the

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6 isopropyl group. The signal was resolved in a doublet of equivalent methyl groups at 80 °C and in
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8 two doublets at -20°C. The signals partially superposed to the methyl signals from the ethoxy
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10 groups. Instead, the ^{13}C NMR showed a broad pair of signals by δ 21 and 23 at room temperature
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12 that was resolved into one signal at 45°C and into two neat signals at -10 °C (Figure 1). Simulation
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14 of the signals with gNMR5.0.4.0¹⁹ gave interchange constants $k(\text{s}^{-1})$ that were plotted as $\log k/T$
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16 versus $1/T$, giving a first order kinetics from which the free energy of transition was calculated to
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18 be $\Delta G^\ddagger = 14.85 \pm 1.49 \text{ kcal mol}^{-1}$. The same value, $14.85 \text{ kcal mol}^{-1}$, was obtained from the Eyring
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20 equation at the coalescence temperature $T_c = 312 \text{ K}$ (Figure 1). Analogously, the ^1H NMR
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22 spectrum of **6b** showed two broad signals at δ 1.1 and 1.4 in deuterated chlorobenzene at room
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24 temperature, corresponding to slowly interchanging methyl groups of the isopropyl group. Its ^{13}C
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26 NMR showed a pair of signals at δ 20 and 23 at room temperature that was resolved into one broad
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28 signal at 90°C (Figure 1). Simulation of the signals with gNMR5.0.4.0¹⁹ gave interchange
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30 constants $k(\text{s}^{-1})$ that were plotted as $\log k/T$ versus $1/T$, giving a first order kinetics from which the
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32 free energy of transition was calculated to be $\Delta G^\ddagger = 16.45 \pm 0.12 \text{ kcal mol}^{-1}$. A similar value, 16.42
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34 kcal mol^{-1} , was obtained from the Eyring equation at the coalescence temperature $T_c = 343 \text{ K}$
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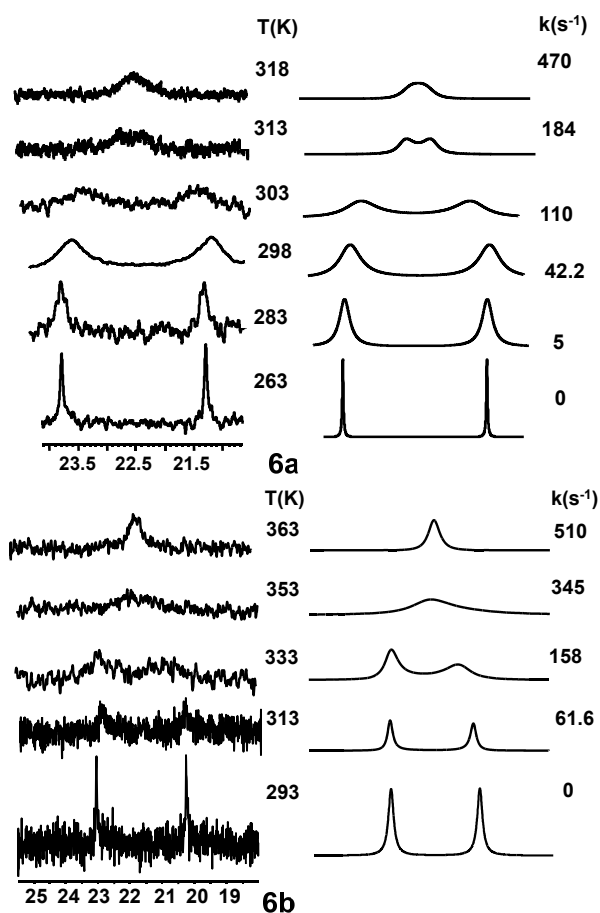


Figure 1. Dynamic ^{13}C NMR signals, simulation of the signals and interchange constants $k(\text{s}^{-1})$ of

6a-b

Compounds **6c-d** showed diastereomeric preferred conformations studied by dynamic NMR of the neopentyl signals. The ^1H NMR spectrum of **6c** showed a broad pair of doublets at δ 2.8 and 3.1 in deuterated chlorobenzene at room temperature, corresponding to slowly interchanging methylene protons of the neopentyl group. The signal was resolved in one singlet of equivalent methylene protons at 80 °C and in two doublets at -30°C . Figure 2 shows the dynamic behaviour of the methylene protons of **6c** in ^1H NMR (left) and simulation of the signals (right) with gNMR5.0.4.0.¹⁹ From these simulations the interchange constants $k(\text{s}^{-1})$ were obtained and plotted

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6 as log k/T versus $1/T$, giving a first order kinetics from which the free energy of transition was
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8 calculated to be $\Delta G^\ddagger = 15.39 \pm 0.99$ kcal mol⁻¹. A similar value, 15.48 kcal mol⁻¹, was obtained
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10 from the Eyring equation at the coalescence temperature $T_c = 323$ K. Similarly, the ¹H NMR
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12 spectrum of **6d** showed a pair of doublets at δ 2.8 and 3.1 in deuterated chlorobenzene at room
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14 temperature, corresponding to slowly interchanging methylene protons of the neopentyl group,
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16 which was resolved in one singlet of equivalent methylene protons at 90 °C. Figure 2 shows the
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18 dynamic behaviour of the methylene protons of **6d** in ¹H NMR (left) and simulation of the signals
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20 (right) with gNMR5.0.4.0.¹⁹ From these simulations the interchange constants $k(s^{-1})$ were obtained
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22 and plotted as log k/T versus $1/T$, giving a first order kinetics from which the free energy of
23
24 transition was calculated to be $\Delta G^\ddagger = 15.21 \pm 0.66$ kcal mol⁻¹. A similar value, 15.18 kcal mol⁻¹,
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26 was obtained from the Eyring equation at the coalescence temperature $T_c = 323$ K. In all cases,
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28 these values of energy were ascribed to slow inversion-rotation processes that placed the isopropyl
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30 or neopentyl groups in diastereotopic environments.
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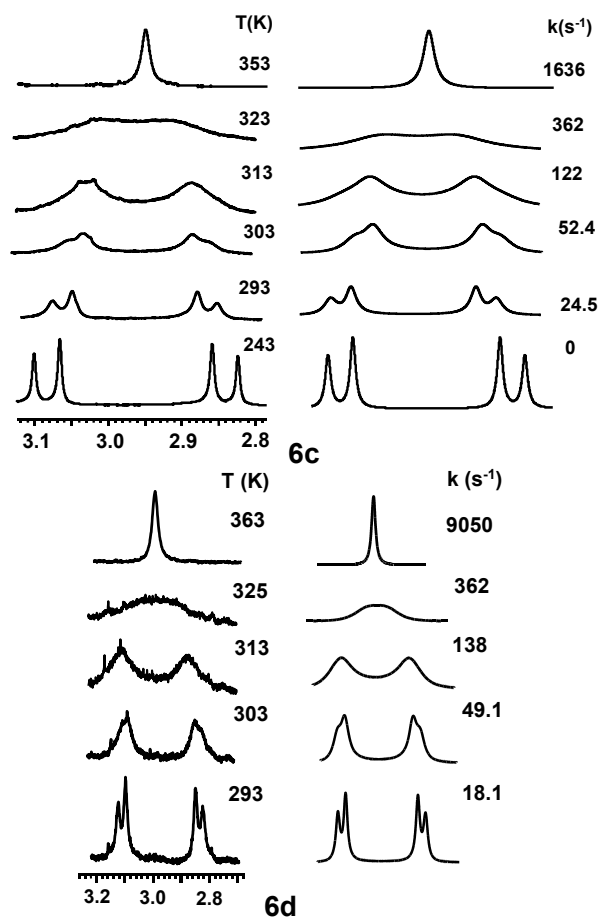


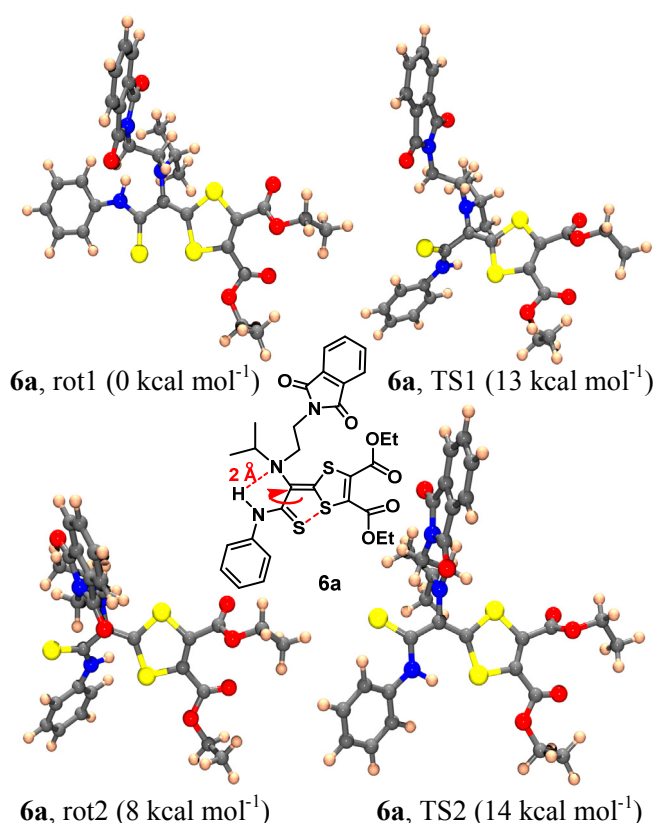
Figure 2. Dynamic ^1H NMR signals, simulation of the signals and interchange constants $k(\text{s}^{-1})$ of

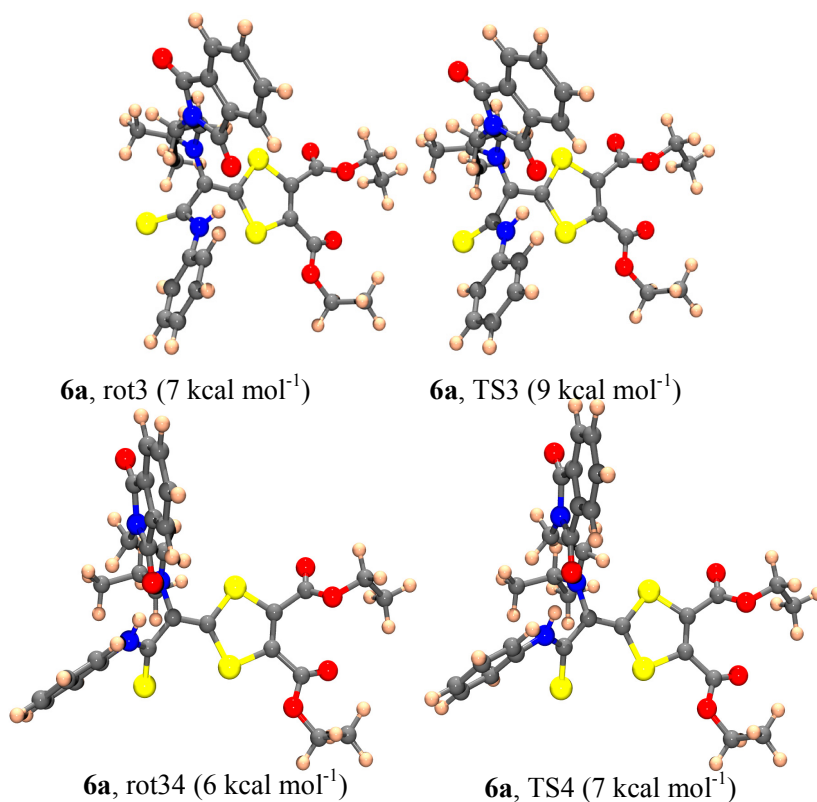
6c-d

The dynamic behavior observed for compound **6a** has been studied by using DFT methods, as a model for all the series. The observed dynamic behavior in solution could be explained by rotations of the groups bonded to the central amine nitrogen atom such as the isopropyl group. In compound **6a**, the observed experimental dynamic process has a barrier of $14.85 \text{ kcal}\cdot\text{mol}^{-1}$. In the theoretical study of the rotation of the isopropyl group we have found several stationary points corresponding to five minima and five transition states connecting the minima. The calculated difference of energy between the global minimum and the highest transition state in gas phase is

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6 5.13 kcal·mol⁻¹, or 4.00 kcal·mol⁻¹ taking into account solvation effects. This value is far from the
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8 14.85 kcal·mol⁻¹ found experimentally indicating that an alternative dynamic process must be
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10 occurring simultaneously. The theoretical study of the rotation of the thiocarboxamide fragment
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12 affords four minima along with four transition states between them (Figure 3). In this second
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14 process the biggest difference in energy between the global minimum and the highest transition
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16 state in gas phase is 13.92 kcal·mol⁻¹, which is in good agreement with the experimental value. The
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18 free energy value obtained taking into account solvation effects is 12.20 kcal·mol⁻¹, which is in
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20 also good agreement with the experimental value. The absolute minimum found in the
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22 optimization of the model **6a** displays a torsional angle between the axes of the bonds C-S (see
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24 Figure 3) of 0 degrees, which is consistent with a planar geometry in the fragment involving these
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26 C-S bonds. This planar configuration is in good agreement with all the structures found on CSD²⁰
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28 with the same fragment, although in none of them the C=S bond was part of a thioamide group.
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30 This absolute minimum **6a** displays a distance of 1.999 Å between the hydrogen atom of the
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32 thioamide group and the amine nitrogen atom. This distance is in the range of the hydrogen bond
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34 interactions and it can be classified as a moderate-weak hydrogen bond.²¹ We noticed that in all
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36 structures, except rot1 and TS1, the addition of the angles around the amine nitrogen atom is very
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38 near to 360, indicating a flat geometry in this atom. The pyramidalization observed in the rotamer
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40 rot1 can be understood by considering the intramolecular hydrogen bond that appears to be the
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42 only reason of the difference with the other rotamers. The flat geometry observed in the other
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44 structures could be reasonable considering the big size of the substituents bonded to the nitrogen
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46 atom. The angles around the anime nitrogen atom found in the calculated structures of the rotation
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48 of the thiocarboxamide fragment in the compound **6a** are summarized in page S71 of the
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50 Supporting Information. A study of the difference on energies between the ground state, rot1, and
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52 the highest transition state in **6a**, TS2, when this difference has been calculated at different
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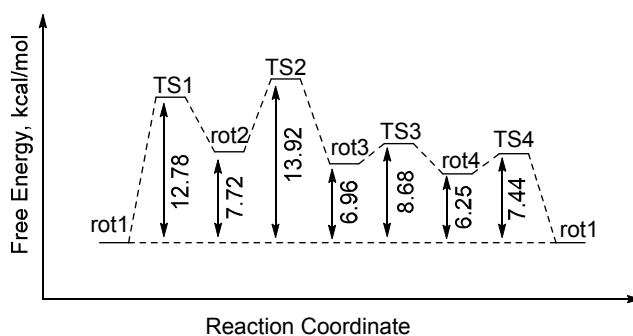
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6 temperatures, has been performed. The calculations show that there is not a big change when the
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8 temperature rises from 263 K to 318 K. The differences of free energies between rot1 and TS2
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10 with the temperature are shown in pages S71-S72 of the Supporting Information. Calculations
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12 were performed in the gas phase at the B3LYP/6-31G(d) level of theory and in solution (PCM,
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14 solvent = chloroform) at the B3LYP/6-311G(2d,p) level of theory. Both, gas phase and solvation
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16 calculations are in good agreement with the experimental results. Although the observed trend is
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18 correct, the calculations taking into account solvation effects with a polarizable continuum model
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20 correct, the calculations taking into account solvation effects with a polarizable continuum model
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22 (PCM) yielded a slight deviation from the experimental values (about 2.6 kcal/mol) (See the
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24 Supporting Infrmation).
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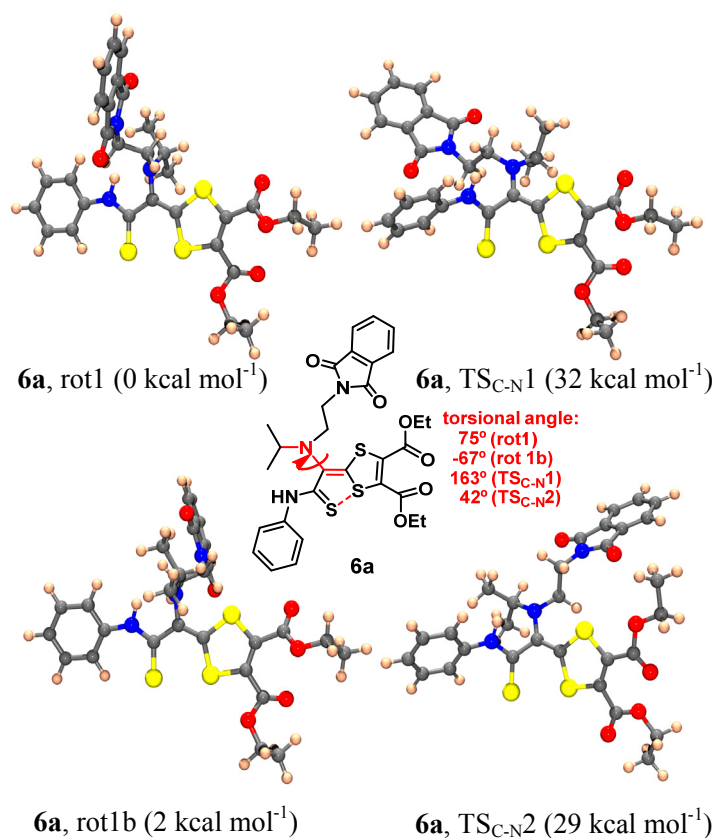
Figure 3. All stationary points found in the process of rotation of the thiocarboxamide fragment in **6a** (full information available in the Supporting Information). Inset: Structure **6a** showing in red the bond rotated and the S-S hypervalent bonding interaction



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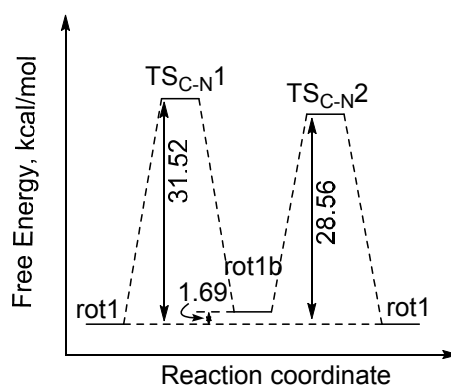
Figure 4. A chart of energies for the four minima and the four transition states of the rotation of the thiocarboxamide fragment in **6a**

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6 An additional rotation can be proposed in which the rotation should involve the N-C bond
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8 connecting the amine nitrogen with the carbon atom that links the thiocarbamide and dithiafulvene
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10 fragments. DFT calculations located two minima in this process, both of them of similar energy
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12 (separated only for 1.69 kcal·mol⁻¹), being the most stable the previously calculated conformer
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14 rot1. In both conformers the calculated torsional angle C(ⁱPr)-N-C-C(dithiafulvalene) is 74.84° and
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16 -67.14°. Two possible transition states connecting these two minima were found. In these two
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18 transition states the values for the similar torsional angle were 162.66° and 41.96°. The
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20 optimization of the geometries of these two transition states was performed by restricting the
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22 relative orientation of the C-S bonds corresponding to the thiocarboxamide and the dithiafulvalene
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24 moieties. The relative orientation was fixed by keeping the same orientation found in rot1. All
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26 attempts to find the transition states without this restriction afforded rotation of the C-C bond of
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28 the thiocarboxamide fragment. Every transition state displayed an imaginary frequency, in good
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30 agreement with the rotation of the N-C bond, but in both cases the IRC calculations tended to
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32 additional rotations of the C-C bond of the thiocarboxamide fragment. The minimum calculated
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34 free energy for the conversion between the rotamers rot1 and rot1b was 28.56 kcal·mol⁻¹ (gas
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36 phase), which was almost twice the calculated value for the rotation of the thiocarboxamide
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38 fragment and the experimental value found from the dynamic behavior by NMR. Therefore that
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40 rotation can't explain the dynamic behavior of **6a**, confirming rotation of the thiocarboxamide
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42 fragment in **6a** as the most plausible explanation for the experimental results.
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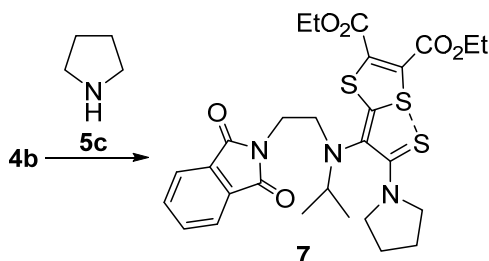
Figure 5. All stationary points found in the process of rotation of the N-C bond connecting the amine nitrogen with the dithiafulvene carbon in **6a** (full information available in the Supporting Information). Inset: Structure **6a** showing in red the bond rotated and the S-S hypervalent bonding interaction



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6 **Figure 6.** A chart of energies for the two minima and the two transition states of the rotation of the
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8 amine fragment in **6a**
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12 In order to compare the stereodynamic behavior observed for **6a-d** with structural features of
13 similar compounds we tried for several times to crystallize related compounds to **6a-d** that could
14 afford clues about the feasibility of the rotation of the thioamide bond. After several trials we got
15 crystals suitable for X-ray diffraction of a related compound **7**, prepared¹³ by reaction of **4b** and
16 pyrrolidine **5c** (Scheme 2). Compound **7** did not showed diastereomeric preferred conformations of
17 the isopropyl signals when studied by dynamic NMR at low temperature so we could only
18 compare experimental results from NMR dynamic behavior and the solid state structure.
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32 **Scheme 2.** Synthesis of a pyrrolidiny thioamide derivative **7** for X-ray diffraction.
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The X-ray diffraction structure of compound **7** showed three different structural conformations of the same molecule in the crystal, showing also molecular disorder in the peripheral ethyl ester groups. Figure 7 shows the three crystallographic independent molecules as they were obtained as part of the same unit cell by single crystal X-ray diffraction structure of compound **7**.

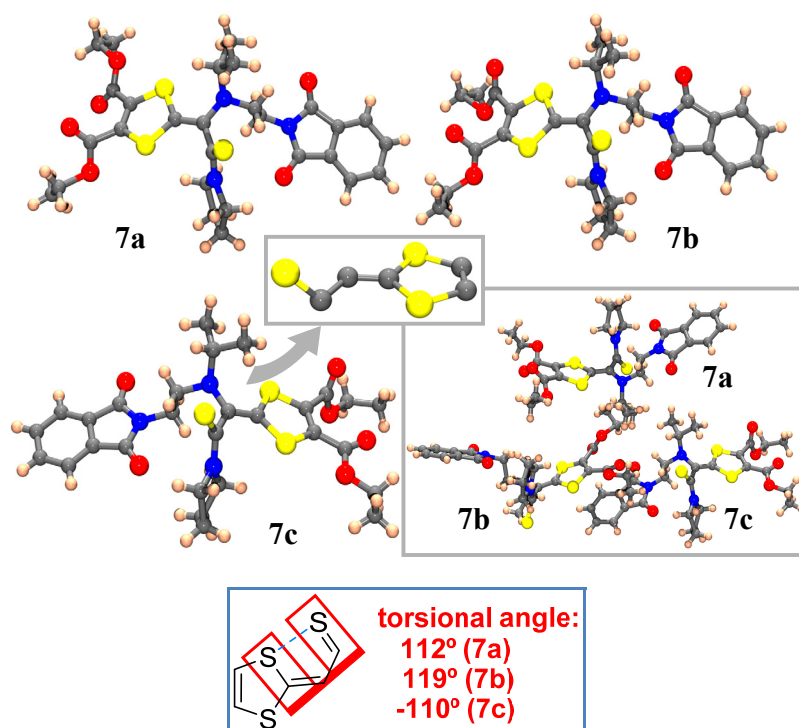


Figure 7. The three crystallographic independent molecules obtained as part of the same unit cell from the single crystal X-ray diffraction structure of **7** and their disposition in the unit cell (red box). Central inset: the 1,3-dithiolanethiocarbonyl group in the closest conformer **7a** from the single crystal X-ray diffraction structure. Bottom inset: Torsional angle used as reference S-C-C-S for structural discussions

Remarkably, the atomic orientation found in compound **7** is different of the expected for this kind of compounds. The axis of both C=S and C-S bonds lie in different planes for every one of the three structures of the asymmetric unit. In the three crystallographic independent molecules the torsional angles between the 1,3-dithiole group and the thiocarboxamide group were 111.90(5)°, 119.4(4)° and -109.5(5)°. These values of the angles are a consequence of a rotation around the single bond C-C contained on the path connecting the C=S and C-S bonds, as displayed in the inset of Figure 5, for all the conformers of structure **7**. This C-C bond in all conformers of structure **7** is

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6 long, with values ranging between 1.489(7) Å and 1.512(8) Å, and these values are only exceeded
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8 for one reported compound (1.52(1) Å and 1.54(1) Å)²² having similar structural fragments as the
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10 ones shown in Scheme 2 (inset). The exocyclic double bond C=C in compound **7** is the shortest
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12 bond found for compounds with this structural fragment, and the C=S bond values are in the
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14 average of the experimentally observed in CSD. The structure **7** shown in Figure 8 constitutes the
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16 first reported example of a solid state structure in which the expected S··S hypervalent bonding
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18 interaction has been broken. The S··S hypervalent bond²³ lies at the foundations of the polysulfur
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20 heterocyclic chemistry. Hypervalent S··S/S··O/S··N interactions are usually important structural
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22 features to understand the structure and properties of heterocyclic systems.²⁴ Such hypervalent
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24 nonbonded S··X interactions usually control the molecular structure and chemical reactivity of
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26 organic molecules, as well as their assembly and packing in the solid state.²⁵ In our case,
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28 compounds **6a-d** showed a very weak S··S interaction, as seen from the calculations of compound
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30 **6a**, that allowed the presence of rotamers in all the series of compounds **6a-d**. On the other hand,
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32 compound **7** showed no S··S hypervalent interaction in the structure obtained in the solid state. In
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34 that case, the structures of the non-planar (starting from the experimental values) and planar
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36 models of **7** have been calculated through DFT calculations. From the calculated structures we
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38 have found that the non-planar structure (similar to one of the rotamers found in the solid state) is
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40 7.9 kcal·mol⁻¹ more stable than the planar one, which is in good agreement with the structures
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42 found in the solid state (Figure 6).
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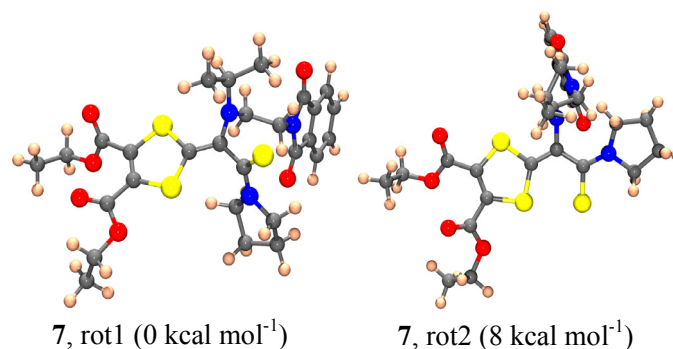


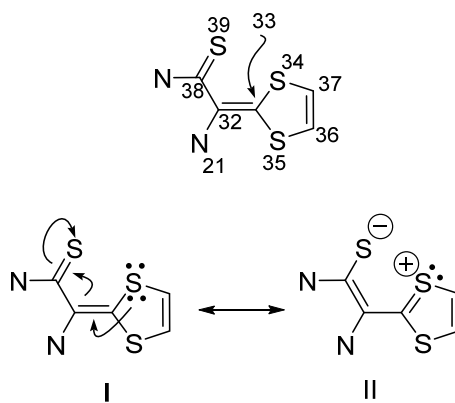
Figure 8. DFT calculated structures of the X-ray diffraction structure **7** and a planar model in which the hypervalent sulfur-sulfur interaction is conserved

In the three experimental structures **7a-c** the nitrogen atom displays a pyramidal geometry. Nevertheless, in the most stable theoretically calculated structure **7**, rot1, showing a very similar arrangement for the sulfur atoms of the dithiafulvalene and the thioamide groups, the amine nitrogen atom displays an almost planar geometry. As in the case of compound **6a**, this flat geometry can be well understood in terms of steric hindrance of the substituents bonded to the nitrogen atom for the calculated geometry of the isolated molecule (gas phase). The pyramidal geometry found in the experimental structure could be due to packing interactions in the solid state that are not present in the gas phase. The values of the angles surrounding the amine nitrogen atom along with the same values found in the two theoretically calculated rotamers for compound **7** are displayed in page S107 of the Supporting Information. Therefore, for compounds **6a** and **7** the big steric hindrance of the substituents of the amine nitrogen favors the planar geometry of the amine. Nevertheless, the pyramidal geometry has to be very easily accessible (low energy process) with the help of an intramolecular hydrogen bond (**6a**) or packing reticular interactions (**7**). This low energy process does not affect to the overall energy of the hypervalent sulfur-sulfur interaction. The only structural difference between **6a-d** and **7** is the presence of a more rigid tertiary thioamide in **7** and a more flexible thioanilide or dithioester in **6a-d**. The thioanilide group favors

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6 the presence of a hydrogen bond between the hydrogen atom of the thioamide and the amine
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8 nitrogen atom, which contributes to the stability of the S-S bonding interaction. The absence of an
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10 N-H amide hydrogen in compound **7** avoids this hydrogen interaction. Although no related
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12 thioamides were found at the CSD database, all found (1,3-dithiol-2-
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14 ylidene)ethanethiocarbonyl,^{12d, 26} carbonyl,²⁷ or imine derivatives²⁸ were always planar, despite a
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16 high steric hindering of the groups.^{27g-i} Therefore a combination of steric hindering of the crowded
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18 substitution at the central amine group, as well as electronic effects from the push-pull electronic
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20 delocalization, in addition of the conjugation due to the thioamide group and the presence of a
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22 hydrogen bond, seem to be the cause of the weak or absent S...S hypervalent interaction. Such
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24 structural motif can be of interest for pharmacological as well as materials design, therefore a
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26 closer inspection of the electronic structure by using the Natural Bond Orbital population approach
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28 (NBO) analyses for the models **6a_rot1** and **7_rot2** (the most stable conformer of **6a** and planar
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30 conformer of **7** respectively) were performed for the evaluation of the electronic delocalization.
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32 For conformer **6a_rot1**, these calculations clearly indicated the presence of two lone pair orbitals
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34 formally attached at the thiocarboxylic sulfur atom and to the dithiafulvene sulfur atoms. The
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36 nature of one of these orbitals on each sulfur atom is a pure *p*-type [*l*_p(S)], having the orbitals of
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38 the sulfur atoms of the dithiafulvene a low electron occupancy of 1.65 and 1.68 e, indicating the
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40 electron-donating capacity for this orbital. Delocalizing interactions evaluated by a second-order
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42 perturbation approach revealed that the lone pair orbital located at the dithiafulvene sulfur atoms
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44 contributed to a resonance interaction with double bond C(32) = C(33) (see scheme 3 for
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46 numbering) *l*_p(S) → π*(C-C). The computed E⁽²⁾ interaction value was 26.1 and 23.3 kcal/mol for
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48 sulfur atoms S(34) and S(35) respectively. Interestingly, in the analysis of more delocalizing
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50 interactions it was possible to find a second delocalization of pair of electrons located at the
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52 bonding orbital π(C-C) involving atoms C(32) and C(33) with the double bond C(38) = S(39),
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 6 $\pi(\text{C-C}) \rightarrow \pi^*(\text{C-S})$. In this second delocalization the computed $E^{(2)}$ interaction value was 19.0
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 8 kcal/mol. The combination of these two delocalization events was in good agreement with the
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 10 resonance structures I and II shown in scheme 3 and both structures accounted for the planar
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 12 geometry found in this structure. In addition, the atomic charges obtained by using the natural
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 14 population analysis (NPA) approach revealed a positive charge +0.34 located at the sulfur atom
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 16 S(34) and a negative charge -0.15 located at the tioamide sulfur atom S(39), in good agreement
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 18 with the resonance structure II of scheme 3. These opposite charges reinforced the hypervalent
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 20 interaction through electrostatic attraction. Interestingly, for conformer **7_rot2** none of these
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 22 delocalizing interactions could be found, leaving the bond C(32)-C(38) as a single bond with
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 24 freedom of rotation to adopt the geometry experimentally found.
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32 **Scheme 3.** Labeling of the atoms used for the NBO analyses for the models **6a_rot1** and **7_rot2**
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To validate the suitability of our DFT calculations, we applied the same methodology to the dynamic behaviour of previously studied compound **2a**, whose dynamic behavior was already studied using a semiempirical level of theory,¹³ and the similar compound **2b** by the same type of calculations using DFT methods. As we previously noticed, the observed dynamic behavior for **2a** in solution could be explained by a rotation around the C-N bond connecting the amine nitrogen atom with the 1,2-dithiol group. In this rotation we have now found several stationary points

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6 corresponding to four minima and four transition states connecting them (see Supporting
7 Information). The calculated difference of energy between the global minimum and the highest
8 transition state was 14.5 kcal mol⁻¹, which was in good agreement with the experimentally
9 calculated value. We also checked the accuracy of our DFT calculations by comparing the
10 minimum obtained for **2a** and the single crystal X-ray diffraction structure obtained for **2a**. Indeed,
11 in both cases the structures were practically superimposable. A similar study developed for
12 compound **2b** afforded close related results, but in this case the higher steric hindrance of the
13 neopentyl fragment hampered a simple explanation of the dynamic behavior observed. For this
14 compound three different dynamic processes have been calculated and all of them are rotations
15 around the three C-N bonds of the amine nitrogen atom. For the rotation around the C-N bond
16 connecting the amine nitrogen atom with the 1,2-dithiol group only one transition state was
17 localized. This transition state connected two rotamers arising from the rotation of the dithiole
18 heterocycle. The energy of the barrier found for this rotation was 11.77 kcal·mol⁻¹. This value was
19 no so far from the experimental value for the dynamic behavior observed on this compound (14.52
20 kcal·mol⁻¹) (Supporting Information, page 4), but it was not so precise, indicating that other
21 dynamic behavior can be occurring simultaneously. This other dynamic behavior could be the
22 rotation of the neopentyl fragment or the phthalimidoethyl fragment or both. The energy of the
23 barriers theoretically calculated for these processes were 6.54 kcal·mol⁻¹ and 5.14 kcal·mol⁻¹
24 respectively. A simultaneous combination of two of these rotations could account for a closer
25 value to the experimentally calculated one (See Supporting Information).
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54 CONCLUSIONS:

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56 In conclusion, new atropisomers of (1,3-dithiol-2-ylidene)ethanethioamides and a dithioester have
57 been studied by a combination of dynamic NMR, simulation of the signals, conformational
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6 analysis by DFT methods, and single crystal X-ray diffraction of one crystalline example, showing
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8 a good correlation between the theoretical calculations, the experimental values of energies and the
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10 preferred conformations in the solid state. The steric hindering of the crowded substitution at the
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12 central amine group, in addition of push-pull electronic delocalization due to the presence of the
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14 thioamide or thioester group, was found to be the reason of the presence of permanent
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16 atropisomers in this series of compounds, and the cause of a unique disposition of the thioxo group
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18 at close-to-right angles with respect to the plane defined by the 1,3-dithiole ring in the
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20 dithiafulvene derivatives, thus breaking the sulfur-sulfur hypervalent bonding interaction
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22 responsible for the planarity of this kind of heterocyclic systems. Because the hypervalent
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24 nonbonded S...S interactions usually control the molecular structure and chemical reactivity of
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26 organic molecules, as well as their assembly and packing in the solid state, we think that such new
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28 structural motif can be of interest for pharmacological as well as materials design.
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33 **EXPERIMENTAL SECTION:**

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36 **General:** The reactions were conducted under dry nitrogen. The solvents were previously distilled
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38 under nitrogen over phosphorous pentoxide, calcium hydride or sodium filaments. Melting points
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40 were not corrected. Infrared spectra were registered in potassium bromide tablets. NMR spectra
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42 were recorded in DMSO-*d*₆, CDCl₃, CD₃CN, and CD₃OD. Chemical shifts are reported in ppm
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44 with respect to residual solvent protons,²⁹ coupling constants ($J_{X-X'}$) are reported in Hz. DEPT
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46 experiments from selected samples permitted assignation of ¹³C NMR chemical shifts. Elemental
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48 analyses of C, H and N were taken for all new products. High resolution mass spectra were taken
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50 in a quadrupole mass spectrometer machine by electronic impact, FAB or LSIMS. Analytical TLC
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52 was performed on silica gel 60 plates. Flash column chromatography was carried out on silica gel
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54 (0.040–0.063 mm).
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6 **Quantum Chemical calculations:** DFT calculations were performed in this study to determine the
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8 optimized geometry, vibrational frequencies, and single-point energy of all stationary points. The
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10 hybrid method known as B3LYP, in which the Becke three-parameter exchange functional³⁰ and
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12 the Lee–Yang–Parr correlation functional was used,³¹ implemented in the Gaussian 03 (Revision
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14 C.02) program suite.³² The geometry optimization of the stationary points was performed at the
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16 B3LYP/6-31G* level of theory. To include solvation effects in our calculations, polarizable
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18 continuum model (PCM)³³ calculation was performed on the single-point energies at the
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20 PCM/B3LYP/6-311++G(2d,p). Natural population analysis and second-order Donor→Acceptor
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22 interaction energies were estimated at the B3LYP/6-311++G(2d,p) level by using the NBO
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24 analysis³⁴ as implemented in the GAUSSIAN03 program.
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31 **Crystal Structure Determination for Compounds 2a and 7.** A suitable crystal was mounted on
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33 a glass fibre. X-ray measurements were made using a CCD area-detector diffractometer with Mo-
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35 K α radiation ($\lambda = 0.71073 \text{ \AA}$).³⁵ Intensities were integrated³⁶ from several series of exposures,
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37 each exposure covering 0.3° in ω , and the total data set being a sphere. Absorption corrections
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39 were applied, based on multiple and symmetry-equivalent measurements.³⁷ The structure was
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41 solved by direct methods and refined by least squares on weighted F^2 values for all reflections.³⁸
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43 All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without
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45 positional constraints, except for compound 7 in which all fragments C-O-CH₂-CH₃ were refined
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47 with positional restraints. All hydrogen atoms were constrained to ideal geometries and refined
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49 with fixed isotropic displacement parameters. Complex neutral-atom scattering factors were
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51 used.³⁹
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57 **Synthesis of 5-chloro-1,2-dithiole-3-thiones.** *N*-[(2-diisopropylamino)ethyl]phthalimide **1a** and
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59 *N*-[2-(*N'*-isopropyl-*N'*-2,2-dimethylpropylamino)ethyl]phthalimide **1b** were prepared as
60

described.¹³ Disulfur dichloride (10 mmol) was added dropwise at -40°C to a stirred solution of isopropylamine **1a-b** (0.55 g **1a**, 0.60 g **1b**, 2 mmol) and DABCO (0.90g, 8 mmol) dissolved in anhydrous chloroform (50 mL) under nitrogen. The mixture was stirred at -40°C for 15 min and at room temperature for 3 days, then triethylamine (1.32 g, 13 mmol) was added at -20°C and the mixture stirred for additional 2 hours at room temperature. Then the mixture was filtered over celite and the solvent was evaporated under reduced pressure. The resulting solid was purified by MPLC (silica C60 Merck, light petroleum, and then light petroleum- CH_2Cl_2 1:1) to give the corresponding product.

4-[N-(2-Phthalimidoethyl)-N-isopropyl]amino-5-chloro-1,2-dithiole-3-thione 2a.¹³ 0.34 g, 43%, dark yellow crystals (light petroleum- CH_2Cl_2), mp $153\text{-}154^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.00-1.40 (m, 6H); 3.47-3.87 (m, 5H); 7.66-7.83 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, CDCl_3 , DEPT) δ 22.2 (2 x CH_3), 37.8 (CH_2), 42.8 (CH_2), 53.2 (CH), 123.0 (CH_{Ar}), 132.0 (C_q), 133.8 (CH_{Ar}), 150.2 (C_q), 158.0 (C_q), 168.1 (2 x $\text{C}=\text{O}$), 209.3 ($\text{C}=\text{S}$); IR (KBr) $\tilde{\nu}$ 3450, 2968, 1700 ($\text{C}=\text{O}$), 1397, 1290 ($\text{C}=\text{S}$), 1028, 723 cm^{-1} ; EIMS m/z 398 (M^+ , 6), 222 (90), 180 (100), 174 (65), 49 (70); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}_3$: 397.9984; found 397.9977; Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}_3$: C, 48.17; H, 3.79; N, 7.02. Found: C, 48.17; H, 3.69; N, 6.95. Crystal data for **2a**, $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}_3$, $M = 398.93$, triclinic, P-1, $a = 7.900(3)$ Å, $b = 11.409(4)$ Å, $c = 11.512(4)$ Å, $\alpha = 63.212(5)^{\circ}$, $\beta = 86.744(6)^{\circ}$, $\gamma = 79.229(6)^{\circ}$; $V = 909.4(6)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.457$ gcm^{-3} , $\mu(\text{Mo-K}\alpha) = 0.566$ mm^{-1} . Yellow needle, (0.40 x 0.30 x 0.10) mm^3 . 7535 measured reflections, 3098 independent ($R_{\text{int}} = 0.0154$), 2721 observed ($I > 2\sigma(I)$). $R_1 = 0.0372$, $wR_2 = 0.1082$ (all data), CCDC 1010581.

4-[N-(2-Phthalimidoethyl)-N-(2,2-dimethylpropyl)]amino-5-chloro-1,2-dithiole-3-thione 2b.¹³ 0.26 g, 30%, orange solid (light petroleum- CH_2Cl_2), mp $135\text{-}136^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 0.87 (s, 9H), 2.94-3.03 (m, 1H), 3.33-3.78 (m, 5H), 7.66-7.88 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz,

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CDCl₃) δ 27.6, 34.6, 36.5, 52.3, 62.6, 123.1, 132.0, 133.9, 150.9, 155.5, 168.1, 208.4; IR (KBr) $\tilde{\nu}$ 1772, 1709 (C=O), 1466, 1433, 1395, 1364 cm⁻¹ (C=S); EIMS m/z 426 (M⁺, 21), 369 (100), 266 (35), 174 (79); HRMS (EI) calcd for C₁₈H₁₉ClN₂O₂S₃: 426.0297; found 426.0308; Anal. Calcd for: C₁₈H₁₉ClN₂O₂S₃: C, 50.63; H, 4.48; N, 6.56. Found: C, 50.58; H, 4.36; N, 6.43.

General procedure for the synthesis of thioacid chlorides 4a-d. Dimethyl or diethyl acetylenedicarboxylate **3a-b** (36 mg **3a**, 43 mg **3b**, 0.25 mmol) was added to a solution of 1,2-dithiole-3-thione **2a-b** (100 mg **2a**, 107 mg **2b**, 0.25 mmol) in dry benzene (5 mL) under nitrogen and the mixture was refluxed for 1.5 hours, then the solvent was evaporated under reduced pressure to yield the corresponding thioacyl chloride.

Dimethyl 6-[N-(2-phthalimidoethyl)-N-isopropyl]amino-6-chlorothiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 4a.¹³ 134 mg, 99%, red sticky solid (benzene); ¹H NMR (200 MHz, C₆D₅Cl) δ 1.09 (d, J = 6.3, 3H), 1.45 (d, J = 6.3, 3H), 3.57-3.76 (m, 9H), 3.98-4.02 (m, 2H), 7.43-7.48 (m, 2H, H_{Ar}), 7.71-7.74 (m, 2H, H_{Ar}); ¹³C NMR (50 MHz, CDCl₃) δ 20.1, 23.4, 38.5, 51.4, 53.3, 53.4, 55.0, 123.2, 132.5, 133.8, 134.4, 135.5, 137.9, 159.7, 159.9, 167.8, 174.6, 182.4; IR (KBr) $\tilde{\nu}$ 3472, 2967, 1710 (C=O), 1568, 1252 cm⁻¹ (C=S); EIMS m/z 540 (M⁺, 9), 505 (39); HRMS (EI) calcd for C₂₂H₂₁ClN₂O₆S₃: 540.0250; found 540.0261.

Diethyl 6-[N-(2-phthalimidoethyl)-N-isopropyl]amino-6-chlorothiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 4b.¹³ 140 mg, 98%, red solid (benzene), mp 80-82°C; ¹H NMR (200 MHz, CDCl₃) δ 1.01 (d, J = 6.2, 3H), 1.23-1.57 (m, 9H), 3.31-3.50 (m, 2H), 3.56 (hept, J = 6.2, 1H), 3.70-3.96 (m, 2H), 4.18-4.41 (m, 4H), 7.61-7.84 (m, 4H, H_{Ar}); ¹³C NMR (50 MHz, CDCl₃, DEPT) δ 13.4 (CH₃), 13.6 (CH₃), 19.7 (CH₃), 23.0 (CH₃), 38.1 (CH₂), 50.8 (CH₂), 54.6 (CH), 62.6 (CH₂), 62.8 (CH₂), 122.9 (CH_{Ar}), 132.4 (C_{Ar}), 133.4 (CH_{Ar}), 134.9 (Cq), 135.5 (Cq), 137.5 (Cq), 159.2 (Cq), 159.5 (Cq), 167.5 (Cq), 174.4 (Cq), 182.4 (Cq); IR (KBr) $\tilde{\nu}$ 1715 (C=O),

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6 1250 cm⁻¹ (C=S); EIMS *m/z* 568 (M⁺, 10), 533 (50); HRMS (EI) calcd for C₂₄H₂₅ClN₂O₆S₃:
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8 568.0563; found 568.0554.

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10 **Dimethyl 6-[*N*-(2-phthalimidoethyl)-*N*-(2,2-dimethylpropyl)]amino-6-chlorothiocabonyl-1,4-**
11 **dithiafulvene-2,3-dicarboxylate 4c.**¹³ 140 mg, 98%, red sticky solid (benzene); ¹H NMR (400
12 MHz, C₆D₅Cl) δ 0.98 (s, 9H), 2.96 (d, *J* = 14.5, 1H), 3.37 (d, *J* = 14.5, 1H), 3.28-3.39 (m, 2H),
13 3.59 (s, 3H), 3.64 (s, 3H), 3.89-4.08 (m, 2H), 7.30-7.34 (m, 2H, H_{Ar}), 7.61-7.68 (m, 2H, H_{Ar}); ¹³C
14 NMR (100 MHz, CDCl₃, DEPT) δ 28.4 (3 x CH₃), 33.0 (Cq), 37.6 (CH₂), 53.3 (CH₃), 53.4 (CH₃),
15 55.8 (CH₂), 67.5 (CH₂), 123.4 (CH_{Ar}), 127.5 (CH_{Ar}), 133.0 (Cq), 134.9 (CH_{Ar}), 135.2 (Cq), 140.2
16 (Cq), 159.6 (Cq), 168.0 (Cq), 170.5 (Cq), 183.0 (Cq); IR (KBr) $\tilde{\nu}$ 1720 (C=O), 1245 cm⁻¹ (C=S);
17 EIMS *m/z* 568 (M⁺, 7), 533 (42); HRMS (EI) calcd for C₂₄H₂₅ClN₂O₆S₃: 568.0563; found
18 568.0569.
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31 **Diethyl 6-[*N*-(2-phthalimidoethyl)-*N*-(2,2-dimethylpropyl)]amino-6-chlorothiocabonyl-1,4-**
32 **dithiafulvene-2,3-dicarboxylate 4d.**¹³ 145 mg, 97% red sticky solid (benzene); ¹H NMR (400
33 MHz, CDCl₃) δ 0.97 (s, 9H), 1.27-1.40 (m, 3H), 2.95 (d, *J* = 14.5, 1H), 3.12-3.33 (m, 2H), 3.34-
34 3.55 (m, 1H), 3.75-4.01 (m, 2H), 4.22-4.41 (m, 4H), 7.66-7.82 (m, 4H, H_{Ar}); ¹³C NMR (100 MHz,
35 CDCl₃, DEPT) δ 13.8 (CH₃), 13.9 (CH₃), 28.4 (3 x CH₃), 33.1 (Cq), 37.1 (CH₂), 54.3 (CH₂), 63.0
36 (CH₂), 63.2 (CH₂), 67.2 (CH₂), 123.1 (CH_{Ar}), 131.8 (C_{Ar}), 133.9 (CH_{Ar}), 140.6 (Cq), 159.1 (Cq),
37 159.2 (Cq), 167.8 (Cq), 170.3 (Cq), 181.6 (Cq); IR (KBr) $\tilde{\nu}$ 1720 (C=O), 1245 cm⁻¹ (C=S); EIMS
38 *m/z* 596 (M⁺, 7), 561 (45); HRMS (EI) calcd for C₂₆H₂₉ClN₂O₆S₃: 596.0876; found 596.0885.
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50 **General procedure for the synthesis of dithiafulvenes 6a-d and 7.** Dimethyl or diethyl
51 acetylenedicarboxylate **3a-b** (36 mg **3a**, 43 mg **3b**, 0.25 mmol) was added to a solution of 1,2-
52 dithiole-3-thione **2a-b** (100 mg **2a**, 107 mg **2b**, 0.25 mmol) in dry benzene (5 mL) under nitrogen
53 and the mixture was refluxed for 1.5 hours. Then aniline **5a** (58 mg, 0.62 mmol), 2-
54 (diethylamino)ethanethiol **5b** (83 mg, 0.62 mmol) or pyrrolidine (44 mg, 0.62 mmol) in benzene (2
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mL) was added at room temperature and the mixture was stirred for 1 hour. Then the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica 230-400 mesh, hexane to hexane/EtOAc 1:1).

Diethyl 6-[N-(2-phthalimidoethyl)-N-isopropyl]amino-6-(N-phenylamino)thiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 6a. 140 mg, 89%, red sticky solid (hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 1.09-1.39 (m, 12H), 3.40-3.48 (m, 2H), 3.67 (hept, $J = 6.4$, 1H), 3.82-3.91 (m, 2H), 4.25-4.39 (m, 4H), 7.12-7.37 (m, 3H, H_{Ar}), 7.58-7.75 (m, 6H, H_{Ar}), 10.60 (s, exch, 1H, NH); ^{13}C NMR (100MHz, CDCl_3 , DEPT) δ 13.9 (2 x CH_3), 21.0 (CH_3 isopropyl), 24.1 (CH_3 isopropyl), 38.6 (CH_2), 48.0 (CH_2), 51.1 (CH), 62.7 (CH_2), 122.4 (CH_{Ar}), 123.1 (CH_{Ar}), 125.7 (CH_{Ar}), 127.3 (Cq), 128.5 (CH_{Ar}), 131.5 (Cq), 133.0 (CH_{Ar}), 137.6 (Cq), 138.5 (Cq), 154.3 (Cq), 159.2 (C=O), 160.4 (C=O), 168.0 (2 x C=O), 186.1 (C=S); IR (KBr) $\tilde{\nu}$ 3396, 2979, 1715(C=O), 1573, 1433, 1237(C=S), 1088 cm^{-1} ; MS (FAB $^+$) m/z 625 (M^+ , 100); HRMS (LSIMS) calcd for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_6\text{S}_3$: 625.1375; found 625.1367; Anal. Calcd for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_6\text{S}_3$: C, 57.58; H, 4.99; N, 6.72. Found: C, 57.64; H, 5.10; N, 6.58.

Dimethyl 6-[N-(2-phthalimidoethyl)-N-isopropyl]amino-6-[2-(diethylamino)ethyl-mercapto]thiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 6b. 130 mg, 82%, red sticky solid (hexane/EtOAc); ^1H NMR (400 MHz, $\text{C}_6\text{D}_5\text{Cl}$) δ 0.98 (t, $J = 7.2$, 6H), 1.09 (d, $J = 6.5$, 3H), 1.37 (d, $J = 6.5$, 3H), 2.48 (q, $J = 7.2$, 4H), 2.67-2.72 (m, 2H), 3.30 - 3.36 (m, 2H), 3.59-3.73 (m, 3H), 3.56 (s, 3H), 3.62 (s, 3H), 3.96-4.02 (m, 2H), 7.20 - 7.32 (m, 2H, H_{Ar}), 7.54-7.62 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $\text{C}_6\text{D}_5\text{Cl}$, DEPT CDCl_3) δ 11.9 (2 x CH_3), 20.1 (CH_3), 23.0 (CH_3), 32.4 (CH_2), 38.3 (CH_2), 47.0 (2 x CH_2), 50.3 (CH_2), 50.5 (CH_2), 53.3 (CH_3), 53.4 (CH_3), 54.0 (CH), 123.1 (CH_{Ar}), 131.4 (Cq), 132.0 (Cq), 133.4 (Cq), 133.8 (CH_{Ar}), 136.1 (Cq), 160.3 (2 x C=O), 168.0 (2 x C=O), 207.6 (C=S); IR (KBr) $\tilde{\nu}$ 1710 (C=O), 1435, 1390, 1245 cm^{-1} (C=S); MS (FAB $^+$) m/z 638 ($\text{M}^+ + 1$, 100), 565 (52), 174 (54); HRMS (LSIMS) calcd for $[\text{C}_{28}\text{H}_{35}\text{N}_3\text{O}_6\text{S}_4+\text{H}]^+$: 638.1481;

found 638.1472; Anal. Calcd for C₂₈H₃₅N₃O₆S₄: C, 52.73; H, 5.53; N, 6.59. Found: C, 52.81; H, 5.61; N, 6.50.

Dimethyl 6-[N-(2-phthalimidoethyl)-N-(2,2-dimethylpropyl)]amino-6-(N-phenyl-amino)thiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 6c. 88 mg, 56%, red sticky solid (hexane/EtOAc); ¹H NMR (400MHz, C₆D₅Cl) δ 0.94 (s, 9H), 2.72 (d, *J* = 12.6, 1H), 3.06 (d, *J* = 12.6, 1H), 3.34-3.38 (m, 2H), 3.58 (s, 3H), 3.63 (s, 3H), 4.80-4.83 (m, 2H), 7.03-7.09 (m, 2H, H_{Ar}), 7.19-7.28 (m, 3H, H_{Ar}), 7.51-7.54 (m, 2H, H_{Ar}), 8.00-8.02 (m, 2H, H_{Ar}), 11.10 (s, exch, 1H, NH); ¹³C-NMR (100MHz, C₆D₅Cl) δ 28.6, 33.2, 37.4, 53.2, 54.9, 67.3, 123.1, 128.5, 132.4, 133.8, 134.2, 141.1, 159.6, 167.6, 170.2, 181.9; IR (KBr) $\tilde{\nu}$ 1709 (C=O), 1432, 1253 cm⁻¹ (C=S); MS (FAB⁺) *m/z* 625 (M⁺, 76), 533 (49), 174 (87), 147 (100); HRMS (FAB⁺) calcd for C₃₀H₃₁N₃O₆S₃: 625.1375; found 625.1388; Anal. Calcd for C₃₀H₃₁N₃O₆S₃: C, 57.58; H, 4.99; N, 6.72. Found: C, 57.64; H, 5.05; N, 6.56.

Diethyl 6-[N-(2-phthalimidoethyl)-N-(2,2-dimethylpropyl)]amino-6-(N-phenyl-amino)thiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 6d. 88 mg, 54%, red sticky solid (hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.00 (s, 9H), 1.32-1.37 (m, 6H), 2.85 (d, *J* = 14.3, 1H), 3.11 (d, *J* = 14.3, 1H), 3.39-3.43 (m, 2H), 3.83-3.87 (m, 2H), 4.28-4.39 (m, 4H), 7.17-7.30 (m, 3H, H_{Ar}), 7.61-7.78 (m, 6H, H_{Ar}), 10.85 (s, exch, 1H, NH); ¹³C NMR (100MHz, CDCl₃) δ 14.0, 28.4, 33.4, 37.2, 51.7, 62.8, 64.9, 122.6, 123.3, 126.0, 127.2, 128.8, 131.1, 131.7, 134.0, 137.8, 138.5, 152.8, 159.3, 160.6, 167.9, 185.2; IR (KBr) $\tilde{\nu}$ 3434, 3215, 1778, 1713 (C=O), 1257 cm⁻¹ (C=S); MS (FAB⁺) *m/z* 653 (M⁺, 100), 561 (58); HRMS (FAB⁺) calcd for C₃₂H₃₅N₃O₆S₃: 653.1688; found 653.1697; Anal. Calcd for C₃₂H₃₅N₃O₆S₃: C, 58.78; H, 5.40; N, 6.43. Found: C, 58.84; H, 5.49; N, 6.36.

Diethyl 6-[N-(2-phthalimidoethyl)-N-isopropyl]amino-6-(pyrrolidin-1-yl)thiocarbonyl-1,4-dithiafulvene-2,3-dicarboxylate 7.¹³ 0.13 g, 90%, red crystals (hexane/EtOAc), mp 113-114°C;

¹H NMR (400 MHz, CDCl₃) δ 1.22-1.40 (m, 12H), 2.05-2.11 (m, 4H), 2.87-2.95 (m, 2H), 3.40 (hept, *J* = 6.4, 1H), 3.57-3.65 (m, 2H), 3.89-3.99 (m, 4H), 4.17-4.31 (m, 4H), 7.65-7.81 (m, 4H, H_{Ar}); ¹³C NMR (100 MHz, CDCl₃, DEPT) δ 14.2 (2 x CH₃), 22.0 (2 x CH₃), 25.5 (2 x CH₂), 38.7 (CH₂), 46.0 (CH₂), 52.9 (2 x CH₂), 56.0 (CH), 62.7 (CH₂), 62.9 (CH₂), 123.4 (CH_{Ar}), 127.0 (Cq), 128.9 (Cq), 131.9 (Cq), 132.3 (Cq), 133.4 (Cq), 134.2 (CH_{Ar}), 159.7 (C=O), 160.5 (C=O), 168.3 (2 x C=O), 190.7 (C=S); IR (KBr) $\tilde{\nu}$ 2968, 2870, 1715 (C=O), 1586, 1391, 1240 (C=S), 1018 cm⁻¹; MS (FAB⁺) *m/z* 603 (M⁺, 100); HRMS (FAB⁺) calcd for C₂₈H₃₃N₃O₆S₃: 603.1531; found 603.1530; Anal. Calcd for C₂₈H₃₃N₃O₆S₃: C, 55.70; H, 5.51; N, 6.96. Found: C, 55.63; H, 5.56; N, 6.90; Crystal data for **7**, C₂₈H₃₃N₃O₆S₃, *M* = 603.75, monoclinic, P2(1)/c, *a* = 16.942(2) Å, *b* = 14.3803(18) Å, *c* = 37.907(5) Å, α = 90°, β = 101.603(3)°, γ = 90°; *V* = 9046.8(19) Å³, *Z* = 12, *D*_{calc} = 1.330 gcm⁻³, μ (Mo-K α) = 0.291 mm⁻¹. Red needle, (0.30 x 0.20 x 0.20) mm³. 66244 measured reflections, 15913 independent (*R*_{int} = 0.0916), 7448 observed (*I* > 2σ(*I*)). *R*₁ = 0.0708, *wR*₂ = 0.1894 (all data), CCDC 1010580.

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Supporting Information Available. Copies of ¹H and ¹³C NMR of the products, X-Ray diffraction structures and coordinates of all stationary points for the calculated structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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