

An Experimental and Theoretical Conformational Study of a Series of Substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones

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Abstract

A series of novel 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one derivatives with substituents on the 2-phenyl ring were synthesized, and a study of their solid state and solution conformations was effected. In solution the thiazolidin-4-one ring preferred the C2 phenyl in a pseudo-equatorial orientation and the solid state indicated a preference for the C2 phenyl being in a pseudo-axial orientation. Less robust substituent chemical shift (SCS) correlations utilizing ¹³C NMR were observed in this instance than in prior studies. Molecular modeling studies using Møller-Plessett second-order perturbation theory (MP2) indicate that the thiazolidinone ring and cyclohexyl ring conformations exhibit a global minimum consistent with the solution studies.

Keywords: thiazolidin-4-ones, ¹H NMR, ¹³C NMR, substituent effects, MP2 calculations

1. Introduction

Studies of the biological activity of many substituted thiazolidinone systems have been undertaken, and a diverse series of activities has been reported with this heterocyclic system (Vazzana, Terranova, Maittioli, & Sparatore, 2004; Barreca et al., 2001; Ravichandran et al., 2008).

Previously, six series of thiazolidinones, shown in Figure 1 (Series 1-6), had been studied (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996; Tierney, Issac, et al., 1996; Tierney, Sheridan, et al., 1996). The sensitivity of electron density shifts at the methine proton (H_x) at C2 and the methylene protons (H_a and H_b) at C5 related to substituents on each phenyl ring (Series 1 and 2) have been determined from ¹H NMR data. Hammett values and Swain Lupton *r* (resonance) and *f* (field or inductive) coefficients have been used as indicators. Two of the studies used different arrays of phenyl substituents with comparable results (Woolston et al., 1992; Tierney et al., 1996). In addition, similar studies had been carried out utilizing ¹³C chemical shift data at C2, C4 and C5, from the substituents attached to the phenyl or benzyl moieties in Series 1 through 6, Figure 1. A prior focus of study for compounds in Series 1, 2 and 5, Figure 1, had been on the conformation of the thiazolidin-4-one ring in both solid state from X-ray analysis (Hickel et al., 1983; Tierney et al., 2005), and in solution from NMR data (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996).

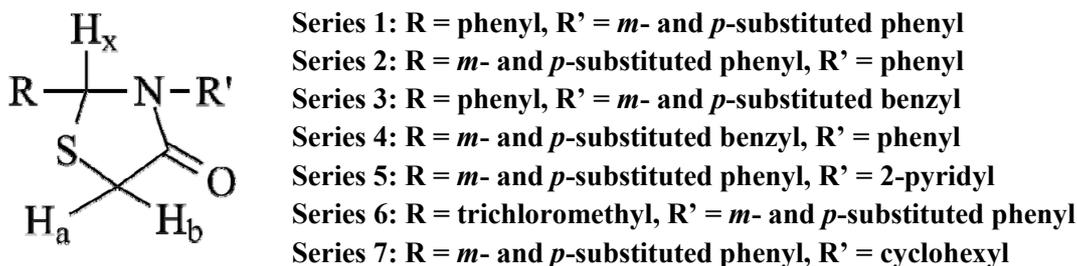


Figure 1. All series of substituted thiazolidinones studied to date. The *meta* and *para* substituents in all series are consistently: *p*-NO₂; *m*-NO₂; *p*-F; *m*-F; *p*-Cl; *m*-Cl; *p*-Br; *m*-Br; H, *p*-Me; *m*-Me; *p*-MeO; *m*-MeO

Solid state conformational studies (Hickel et al., 1983; Tierney et al., 2005) of diaryl compounds (Series 1, 2 and 5) showed that their conformation is different in the solid state from that in solution. Using X-ray data, Woolston concluded that conformer A (Figure 2) is the preferred solid state conformer, with the C2 aryl group (R) pseudo-axial and conformer B (Figure 2) is the preferred conformer in solution (Woolston et al., 1992; Hickel et al., 1983). The thiazolidin-4-one ring has a chiral center at C2 ensuring that the methylene protons at C5 are nonequivalent, leading to an ABX splitting pattern in ¹H NMR. The conformational assignments were made based on NMR NOE experiments. Additional ¹H NMR data also links the methine proton, H_x, coupling to the lower field *trans* methylene proton H_b for 2,3-diphenyl-1,3-thiazolidin-4-one.

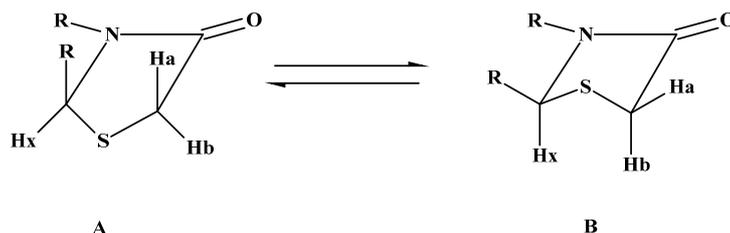


Figure 2. Thiazolidin-4-one ring conformers

In this present study (Figure 1, Series 7) NMR data and X-ray data for the same compound were utilized rather than comparing compounds that have the same heterocyclic nucleus but different aryl moieties at C2 and N3, as in the case of the Woolston study (Woolston et al., 1993; Hickel et al., 1983). In addition, *ab initio* molecular modeling information is introduced to enhance the understanding of the solution state conformers in the C2 phenyl N3 cyclohexyl series of substituted thiazolidin-4-ones.

2. Results and Discussion

2.1 General

The series of compounds described here is shown in Figure 1, Series 7. One major difference compared to observations made in previous studies utilizing ¹³C NMR data was the weaker substituent chemical shift correlations at the C2 site, Figure 3 (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996; Tierney, Issac, et al., 1996; Tierney, Sheridan, et al., 1996). At first sight it appears that very good correlation is lacking, but on closer inspection one sees that the *p*-methoxy and the *m*-nitro substituents are the most divergent from the trend line. In previous studies (Tierney et al., 2005; Tierney et al., 2008) of additivity effects in the predictions of NMR chemical shift values for substituted diphenylthiazolidin-4-ones it has been shown that the *meta*-nitro compounds have the least predictable chemical shifts for these systems. However, this is the first instance where divergence with the *p*-methoxy group has manifested itself when investigating Hammett correlations. Johnson has previously addressed the situations in which strongly electron donating groups, in particular the *p*-methoxy group, show significant deviations when using Hammett σ , σ^+ or σ^- correlations (Johnson, 1978). One explanation for this deviation is that the substituted phenyl ring is twisted out of full conjugation with the site being observed. This appears to be the case here, but why it does not similarly affect the

other substituents in this system is still not clear. If the *p*-methoxy and the *m*-nitro substituents are excluded from the observations the results can be seen in Table 1. Correlations were improved if the *meta* substituted compounds are removed from consideration in Series 1-6, Figure 1, so this improved outcome is not surprising. As in all the prior studies (Series 1-6, Figure 1) the ρ value is negative showing that C2 prefers a positive charge density. Interestingly, where reasonable correlations were also seen for the ^{13}C chemical shift data versus Hammett σ values at C4 and C5 for Series 1-6, Figure 1, this was not the case here. The limited ability to see the effective transmission of substituent effects to more distant sites is probably in concert with the slight twisting of the phenyl group at C2 in the thiazolidinone ring as proposed by Johnson (Johnson, 1978).

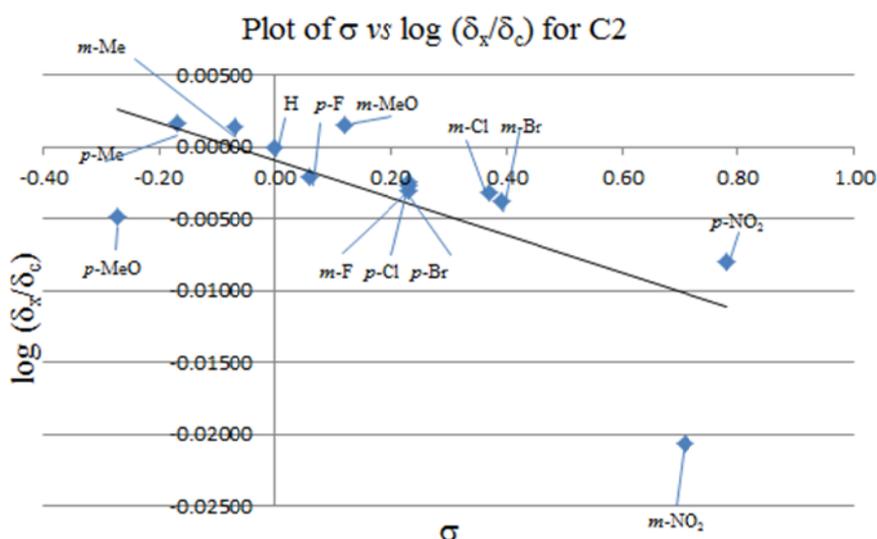


Figure 3. Plot of Hammett versus all ^{13}C values for the C2 carbon in the thiazolidin-4-one ring

Table 1. The equations for correlations of Hammett with substituent chemical shifts

Equation	R ²	Comment
C2		
$y = -0.0131x - 0.0009$	0.488	all substituents, n = 13
$y = -0.0104x - 0.0002$	0.870	minus <i>m</i> -NO ₂ and <i>p</i> -MeO, n = 11
$y = -0.0099x - 0.0004$	0.971	all <i>para</i> substituted except <i>p</i> -MeO, n = 6

2.2 Solid State Study

It can be seen from the ORTEP model (Figure 4) that the phenyl ring and the cyclohexyl ring positions are best described by conformer A in Figure 2. This observation is in concert with the X-ray structure for 2-(2'-methylphenyl)-3-(2"-pyridyl)-1,3-thiazolidin-4-one (Hickel et al., 1983) and for the 2,3-diphenylthiazolidin-4-one ligand coordinated to triphenyltin chloride (Smith et al., 1996). Even though the 2,3-diphenyl-thiazolidin-4-one was coordinated to the tin through the carbonyl oxygen, the heterocyclic ring preferred having the two phenyl groups with one pseudo axial orientation. Woolston attributed the previously observed difference between the solid state conformation from Hickel's X-ray data and the solution conformation to be due to the presence of the methyl group in 2-(2'-methyl-phenyl)-3-(2"-pyridyl)-1,3-thiazolidin-4-one, but this cannot be the case (Woolston et al., 1992; Hickel et al., 1983). It is also evident that the favored solid state conformation shown by Hickel's data is the same when the groups at C2 and N3 are replaced by a phenyl and a cyclohexyl group. Clearly the packing forces

required for crystalline systems are different to those observed in the solution, liquid, or gaseous states. By having the rings assume these orientations, this adapted conformation appears to be the most energetically favorable for crystal packing regardless of substituents in the rings or the type of ring.

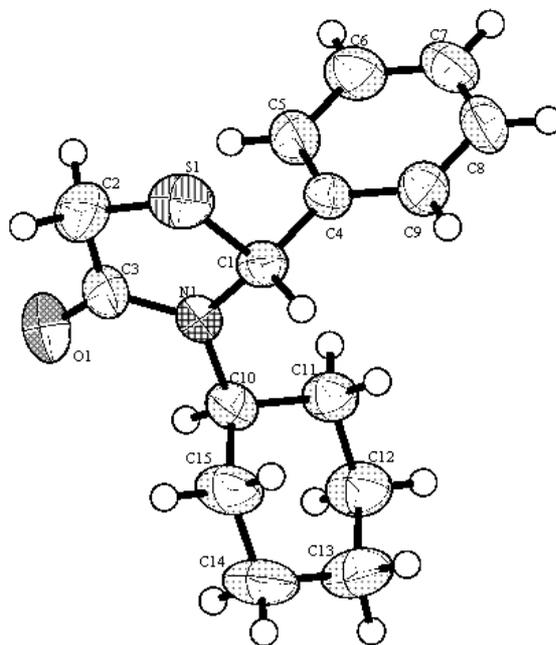


Figure 4. Note: the numeric assignments for atoms in the ORTEP model do not concur with IUPAC nomenclature

2.3 Solution Study

In the prior studies on 2,3-diphenylthiazolidin-4-ones, the solution NMR studies focused solely on the conformation of the thiazolidinone ring (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996; Tierney, Issac, et al., 1996; Tierney, Sheridan, et al., 1996). However, in this instance there are two rings whose conformers can change simultaneously, the thiazolidinone and cyclohexyl rings. In the previous studies, the presence of the aryl moieties at C2 and N3 produced a more rigid environment due to the array of sp^2 hybridized atoms in the phenyl rings. There is an increase in the number of degrees of freedom by the introduction of a cyclohexyl group at N3. This ring can flip from one chair conformation to the other. In addition there is also the possibility that the cyclohexyl ring can point towards or away from the carbonyl group. It was envisaged, in advance of the study, that a number of possible conformational outcomes would be possible, and these are shown in Figure 5. To simplify the calculations an initial decision was made to exclude a pyramidal nitrogen geometry, focusing only on a planar nitrogen for the amide in the heterocyclic ring. A planar nitrogen had already been proposed as the preferred geometry in prior studies series, but it should be noted that the X-ray analysis does show a slightly nonplanar configuration (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996).

The sulfur atom has the possibility of being puckered up or down with the respect to the rest of the thiazolidinone ring. The phenyl ring can either take up a pseudo axial or pseudo equatorial position on the thiazolidinone ring. In addition, the cyclohexyl ring itself can show either an axial or equatorial geometry at the amide nitrogen of the thiazolidinone ring. Additionally, as already mentioned, the cyclohexyl ring can point either towards or away from the carbonyl oxygen. Because of the near planarity around the amide nitrogen, the cyclohexyl ring is orthogonal to the plane of the thiazolidinone ring. Those conformers with the sulfur atom puckered down in the thiazolidinone ring are shown in structures 5a, 5b, 5e, and 5f, and those with the sulfur atom puckered up are shown in structures 5c, 5d, 5g, and 5h. The axial and equatorial conformations exhibiting the cyclohexyl ring pointing towards the carbonyl oxygen of the heterocyclic ring are shown in structures 5a through 5d, and structures 5e through 5h show the cyclohexyl ring pointing away from the carbonyl oxygen.

The ABX coupling pattern observed in the ^1H NMR between the methine proton, H_x , and the methylene protons are in concert with the previously reported NMR studies for thiazolidinone ring conformations in solution (Woolston et al., 1992; Woolston et al., 1993; Tierney, Houghton, et al., 1996). The long range coupling between the methine proton H_x at C2 and the *trans* lower field methylene proton H_b , at C5 can be seen in Figure 6. The reason that W-plane coupling is not seen in this system is because the C2-S-C5 atoms in the thiazolidinone ring are not coplanar. This is evident in the solid state analysis and the structures generated in the MP2 calculations.

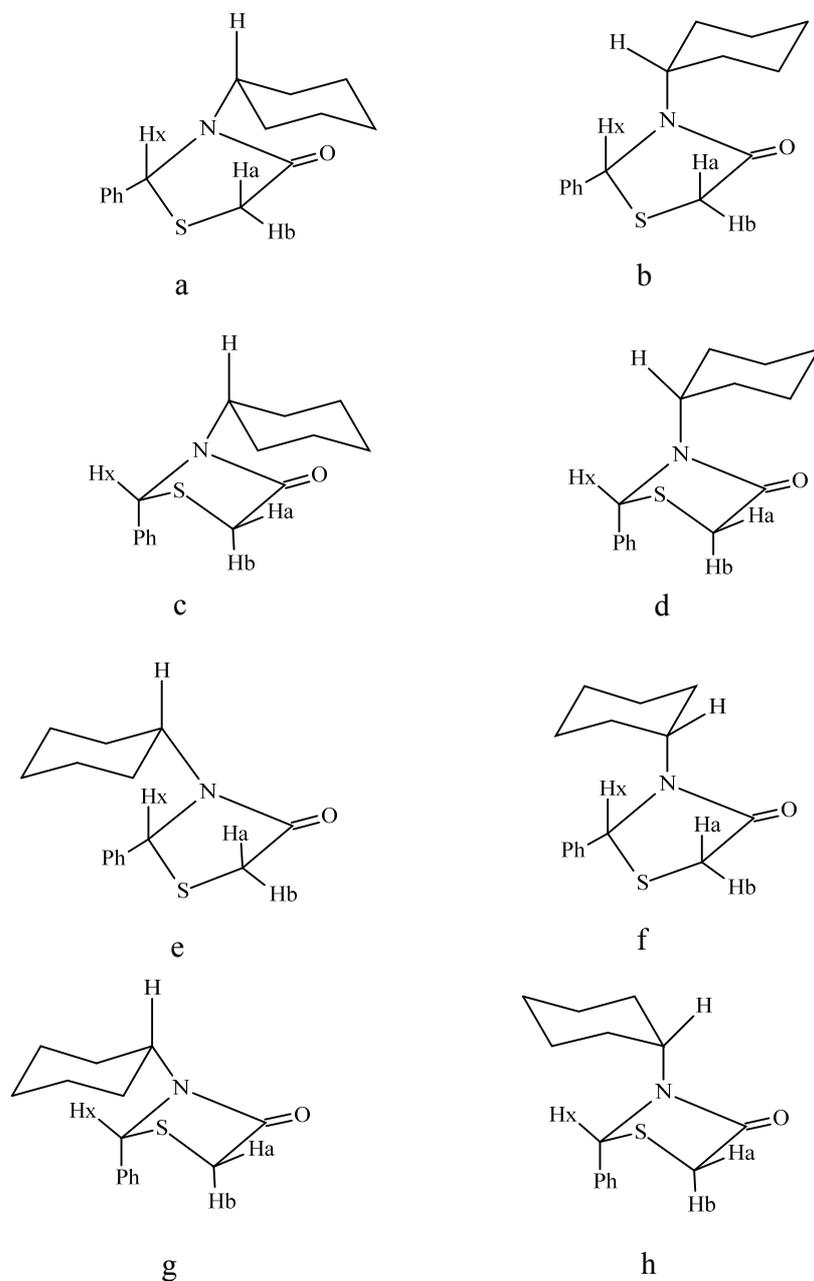


Figure 5. Possible conformations of the thiazolidinone cyclohexane rings

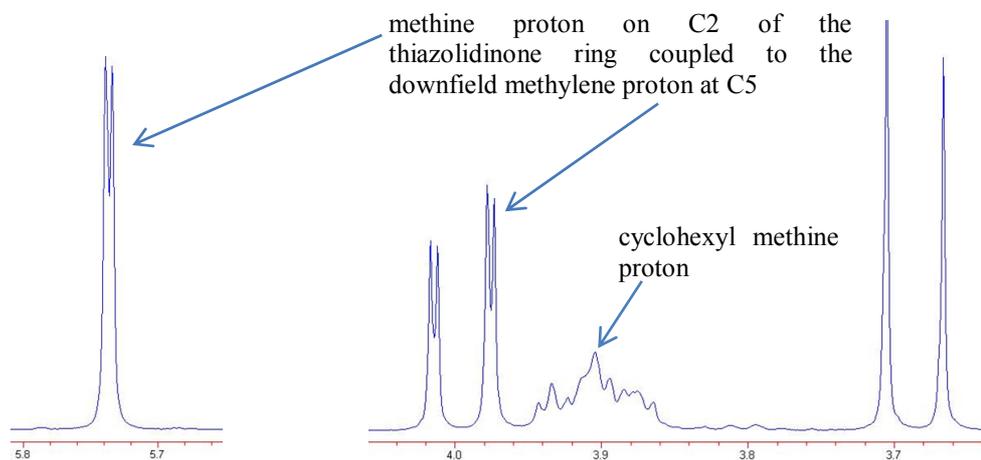


Figure 6. ^1H NMR spectra of the methine and methylene regions for 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one

2.4 Molecular Modeling Study

As previously discussed in this report, the amide ring nitrogen has been shown to be either planar or close to planar geometry. Nonetheless, in order to more fully explore the ground state potential surface for possible local and global minima, geometry optimizations using Møller-Plesset second-order perturbation theory (MP2) and the correlation-consistent basis set cc-pVDZ (Dunning, 1989) were carried out starting with each of the eight conformers given in Figure 5, using the GAMESS suite of quantum programs (Frisch et al., 2010). Molecular visualizations were done with MOLDEN.

Two different local minima were located at this level of theory. Their optimized structures are shown in Figure 7. One, which is slightly more stable at this level of theory, corresponds to the configuration with a pseudo equatorial phenyl, oriented up, sulfur puckered up, the cyclohexyl ring oriented orthogonal to the thiazolidinone ring with the C1 hydrogen of the cyclohexyl ring pointing away from the carbonyl, and the cyclohexyl ring in a chair conformation its C3 and C5 atoms pointing away from the carbonyl. The amide nitrogen is slightly pyramidalized up by about 10.5° . Its MP2 energy with this basis set is -1108.52628 Hartree. This minimum also corresponds to the energetically degenerate enantiomeric conformer having a pseudo equatorial phenyl, oriented down, sulfur puckered down, the cyclohexyl is the same as above, and the amide nitrogen pyramidalized slightly down. In terms of the phenyl and sulfur orientation this is qualitatively commensurate with structure 7a (and is equivalent to 5a).

The second minimum is for Figure 7d (and is equivalent to 5d), and its MP2 energy using this basis set is -1108.51718 Hartree. This minimum corresponds to a geometry having a pseudo axial phenyl pointing down, the sulfur puckered up, the chair conformation of the cyclohexyl ring oriented orthogonal to the thiazolidinone ring with its C1-H pointing away from the carbonyl, but now with C3 and C5 pointing towards the carbonyl.

The difference in energies of these two minima is 0.00910 Hartree, or 5.69 kcal/mol. If we approximate this energy difference to be the free-energy difference, it is large enough to predict 7a as the global minimum, which supports the experimental data previously reported for other similarly disubstituted thiazolidinones (Tierney, Houghton, et al., 1996). Interestingly, if the chair conformation of the cyclohexyl ring in structure 7d is inverted, that is, changed to a chair conformer now oriented orthogonal to the ring with C3 and C5 pointing away from the carbonyl, this new structure with the inverted cyclohexyl ring is allowed to optimize at the MP2/cc-pVDZ level to the other minimum, 7a, which is located without any energetic barriers other than that required to overcome the inversion of the cyclohexyl's chair conformation. Likewise, if the cyclohexyl ring of the optimized structure 7a is inverted to a chair conformer with C3 and C5 oriented towards the carbonyl, further optimization at this level of theory locates the local minimum corresponding to structure 7d without further energetic barriers. At this time a theoretical value for the barrier of this cyclohexyl inversion is not known, but if it is assumed that this inversion of the cyclohexyl ring between these two chair orientations occurs at room temperature, and the system reaches equilibrium between structure 7a and 7d, the energy difference would still place 7a as the dominant conformer in solution, and 7d present as only a minor conformer.

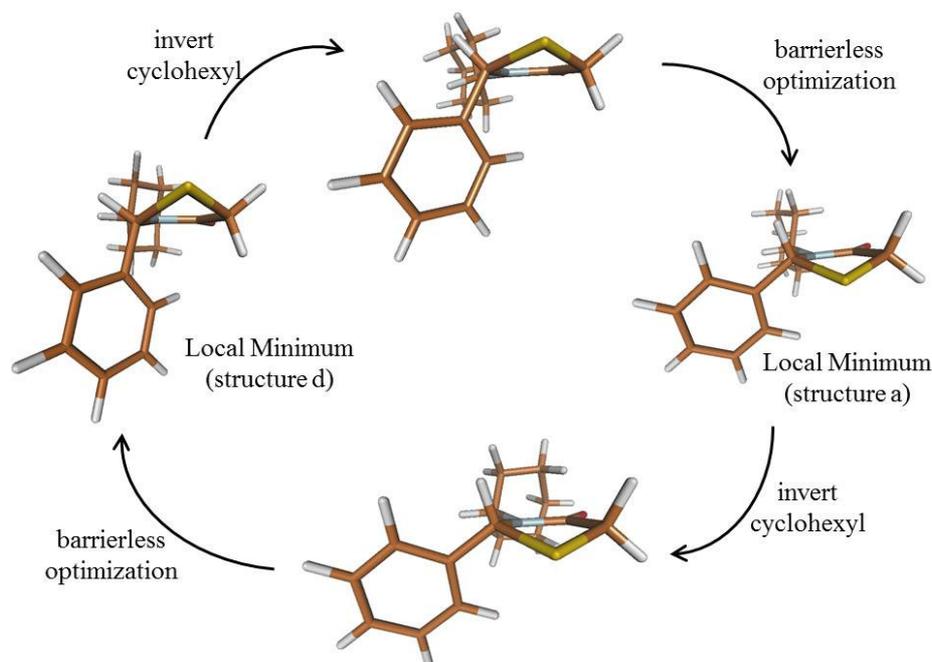


Figure 7. The two local minima are shown, corresponding to structures 5a and 5d in Figure 5. Inverting the cyclohexyl chair conformation, as described in the text, of one minimum, followed by MP2 optimization, leads without barrier to the other minimum

3. Conclusion

The results show that regardless of the bulky groups at C2 and N3 on the thiazolidinone ring, it is clear that in the solid state the preferred conformation for efficient packing requires that the group at C2 be in a pseudo axial position. In this instance with a cyclohexyl ring attached to N3 of the thiazolidinone ring, the cyclohexyl ring orients itself with the thiazolidinone ring in an equatorial position from the cyclohexyl carbon to the N3 thiazolidinone nitrogen, and the proton on that cyclohexyl carbon is axial and points away from the thiazolidinone ring. In addition, the cyclohexyl ring is orthogonal to the thiazolidinone ring and points towards the carbonyl group of the thiazolidinone ring.

When the solution conformation for 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one is considered from the perspective of the ^1H NMR in CDCl_3 , the preferred conformation appears to be B (Figure 2) or 7a (Figure 7). The molecular modeling studies best emulate the solution state, and calculations at the MP2 level indicate that there could be equilibration between two thiazolidinone conformers 7a and 7d (Figure 7), with 7a being the global minimum of the two, more stable by 5.69 kcal/mol. It should be noted that in these two conformations the thiazolidinone ring is orthogonal to the cyclohexyl ring in both instances, one equatorial at the cyclohexyl C1, 7a (and equivalent to 5a) and the other axial, 7d, (and equivalent to 5d). In the case of the equatorial cyclohexyl conformer the sulfur in the thiazolidinone ring is puckered down and in the axial cyclohexyl conformer the sulfur is puckered up. In both these configurations one would see the same methine proton at C2 coupling to the downfield methylene proton at C5 shown in Figure 6. The proton on C1 of the cyclohexyl ring appears as a multiplet at 3.9 ppm, consistent with expectations for a flipping ring on the NMR time scale (Figure 6). It should be noted that in the cyclohexyl equatorial conformer, the cyclohexyl ring moves into closer proximity to the phenyl group, and when it flips into the axial conformation it moves away from the phenyl ring but closer to the carbonyl group. We are currently using theory to further probe more energetic details of these possible conformational changes, and their commensurate energy barriers, and these results will be reported in the future.

As mentioned previously, one of the goals of this study was to measure electronic effects of substituents in the phenyl ring at sites in the thiazolidinone ring at C2, C4 and C5 utilizing ^{13}C NMR data. No discernible correlations were observed using Hammett or Swain Lupton Dual Substituent Parameter constants for C4 or C5. However, a weak Hammett correlation was noted if the *p*-methoxy and *m*-nitro substituents were removed from consideration. The *meta*-nitro substituted compounds in Series 1-6 (Figure 1) have well documented deviations.

This is the first case where a *p*-methoxy substituted molecule has shown a marked deviation, and appears to be due to the reasons addressed by Johnson (Johnson, 1978). Uniformly improved correlations have been observed in previous studies when only the *para*-substituted molecules are considered, and this included the *p*-methoxy group (Woolston et al., 1992; Tierney, Houghton, et al., 1996; Tierney, Sheridan, et al., 1996; Tierney et al, 2005; Tierney et al, 2008). It would appear that the weakness in the overall Hammett correlation at C2 and the lack of any noticeable correlation at C4 and C5 can possibly be accounted for by the lack of an aryl group at N3 which has been shown to attenuate conjugation from substituents to reaction site. Because of the presence of an alkyl over an aryl group at N3, our assumption that N3 is planar may also be incorrect as witnessed by the MP2 calculations. This slight pyramidalization of the nitrogen and the increased perturbations from the flipping of the cyclohexyl ring at N3 could possibly explain the decrease in sensitivity to the transmission of substituent effects from the C2 phenyl ring and the complete absence of transmission to C4 and C5.

4. Experimental

4.1 General

The thiazolidine-4-ones were prepared using the procedure previously described by adapting a method originally utilized by Surrey (Surrey, 1947). Melting points are uncorrected; a Uni-Melt capillary melting point apparatus was used. All spectra were recorded on a Bruker 400 at 298 K observing ^1H and ^{13}C at 400.13 and 100.61 MHz, respectively. All samples were dissolved in CDCl_3 at a concentration of 50 mg/mL using precision bore 5 mm NMR tubes supplied by Norell, Inc.

^1H spectra were collected into 32 K data sets over a spectral width of 8012.8 Hz using a 30° pulse; pulse width, 3.9 ms; acquisition time, 4.09 s; relaxation delay, 2.0 s; number of scans, 128. ^{13}C spectra were collected into 16K data sets over a spectral width of 25125 Hz with a 60° observed pulse using Waltz-16 decoupling; pulse width, 19.9 ms; acquisition time 1.304 s; relaxation delay, 4.0 s; number of scans, 2048. The spectrometer was locked to the deuterium resonance of the solvent (CDCl_3) and all chemical shifts were referenced to residual CHCl_3 . Infrared spectra were obtained as an evaporated thin film on a sodium chloride plate (Janos Technology, Inc) on a Nicolet Nexus 670 spectrometer using 32 scans at a 2 cm^{-1} resolution. Mass spectra were recorded on a Varian 2100 G ion trap mass spectrometer, fitted with a Varian 3900 gas chromatograph: column—Factor 4 VF-5 ms 0.25 mm id, 30 m, 0.25 μm film thickness, He carrier gas, 1.0 ml/min flow, 80°C for 1 minute isothermal $15^\circ\text{C}/\text{min}$ to 275°C then 275°C for 3 minutes isothermal, injector temp 250°C , 0 min, 1:50 split. Isolated yields are based on starting amounts for the imines (amine is the limiting reactant) and it was assumed that 100% of the imine was produced *in situ*. No attempt was made to maximize the product yields. Hammett and Swain-Lupton correlations were obtained using Excel in Microsoft Office.

The X-ray crystallographic analysis was obtained from a colorless block shaped crystal of formula $\text{C}_{15}\text{H}_{19}\text{NOS}$ with approximate dimensions 0.08 x 0.11 x 0.18 mm. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK α fine-focus sealed tube ($\lambda = 0.71073\text{\AA}$) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in w and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 7520 reflections to a maximum q angle of 28.33° (0.90\AA resolution), of which 3744 were independent, completeness = 97.2%, $R_{\text{int}} = 0.0217$, $R_{\text{sig}} = 0.0317$ and 2310 were greater than $2s(I)$. The final cell constants: $a = 13.002(3)\text{\AA}$, $b = 10.044(2)\text{\AA}$, $c = 10.687(2)\text{\AA}$, $a = 90^\circ$, $b = 98.150(5)^\circ$, $g = 90^\circ$, volume = $1381.5(5)\text{\AA}^3$, are based upon the refinement of the XYZ-centroids of 1554 reflections above $20s(I)$ with $2.572^\circ < q < 20.977^\circ$. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.7970.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group $P2(1)/c$, with $Z = 4$ for the formula unit, $\text{C}_{15}\text{H}_{19}\text{NOS}$. The final anisotropic full-matrix least-squares refinement on F^2 with 163 variables converged at $R1 = 5.56\%$, for the observed data and $wR2 = 15.10\%$ for all data. The goodness-of-fit was 1.033. The largest peak on the final difference map was $0.386\text{ e}/\text{\AA}^3$ and the largest hole was $-0.257\text{ e}/\text{\AA}^3$. Based on the final model, the calculated density of the crystal is $1.257\text{ g}/\text{cm}^3$ and $F(000)$ amounts to 560 electrons.

4.2 Synthesis and Characterization of Compounds

3-cyclohexyl-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (**a**) (60%); m.p. 91-92 °C; cm^{-1} 1665.8 (C=O); ^1H NMR (CDCl_3): 8.17-7.23 (4H, m, aromatics), 5.66 (1H, d, C2, $J=1.6$ Hz), 3.83 (1H, dd, C5, $J=1.6$ Hz, and $J=15.6$ Hz), 3.68 (1H, m, NCH), 3.55 (1H, d, C5, $J=15.6$ Hz), 1.92-0.81 (10H, m, cyclohexyls); ^{13}C NMR: 171.96 (C4), 150.73, 148.13, 127.06, 124.77, 61.39 (C2), 56.27, 33.15 (C5), 31.81, 30.48, 26.09, 25.46; (m/z) 306 (M^+), $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ (306.38).

3-cyclohexyl-2-(3-nitrophenyl)-1,3-thiazolidin-4-one (**b**) (64%); oil; cm^{-1} 1665.4 (C=O); ^1H NMR (CDCl_3): 8.13-7.41 (4H, m, aromatics), 5.66 (1H, d, C2, $J=1.6$ Hz), 3.85 (1H, dd, C5, $J=2.0$ Hz, and $J=15.6$ Hz), 3.70 (1H, m, NCH), 3.55 (1H, d, C5, $J=15.6$ Hz), 1.97-0.81 (10H, m, cyclohexyls); ^{13}C NMR: 169.92 (C4), 146.76, 143.82, 130.35, 128.52, 121.95, 119.32, 59.64 (C2), 54.35, 31.18 (C5), 29.69, 28.40, 24.11, 23.43; (m/z) 306 (M^+) $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ (306.38).

3-cyclohexyl-2-(4-fluorophenyl)-1,3-thiazolidin-4-one (**c**) (75%); m.p. 87-89 °C; cm^{-1} 1655.0 (C=O); ^1H NMR (CDCl_3): 7.23-6.95 (4H, m, aromatics), 5.57 (1H, d, C2, $J=1.6$ Hz), 3.79 (1H, dd, C5, $J=1.8$ Hz and $J=15.8$ Hz), 3.70 (1H, m, NCH), 3.51 (1H, d, C5, $J=15.6$ Hz), 1.65-0.82 (10H, m, cyclohexyls); ^{13}C NMR: 171.67 (C4), 164.23, 161.76, 138.94, 128.43, 116.23, 62.24 (C2), 56.33, 33.36 (C5), 31.24, 30.24, 26.21, 25.52; (m/z) 297 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSF}$ (297.37).

3-cyclohexyl-2-(3-fluorophenyl)-1,3-thiazolidin-4-one (**d**) (58%); m.p. 101-2 °C; cm^{-1} 1669 (C=O); ^1H NMR (CDCl_3): 7.02-6.92 (4H, m, aromatics), 5.55 (1H, d, C2, $J=1.5$ Hz), 3.83 (1H, dd, C5, $J=1.5$ Hz and $J=15.7$ Hz), 3.71 (1H, m, NCH), 3.51 (1H, d, C5, $J=15.5$ Hz), 1.67-0.829 (10H, m, cyclohexyls); ^{13}C NMR: 171.86 (C4), 164.51, 162.05, 145.99, 130.91, 121.92, 116.01, 113.37, 62.11 (C2), 56.31, 33.24 (C5), 31.35, 30.34, 26.18, 25.54; (m/z) 297 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSF}$ (297.37).

2-(4-chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**e**) (44%); m.p. 110-111 °C; cm^{-1} 1667.8 (C=O); ^1H NMR (CDCl_3): 7.27-7.16 (4H, m, aromatics), 5.55 (1H, d, C2, $J=1.6$ Hz), 3.80 (1H, dd, C5, $J=1.8$ Hz and $J=15.4$ Hz), 3.68 (1H, m, NCH), 3.52 (1H, d, C5, $J=15.6$ Hz), 1.67-0.85 (10H, m, cyclohexyls); ^{13}C NMR: 171.83 (C4), 141.82, 134.78, 129.51, 127.88, 114.94, 62.15 (C2), 56.35, 33.62 (C5), 31.40, 30.33, 26.19, 25.53. (m/z) 295 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSCl}$ (295.83).

2-(3-chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**f**) (41%); m.p. 62-65 °C; cm^{-1} 1660.7 (C=O); ^1H NMR (CDCl_3): 7.24-7.11 (4H, m, aromatics), 5.52 (1H, d, C2, $J=1.8$ Hz), 3.82 (1H, dd, C5, $J=1.8$ Hz and $J=15.4$ Hz), 3.76 (1H, m, NCH), 3.52 (1H, d, C5, $J=15.6$ Hz), 1.67-0.87 (10H, m, cyclohexyl); ^{13}C NMR: 171.94 (C4), 145.47, 135.15, 130.62, 129.23, 126.49, 124.45, 62.08 (C2), 56.33, 33.27 (C5), 31.62, 30.46, 26.19, 25.54; (m/z) 295 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSCl}$ (295.83).

3-cyclohexyl-2-(4-bromophenyl)-1,3-thiazolidin-4-one (**g**) (67%); m.p. 108-109 °C; cm^{-1} 1666.4 (C=O); ^1H NMR (CDCl_3): 7.43-7.10 (4H, m, aromatics), 5.53 (1H, d, C2, $J=2.0$ Hz), 3.80 (1H, dd, C5, $J=1.8$ Hz and $J=15.4$ Hz), 3.75 (1H, m, NCH), 3.52 (1H, d, C5, $J=15.6$ Hz), 1.71-1.43 (10H, m, cyclohexyls); ^{13}C NMR: 171.84 (C4), 142.37, 132.45, 128.44, 129.90, 62.19 (C2), 58.35, 33.33 (C5), 31.44, 30.36, 26.19, 25.54; (m/z) 339 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSBr}$ (340.28).

3-cyclohexyl-2-(3-bromophenyl)-1,3-thiazolidin-4-one (**h**) (45%); oil; cm^{-1} 1664.4 (C=O); ^1H NMR (CDCl_3): 7.42-7.15 (4H, m, aromatics), 5.52 (1H, s, C2), 3.81 (1H, d, C5, $J=15.2$ Hz), 3.75 (1H, m, NCH), 3.51 (1H, d, C5, $J=15.2$ Hz), 1.70-0.87 (10H, m, cyclohexyls); ^{13}C NMR: 171.86 (C4), 145.71, 132.07, 130.87, 129.40, 124.93, 123.23, 61.99 (C2), 56.31, 32.26 (C5), 31.43, 30.37, 26.20, 25.54. (m/z) 339 (M^+), $\text{C}_{15}\text{H}_{18}\text{NOSBr}$ (340.28).

3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one (**i**) (64%); m.p. 115-116 °C, cm^{-1} 1658.6 (C=O); ^1H NMR (CDCl_3): 7.47-7.36 (4H, m, aromatics), 5.74 (1H, d, C2, $J=1.8$ Hz), 3.99 (1H, dd, C5, $J=1.8$ Hz and $J=15.2$ Hz), 3.90 (1H, m, NCH), 3.68 (1H, d, C5, $J=15.2$ Hz), 1.86-1.59 (10H, m, cyclohexyls); ^{13}C NMR: 171.94 (C4), 13.161, 129.28, 129.07, 126.47, 62.83 (C2), 56.28, 33.47 (C5), 31.28, 30.32, 26.24, 25.58. (m/z) 261 (M^+), $\text{C}_{15}\text{H}_{19}\text{NOS}$ (261.38).

3-cyclohexyl-2-(4-methylphenyl)-1,3-thiazolidin-4-one (**j**) (42%); m.p. 68-70 °C; cm^{-1} 1664.9 (C=O); ^1H NMR (CDCl_3): 7.20-7.07 (4H, m, aromatics), 5.55 (1H, d, CH, $J=1.6$ Hz), 3.81 (1H, dd, C5, $J=2.0$ Hz and $J=15.6$ Hz), 3.70 (1H, m, NCH), 3.50 (1H, dd, C5, $J=15.6$ Hz), 2.28 (3 H, s, CH_3), 1.67-0.81 (10H, m, cyclohexyls). ^{13}C NMR: 171.89 (C4), 140.12, 138.96, 129.93, 126.41, 62.78 (C2), 56.31, 33.47 (C5), 31.20, 30.29, 26.27, 25.59, 21.59; (m/z) 275 (M^+), $\text{C}_{16}\text{H}_{21}\text{NOS}$ (275.41).

3-cyclohexyl-2-(3-methylphenyl)-1,3-thiazolidin-4-one (**k**) (69%); m.p. 64-68 °C; cm^{-1} 1666.8 (C=O); ^1H NMR (CDCl_3): 7.22-7.07 (4H, m, aromatics), 5.59 (1H, d, C2, $J=2.0$ Hz), 3.88 (1H, dd, C5, $J=1.8$ Hz and $J=15.4$ Hz), 3.80 (1H, m, NCH), 3.56 (1H, d, C5, $J=15.2$ Hz), 2.34 (3H, s, CH_3), 1.76-0.94 (10H, m, cyclohexyls). ^{13}C NMR:

171.99 (C4), 158.75, 141.17, 139.07, 129.82, 129.13, 126.94, 123.44, 62.74 (C2), 56.31, 33.46 (C5), 31.23, 30.33, 26.23, 25.57, 21.85; (m/z) 275 (M⁺), C₁₆H₂₁NOS (275.41).

3-cyclohexyl-2-(4-methoxyphenyl)-3-1,3-thiazolidin-4-one (**l**) (43%); oil; cm⁻¹ 1664.4(C=O); ¹H NMR (CDCl₃): 7.17-6.79 (4H, m, aromatics), 5.55 (1H, d, C2, J = 2.0 Hz), 3.81 (1H, dd, C5, J=2.0 Hz and J=15.4 Hz), 3.70 (1H, tt, NCH), 3.52 (1H, dd, C5, J = 15.6 Hz), 3.74 (3 H, s, OCH₃), 1.68-0.84 (10H, m, cyclohexyls). ¹³C NMR: 171.82 (C4), 159.27, 133.94, 127.17, 113.63, 61.84 (C2), 55.42, 54.81, 32.65 (C5), 30.27, 29.33, 25.39, 24.67; (m/z) 291 (M⁺), C₁₆H₂₁NO₂S (291.41).

3-cyclohexyl-2-(3-methoxyphenyl)-1,3-thiazolidin-4-one (**m**) (73%); m.p. 100-101 °C; cm⁻¹ 1666.4 (C=O); ¹H NMR (CDCl₃): 7.22-6.74 (4H, m, aromatics), 5.53 (1H, d, C2, J = 2.0 Hz), 3.82 (1H, dd, C5, J=2.0 Hz and J=15.6 Hz), 3.76 (1H, tt, NCH), 3.50 (1H, d, CH₂, J = 16.0 Hz), 3.74 (3H, s, OCH₃), 1.23-0.81 (10H, m, cyclohexyls). ¹³C NMR: 172.00 (C4), 160.31, 144.82, 130.36, 118.62, 114.22, 112.06, 62.76 (C2), 56.34, 55.67, 32.43 (C5), 31.20, 30.31, 26.23, 24.57; (m/z) 291 (M⁺), C₁₆H₂₁NO₂S (291.41).

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