E and *Z* Conformations of Esters, Thiol Esters, and Amides

Diwakar M. Pawar, Abdelnaser A. Khalil, Denise R. Hooks, Kenneth Collins, Tijuana Elliott, Jefforey Stafford, Lucille Smith, and Eric A. Noe*

Contribution from the Department of Chemistry, Jackson State University, Jackson, Mississippi 39217-0510

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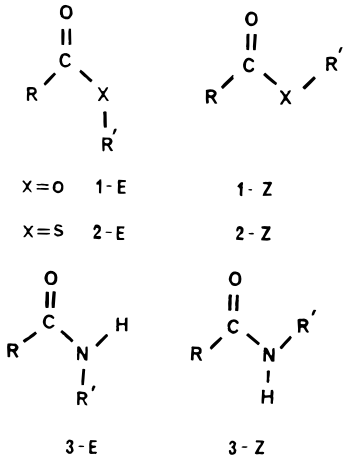
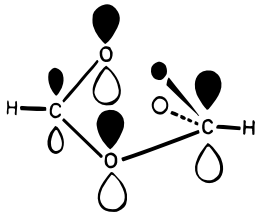
Abstract: Populations and free-energy differences for the *E* and *Z* conformations of *S*-methyl, cyclopropyl, isopropyl, and cyclopentyl thioformate were determined by low-temperature ^{1}H NMR spectroscopy, and free-energy barriers of 10.63 and 11.84 kcal/mol were obtained for interconversion of *E* and *Z* conformations of *S*-methyl thioformate at −52.4 °C. Populations and free-energy differences were also determined at room temperature by using ^{13}C NMR for a series of N-substituted formamides and *N*-cyclopropylacetamide in 1% solutions in CD_2Cl_2/CH_2Cl_2. In both sets of compounds, electron-withdrawing groups attached to sulfur or nitrogen appear to favor the *E* conformations. The electronegativities of the groups are taken to increase in the order methyl < vinyl ∼ phenyl ∼ cyclopropyl < hydrogen < ethynyl. Data from the literature are discussed in these terms, including the *E*−*Z* energy differences for formic acid and its ethynyl, vinyl, and methyl esters.

The amide and ester groups are of fundamental importance in biological systems and in organic chemistry. The general preference[1] of esters and related compounds for the *Z* conformation can be partially understood in terms of steric interactions when R is large, as repulsion between R and R′ should



destabilize the *E* conformation, particularly when R′ is also large. Steric effects are reversed for esters of formic acid because the formyl hydrogen is smaller than the carbonyl oxygen. This is shown[2] by the *E*−*Z* free-energy differences for methyl, ethyl, isopropyl, and *tert*-butyl formate in 50:50 acetone-d_6−DMF (2.15, 1.67, 1.36, and 0.48 kcal/mol). Although the *Z* conformation is favored in each case, the formate esters with larger groups have increasing amounts of the *E* conformation. Steric interactions should favor the *E* isomer for methyl formate, but the population of this conformation at −83 °C in a favorable solvent[2] is only 0.3%. It has been recognized for some time[3,4] that the *E* isomers of esters are destabilized by dipole−dipole interactions, as indicated by the dipole moments of formic acid (*E*, 3.79 D; *Z*, 1.420 D),[5] and this effect undoubtedly accounts for a large part of the preference of esters for the *Z* conformation. A detailed NMR study of the effects of solvent polarity and temperature on the *E*−*Z* conformational equilibria of *tert*-butyl formate has been reported.[6] The effect of solvent on the *E*−*Z* energy difference has also been calculated by using reaction field theory and the spherical cavity approximation.[7] For methyl formate, the free-energy difference was reduced from 5.16 kcal/mol in the gas phase to 1.66 kcal/mol for a dielectric constant of 35.9 (acetonitrile). The difference for methyl acetate was similarly reduced from 8.51 to 5.24 kcal/mol.

Other effects have been proposed to contribute to the *E*−*Z* energy differences of esters, and two of those will be mentioned here. "Aromaticity" has been suggested[8] to stabilize the *Z* conformations; for example, in (*Z*)-methyl formate, the carbonyl π bond, an "ether" oxygen lone-pair, and a π-type orbital of the methyl group would each contribute two electrons to the aromatic sextet, as shown below. Another effect suggested[9] to contribute to the preference for the *Z* conformation in esters is



a dominant hyperconjugative interaction between an "ether"

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oxygen lone pair and σ^* of the carbonyl group, which is maximized in the antiperiplanar arrangement of these orbitals.

Some observations indicate that factors other than steric interactions may be important for determining the relative populations of *E* isomers for different esters. For example, high-level *ab initio* calculations indicate[4] that the gas-phase $E-Z$ energy difference is about 1 kcal/mol higher in methyl formate than in formic acid, although the relative sizes of the acidic hydrogen and methyl group should change the energy differences in the opposite direction. Amides in solution show a similar, though less pronounced, preference for the *Z* conformation, and *N*-methylformamide has 11.1% of the *E* isomer in dilute solution in CH_2Cl_2. Again, steric interactions should favor the *E* conformation. Cyclic, intermolecular hydrogen bonding in amides, even in dilute solutions,[10] is a possible complication and could favor the *E* conformation of formamides, as discussed later in greater detail.

We have used dynamic NMR spectroscopy to study the possibility that esters, thiol acids, and thiol esters, with groups such as vinyl, phenyl, or hydrogen, which could not provide a pair of electrons to complete an "aromatic" sextet in the *Z* conformations, would have enhanced populations of the *E* isomers. The conformational equilibria for *S*-phenyl thioformate,[11] phenyl formate,[12] vinyl formate,[13] thioacetic acid,[14] and dithioacetic acid[15] could be rationalized in terms of an effect of this type. The ethynyl group also could not support an aromatic sextet in the *Z* conformation, and an $E-Z$ energy difference of only 1.7 kcal/mol was estimated[16] for ethynyl formate by ab initio calculations. This difference is lower than expected, based on the small size of the ethynyl group, and suggests that an explanation other than aromaticity may be responsible for the larger amounts of *E* conformations in compounds with R′ as vinyl, phenyl, hydrogen, or ethynyl. In the present work, the $E-Z$ free-energy difference was determined for methyl thioformate and was found to be larger than that for thioformic acid.[17] Also, a cyclopropyl group attached to sulfur or nitrogen was found to give a larger amount of the *E* conformation for thioformate esters or amides than for other simple secondary alkyl groups. The electron-withdrawing ability of R′ is proposed to affect the *E/Z* ratio of **1**, **2**, and **3**, in addition to the known steric effects.

Experimental Section

Amides. The following substituted formamides were purchased from the indicated vendors: *N*-methyl and *N*-phenyl, Aldrich Chemical Co.; *N*-ethyl and *N*-*tert*-butyl, Fluka Chemica; *N*-propyl, Chemica Alta, Ltd., Edmonton, Alberta, Canada; *N*-isopropyl, Dixon Fine Chemicals, Canada. A pure sample of *N*-vinylformamide was provided by Air Products and Chemicals, Inc. *N*-Cyclopropyl, *N*-cyclobutyl, and *N*-cyclopentylformamide were synthesized by refluxing a mixture of ethyl formate and the corresponding amine,[18] and purified by distillation. *N*-Cyclopropylacetamide was prepared by treatment of *S*-ethyl thioacetate with cyclopropylamine, followed by distillation, recrystallization from hexane, and preparative gas chromatography, using a 1/4″ x 4′ column containing 20% DC 200 on 80/100 mesh chromosorb P; mp 46−48 °C (lit. mp, 44−48[19a] and 54 °C[19b]). ^{13}C peaks for a 1% solution in CD_2Cl_2/CH_2Cl_2 at δ 171.49, 23.26, 22.90, and 6.57 were assigned to the *Z* isomer, and the smaller peaks from the *E* conformation were observed at δ 175.08, 24.66, 21.28, and 8.35. The *E* conformations of amides generally absorb at higher frequency in the carbonyl region of the ^{13}C spectra than the *Z* conformations.[20]

Alkyl Thioformates. *S*-Cyclopropyl thioformate was prepared from cyclopropyl mercaptan[21] and formic anhydride.[22] ^1H NMR spectrum (acetone-d_6): δ 10.41 (s, formyl H), δ 2.28 (m, ring CH), δ 1.13 (m, 2H), δ 0.650 (m, 2H). ^{13}C NMR: δ 192.21 (C═O), 8.93 (CH), 7.69 (CH_2). The ^{13}C and ^1H shifts for *S*-cyclopropyl thioformate are similar to those for the corresponding positions in *S*-cyclopropyl thioacetate,[21] except that the CH and CH_3 ^{13}C shifts of the thioacetate have apparently been transposed.[23] The spectra of *S*-cyclopropyl thioformate show traces of other peaks, which probably account for the slightly elevated carbon in the C,H analysis: calculated for C_4H_6OS: C, 47.03; H, 5.92. Found: C, 47.63; H, 6.34. The other thioformate esters were prepared from the mercaptan and a mixture of formic acid and acetic anhydride.[24,25] *S*-Methyl thioformate retained a small amount of *S*-methyl thioacetate after several distillations.

^{13}C and ^1H NMR spectra were recorded on a General Electric GN-300 wide-bore NMR spectrometer, operating at a frequency of 75.58 MHz for carbons and 300.52 MHz for protons. ^{13}C spectra of amides were taken, using a 20 mm probe, for dilute solutions in 50:50 CH_2Cl_2/CD_2Cl_2 (1% v/v except for formanilide and *N*-cyclopropylacetamide, which were 1 wt %/v). T_1 was estimated for each amide by the inversion−recovery method. A tip angle of 83° and a pulse-repetition period of at least 4.5 T_1 (11−30 s) were used for the amides. Other parameters were as follows: sweep width, ±19000 Hz; line broadening, 3 Hz; data size, 64K; number of acquisitions, 5000 ± 1000.

Spectra of *S*-cyclopropyl thioformate were taken for an 8% solution in acetone-d_6, and concentrations for the other thioformate esters were 15%. A 5 mm probe was used, with a pulse width and tip angle of 4.2 μs and 45° for ^1H and 5.0 μs and 45° for carbon. A pulse-repetition period of 8 s was used for both ^1H and ^{13}C spectra. The data size was 64K, and the number of acquisitions was 150 ± 50 for ^1H and 350 ± 50 for ^{13}C. Temperatures were measured with a copper−constantan thermocouple, as described previously.[26] Rate constants and populations of 6% and 94% for *S*-methyl thioformate at coalescence were determined by comparison of calculated and experimental spectra on the monitor of the NMR spectrometer. Program GEMXCH, a part of the spectrometer's operating system, GEM, was used for the calculated spectra. The rate constants and temperature were used in the Eyring equation to obtain the free-energy barriers.

Results and Discussion

The influence of different groups R′ in **1** on the conformational equilibria will be a combination of the steric effects noted earlier and any electronic effects. A plot of the $E-Z$ energy differences for formic acid and several of its esters versus the axial−equatorial free-energy differences for cyclohexanes substituted by R′ gave a straight line when *tert*-butyl was not included, and a similar plot versus another measure of steric size also gave a straight line when phenyl was excluded.[27]

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Table 1. *E*−*Z* Energy Differences for Formic Acid and Some Esters

compd	energy diff (kcal/mol)	solvent or phase	method	ref
methyl formate	6.03[a]	*b*	MP3/6-31G**//6-31G*	*c*
vinyl formate	4.7[a]	*b*	MP2/6-31G*//6-31G*	*d*
formic acid	5.48[a]	*b*	MP3/6-31G**//6-31G*	*c*
ethynyl formate	1.7[a]	*b*	MP3/6-31G*//6-31G*	*d*
methyl formate	5.59[a]	*b*	MP3/6-311+G**//6-31G*	*c*
formic acid	4.61[a]	*b*	MP3/6-311+G**//6-31G*	*c*
methyl formate	5.16[e]	*b*	MP2/6-31+G**//6-31G*	*f*
methyl formate	1.66[e]	*g*	MP2/6-31+G**//6-31G*	*f*
methyl formate	2.15[e]	*h*	dynamic NMR	*i*
formic acid	3.90	*b*	microwave	*j*
vinyl formate	0.95[e]	*k*	dynamic NMR	*l*
phenyl formate	0.43[e]	*k*	dynamic NMR	*m*
phenyl formate	0.60[e]	*n*	dynamic NMR	*o*
tert-butyl formate	0.48[e]	*h*	dynamic NMR	*i*
tert-butyl formate	0.57[e]	*k*	dynamic NMR	*m*

[a] Electronic energies from ab initio calculations. [b] Gas phase. [c] Reference 4. [d] Reference 16. [e] Free-energy difference. [f] Reference 7. [g] Calculated for a dielectric constant of 35.9 (acetonitrile). [h] 1:1 acetone-d_6 and DMF. [i] Reference 2. [j] Reference 5. [k] 3:1 acetaldehyde/acetone. [l] Reference 13. [m] Reference 12. [n] 1:1:2 CD_2Cl_2/$CBrF_2CHClF$/CF_2Cl_2. [o] Reference 27.

Table 2. Axial−Equatorial Free-Energy Differences for Several Substituted Cyclohexanes

group	$\Delta G°$ (kcal/mol)	ref
tert-butyl	4.7[a]	28
phenyl	2.7	29
isopropyl	2.21	30
ethyl	1.79	28
methyl	1.74	31
vinyl	1.49	32
ethynyl	0.41	33

[a] $\Delta H°$, from molecular mechanics.

Several *E*−*Z* energy differences are summarized in Table 1, and axial−equatorial energy differences for substituted cyclohexanes are listed in Table 2. The authors concluded[27] that differences in the *E*/*Z* ratios were caused by steric interactions, with no significant contribution from any electronic effects. However, the graphs use energy differences determined in the gas phase (for formic acid),[5] in a 1:1 mixture of acetone-d_6 and DMF (methyl, ethyl, isopropyl, and *tert*-butyl formate),[2] and in a second, less-polar solvent consisting of a 1:1:2 mixture of CD_2Cl_2, $CBrF_2CHClF$, and CF_2Cl_2 (phenyl formate).[27] As described earlier, the free-energy differences for the *E* and *Z* conformations of methyl formate were calculated[7] to be 5.16 and 1.66 kcal/mol in the gas phase and for a solution in acetonitrile ($\epsilon = 35.90$), respectively. The dielectric constants of acetone and DMF at 24 °C are 21.0 and 26.4 D[34] (av, 23.7 D), and will be higher at the slow-exchange temperature used by Grindley.[2] Similarly, the free-energy difference of 0.60 kcal/mol for phenyl formate[27] in the graph will be too high for comparison with the values for methyl, ethyl, isopropyl, and *tert*-butyl esters. The value of 0.43 kcal/mol reported[12] for phenyl formate in 3:1 acetaldehyde/acetone-d_6 demonstrates the importance of dielectric constant for this compound, and in the more-polar acetone-d_6/DMF mixture used by Grindley,[2] the difference could be expected to be even smaller. The *E*−*Z* energy differences used[27] for formic acid and phenyl formate are clearly too high, and the graphs actually demonstrate the existence of a significant electronic effect that favors the *E* conformations when R in **1** is hydrogen and R′ is hydrogen or phenyl.

Table 3. Populations and Free-Energy Differences for Thioformic Acid and Esters, HCOSR

R	solvent	temp (°C)	P_E[a] (%)	$\Delta G°$ (kcal/mol)	ref
hydrogen	*b*	−113	52.5	−0.03	17
methyl	*b*	−81.2	1 0.6	1.57	this work
methyl	*c*	−86.0	3.0	1.29	this work
methyl	*d*	−84.8	3.1	1.29	this work
cyclopropyl	*c*	−96.1	29.3	0.31	this work
isopropyl	*c*	−96.9	6.5	0.93	this work
cyclopentyl	*c*	−96.3	7.1	0.90	this work
tert-butyl	*c*	−105	18	0.51	36
phenyl	*e*	−104	40	0.13	11

[a] Populations of the *E* isomers, determined by integration of proton NMR spectra. [b] CD_2Cl_2. [c] Acetone-d_6. [d] 1:1 DMF and acetone-d_6. [e] 2:1 $CHClF_2$/$CHCl_2F$.

Allinger et al.[35] have surveyed the experimental work on the *E*−*Z* energy differences in formic acid and methyl formate, and the parameters chosen for their MM3 force field give these differences as 3.98 and 4.75 kcal/mol, respectively. In thiol acids and thiol esters, the differences in energy are generally smaller for the two conformations than for the corresponding carboxylic acids and esters, but the effects of changing R′ appear to be qualitatively similar in **2** and **1**. Thioacetic acid was shown[14] to have 25% of the *E* conformation, and the population of this conformation of thioformic acid[17] in CD_2Cl_2 was later reported to be 52.5%, corresponding to a free-energy difference of −0.03 kcal/mol (Table 3). The formyl hydrogen signal at higher frequency was assigned[17] to the *E* conformation, which is consistent with our results for thioformate esters; on the basis of the solvent dependence of the conformational equilibria for *S*-methyl thioformate and *S*-*tert*-butyl thioformate, the chemical shifts of the formyl hydrogens and carbonyl carbons are both at higher frequency for the *E* isomers. In a later study[37] of thioformic acid, proton chemical shifts were assigned incorrectly to *E* and *Z* conformations.

An *E*−*Z* free-energy difference of 1.57 kcal/mol was determined in this work by dynamic NMR spectroscopy for *S*-methyl thioformate in CD_2Cl_2. As expected, the difference is larger for this thiol ester than for the thiol acid. The series *S*-cyclopropyl thioformate (29.3% *E* in acetone-d_6), *S*-isopropyl thioformate (6.5% *E*), and *S*-cyclopentyl thioformate (7.1% *E*) shows the effect of a cyclopropyl group in enhancing the populations of the *E* isomers. The free-energy barriers determined for interconversion of *E* and *Z* conformations of *S*-methyl thioformate in acetone-d_6 solution (10.63 and 11.84 kcal/mol at −52.4 °C) are somewhat larger than the values reported for methyl formate in 1:1 acetone-d_6/DMF (7.97 and 9.93 kcal/mol at −53 °C).[2]

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Table 4. Populations and Free-Energy Differences for N-Substituted Formamides, HCONHR, at Room Temperature

R	P_E[a] (%)	$\Delta G°$ (kcal/mol)	temp (°C)
methyl	11.1	1.22	21.4
vinyl	32.7	0.42	21.4
ethyl	16.8	0.93	20.8
propyl	17.0	0.93	21.3
cyclopropyl	35.3	0.35	21.0
isopropyl	19.5	0.83	21.7
cyclopentyl	19.9	0.81	21.2
cyclobutyl	24.6	0.65	22.5
phenyl	44.1	0.14	21.4
tert-butyl	42.6	0.17	21.6

[a] Determined by integration of the ^{13}C carbonyl carbon signals; the high-frequency signal was assigned to the *E* isomer.[20] Solutions were 1% v/v in CH_2Cl_2/CD_2Cl_2 except for formanilide, which was 1% w/v.

The conformations of formamides also suggest an electronic effect of the R′ group in **3** on the conformational equilibria. Several NMR studies of conformational equilibria in secondary amides have been published,[18,20,38] but neat liquids or concentrated solutions have generally been used, and the *E/Z* ratios can be sensitive to concentrations. Populations of (*E*)-formanilide were shown[38e] by NMR to increase from 27% to 55% as the concentrations of $CDCl_3$ solutions were decreased form 52.5 to 1.5 mol %. A detailed IR and dipole-moment study[10] of formanilide in carbon tetrachloride at various concentrations showed that polymeric hydrogen bonding decreased at lower concentrations, but hydrogen bonding in cyclic dimers of the *E* conformation persisted at much lower concentrations. At a concentration of 0.008 M, the *Z* conformation of formanilide was found to be favored by 0.620 ± 0.06 kcal/mol by measuring the intensity ratios for the N−H stretching bands of the monomers for a series of temperatures. A gas-phase study of formanilide using vibrationally resolved electronic spectra obtained by resonant two-photon ionization in a supersonic jet expansion concluded[39] that the population of the *E* conformation was only 6.5% at +100 °C, corresponding to an energy difference of 2.5 kcal/mol for the two conformations at this temperature. On the other hand, a microwave study[40] of *N*-*tert*-butylformamide indicated that the *Z* conformation was favored by about 0.24 kcal/mol in the gas phase, which is close to the value found by us in an NMR study of a 1% solution in CD_2Cl_2 (Table 4). It should be noted that hydrogen bonding, particularly for the cyclic dimer, may occur at the concentrations of 1% v/v or w/v used to collect the data of Table 4,[10] and if this occurs, populations of the *E* isomers could be enhanced for the amides. The trends observed by changing R′ in **3** may still be useful.

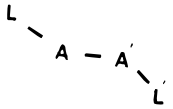
A comparison of *N*-cyclopropyl, *N*-isopropyl, and *N*-cyclopentylformamides (35.3, 19.5, and 19.9% *E*) indicates less stabilization of the *Z* conformation by the cyclopropyl group. Other relevant comparisons include *N*-vinyl- and *N*-ethylformamide (32.7 and 16.8% *E*) and *N*-*tert*-butylformamide and formanilide. The populations for the latter two compounds are similar (42.6 and 44.1% *E*), but the phenyl group is smaller than *tert*-butyl (Table 2).

N-substituted derivatives of acetamides generally have small populations of the *E* isomers, due to steric effects. *N*-Methylacetamide has been reported[41] to have 2.3 and 7% of this conformation for 1 M solutions in $CDCl_3$ and water, respectively. On the basis of steric interactions only, *N*-cyclopropylacetamide would be expected to have *less* of the *E* isomer than *N*-methylacetamide, but instead, the population of the *E* conformation in a 1% CD_2Cl_2/CH_2Cl_2 solution was found in this work to be much larger (15.4%). *N*-Vinylacetamide was reported[38d] to show signals only for the *Z* conformation in the ^{13}C NMR spectrum. This result was not expected, based on our spectra for *N*-cyclopropylacetamide.

From Table 1, the *E*−*Z* energy differences for formic acid esters decrease in the order R′ = methyl > vinyl > ethynyl. This is opposite the order expected from the relative sizes of the groups (Table 2), and demonstrates the importance of one or more electronic effects. The hybridization of carbon in the corresponding hydrocarbons R′H changes from sp^3 to sp^2 to sp in the series, suggesting that the electron-withdrawing abilities[42] of the groups may be important in enhancing the populations of the *E* isomers. The small *E*−*Z* energy difference for ethynyl formate[16] is particularly noteworthy; the increase in percent s character on going from sp^2 to sp is more than twice the increase resulting from a change from sp^3 to sp^2. If the electronegativity of R′ may be important in affecting the conformational equilibria in **1,** then this effect for cyclopropyl[43] and phenyl should be similar to that of vinyl, and the electronegativity of hydrogen relative to methyl, vinyl, and ethynyl is of interest.

In most organic chemistry texts, carbon is listed as having a higher electronegativity than hydrogen (e.g, C, 2.5 and H, 2.1).[44] However, evidence that the C−H bonds in methane and ethylene are polarized in the direction C^+H^- and in acetylene as C^-H^+ has been reported.[45] Thus, it is likely that electronegativity increases in the order $CH_3 < CH_2 = CH < H < HC \equiv C$. The smaller *E*−*Z* energy difference for formic acid than for methyl formate would then be related to the greater electronegativity for hydrogen than for methyl.

The electronegativities of R′ in **1** could affect the energies of conformations in several ways, including changes in the dipole moments and bond angles[46] of the compounds. For the groups considered here, changes in the hyperconjugation interactions of the OR′ bond with σ^* of RC and C═O may be important. Weinhold[47] has noted that the strongest (vicinal) bond−antibond interactions occur between A-polar bonds and L-polar antibonds. A ("axial") and L ("ligand") indicate atoms of a general A−L bond in which A lies on the rotor axis, as shown below. The A,L pair is described as "A-polar" if A is more electronegative than L and "L-polar" if L is more



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electronegative than A. A lone pair of electrons will then be an extreme example of an A-polarized "bond". In an ester, the OR′ bond will also be an A-polar bond if R′ is a simple alkyl group. As the electronegativity of R′ is increased, the bond will become less A-polar, and this will change the bond−antibond interactions involving this orbital. It is not known at this time which conformation, *E* or *Z*, will be favored by the $\sigma-\sigma^*$ interactions with σ as the OR′ bond. Electron-withdrawing groups R′ may also change the hybridization for the lone pair on the "ether" oxygen, which would affect its ability to interact with σ^* of RC and C═O.

Conclusions

Although the possibility that aromaticity may stabilize the *Z* conformations of compounds such as methyl formate is not excluded, this explanation does not predict the smaller *E*−*Z* energy difference of ethynyl formate,[16] relative to vinyl formate. In addition to known steric effects, the electronegativity of R′ in an ester RCO_2R' appears to be important, with electron-withdrawing groups favoring the *E* conformation. Electronegativity is taken to increase in the order methyl < vinyl∼ phenyl ∼ cyclopropyl < hydrogen < ethynyl. Thiol esters (**2**) and amides (**3**) also seem to be affected similarly by the electronegativity of groups on sulfur or nitrogen. Electron-withdrawing groups in **1**, **2**, and **3** could affect the *E*/*Z* ratio in several ways, some of which may not have been identified, and it is not possible at this time to determine which of these are responsible for increasing the populations of the *E* conformations. A recent book describing a new theory of chemical bonding includes a chapter titled "Why 'Crowded' Rotational Isomers End Up Being Global Minima", which is of interest in connection with the conformational preferences of these compounds. Carbon and hydrogen do not differ greatly in electronegativity, and the direction of polarity for the C−H bonds in methane and other compounds is not firmly established. In the book cited above, the C−H bond in methane is taken to be polarized in the direction C^-H^+.

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