Dynamic NMR Studies of Phenyl Formate and 2,6-Dimethylphenyl Formate

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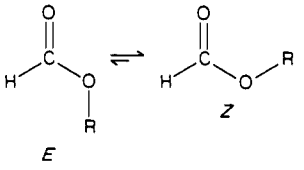
Abstract: ^{13}C NMR spectra of phenyl formate in acetaldehyde/acetone solvent show separate signals at −117 °C for the *E* and *Z* conformations, with populations of 0.20 and 0.80, respectively. The large population of the *E* isomer is attributed to the lack of aromaticity of the *Z* isomer. Free energy barriers at −98 °C of $8.1_2 \pm 0.2$ and $8.5_4 \pm 0.2$ kcal/mol were calculated for the $E \rightarrow Z$ and $Z \rightarrow E$ conversions. 2,6-Dimethylphenyl formate has a much smaller population of the *E* isomer at −100 °C ($0.03_5 \pm 0.01$), and the free energy barriers are higher ($9.4_9 \pm 0.2$ and $10.6_3 \pm 0.2$ kcal/mol at −64 °C).

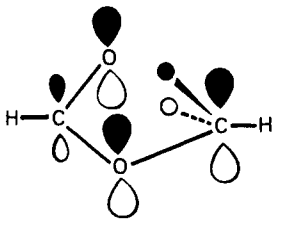
The planar *Z* conformation is strongly preferred over the *E* conformation by most esters,[1] as illustrated by methyl formate, which has only 0.3% of the *E* isomer at −83 °C in DMF/acetone-d_6 solvent.[2] This preference is not due to steric interactions, which in alkyl formates (but not acetates or higher esters) should actually favor the *E* isomers. Because the *E*–*Z* energy differences are generally smaller for formates than for other esters, the five compounds for which the conformational equilibria have been studied by dynamic NMR spectroscopy have all been esters of formic acid (methyl,[2] ethyl,[2] isopropyl,[2] *tert*-butyl,[2-5] and 1,1-diethylpropyl[5] formates).[6] The *Z* isomers predominate in each of these cases, but the free energy differences for methyl formate (2.2 kcal/mol)[2] and *tert*-butyl formate (**1**, 0.48 kcal/mol)[2] demonstrate the increases in the populations of *E* isomers that occur with bulky R groups, as a consequence of increased steric interactions in the *Z* conformations.



E *Z*

1, R = $(CH_3)_3C$
2, R = C_6H_5
3, R = 2,6-$(CH_3)_2C_6H_3$

Three factors are probably responsible for the large preference of methyl formate for the *Z* conformation: (1) Dipole–dipole interactions in the *Z* isomer are more favorable than in the *E* isomer, as indicated by the dipole moments of (*E*)- and (*Z*)-formic acid.[7] (2) Interaction of an "ether" oxygen lone pair with σ^* of the carbonyl group of the *Z* conformation may stabilize this conformation.[8] (3) The *Z* isomer has a cyclic, "aromatic" system of six electrons, with two electrons each coming from the carbonyl group, the "ether" oxygen, and the methyl group,[9] as shown in I. A similar aromatic system is not possible for the *E* isomer.



I

Unlike methyl and other alkyl groups, phenyl groups cannot complete an aromatic sextet, and we have found a large population (0.40)[10] for the *E* conformation of phenyl thiolformate at −104 °C. Recent calculations[11] for phenyl formate (**2**) predict that the minimum-energy conformation has the phenyl group rotated about 60° out of plane ($\theta = 60°$), and from the six-bond coupling constants between the carbonyl carbons and the fluorines in several esters of *p*-fluorophenol, the authors also found a large deviation from planarity ($\langle\theta\rangle \sim 55°$). According to the STO-3G MO calculations,[11] the most stable *Z* conformation of phenyl formate is 2.12 kcal/mol lower in energy than the *E* isomer, with a *Z*-to-*E* barrier of 7.4 kcal/mol. However, the calculations are for the gas phase, and the energy difference should be lower in solution.[12] We have found[10] that phenyl thiolformate has a larger population of the *E* isomer than *tert*-butyl thiolformate, and a similar situation exists for formanilide[13] and *N*-*tert*-butylformamide.[14] The free energy difference[2] of only 0.48 kcal/mol for (*E*)- and (*Z*)-*tert*-butyl formate in DMF/acetone-d_6 suggested that a dynamic NMR study of phenyl formate should be possible, provided that the temperature required for slow exchange was not too low.

Oxygen-17 NMR provides a sensitive probe of conjugation, with electron donation by X in RCOX causing an upfield shift of the carbonyl oxygen[15] (chemical shifts for acetaldehyde and *N*,*N*-dimethylacetamide are δ 596 and 342). We have found shifts of δ 372.2 and 362.3 for the carbonyl oxygens of phenyl formate and methyl formate,[15b,16] and the small downfield shift of the phenyl ester suggested that the barriers for the two compounds should

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Table I. Slow-Exchange ^{13}C Chemical Shifts (δ)[a] for Formate Esters 1-3

	C=O		O—C		O—C—C	
ester	E	Z	E	Z	E	Z
1	164.53	161.82	80.13	81.26	28.60	27.63
2[b]	163.46	161.44	152.15	150.21	121.18	122.71
3[c]	164.15	160.47	148.89	147.88	131.40	130.67

[a] At −116 °C for 1 and −117 °C for 2 and 3. [b] Chemical shifts for meta carbons are as follows: E, 130.95; Z = 130.55. [c] The meta and para carbons also show splitting by −117 °C. Meta: E, 129.75; Z, 129.43. Para: E, 127.61; Z, 127.04.

not be greatly different.[17] We report here the results of dynamic NMR studies of phenyl formate and 2,6-dimethylphenyl formate (3). For comparison, *tert*-butyl formate was also studied in the same solvent system.

Experimental Section

Formate esters 2 and 3 were prepared from formic acid, acetic anhydride, sodium formate, and phenol or 2,6-dimethylphenol.[19-21] The carboxylic acids and anhydrides were removed at the end of the reactions by *low-temperature* (ice) extraction with aqueous sodium bicarbonate solution. The phenyl formate (but not 3) appeared to contain several percent of the corresponding acetate, as reported.[21]

Carbon-13 NMR spectra were taken on a General Electric GN-300 NMR spectrometer operating unlocked at 75.57 MHz. Temperatures were measured by replacing the sample with an NMR tube containing solvent and a copper–constantan thermocouple. The coalescence temperature for C-1 of 2 did not change observably when the decoupler was turned off, indicating that the decoupler could be turned off for the thermocouple emf measurements without altering the temperatures. The accuracy of the thermocouple was checked by measuring the temperature of a pentane slush obtained by adding liquid nitrogen to pentane. Concentrations of 20% by volume in acetaldehyde/acetone (3:1, v:v) were used.

Spectra were taken with a 5-mm probe, and the signal-to-noise ratio was improved by exponential multiplication of the FID, resulting in a line broadening of 3 Hz. Populations at slow exchange were determined by electronic integration, and the populations at coalescence were calculated with the assumption that $\Delta G°$ is independent of temperature. Rate constants at coalescence were determined by comparison of the experimental spectra with calculated line shapes,[22] and the corresponding barriers were obtained from the Eyring equation.

Results and Discussion

Esters 2 and 3 showed coalescence for the carbonyl carbon and at least three of the other carbons, and the chemical shifts are summarized in Table I, along with those for *tert*-butyl formate. The downfield carbonyl signal for each compound is assigned to the *E* isomer, as has been observed previously for formate esters.[2,5] The population of the *E* isomer is higher for phenyl formate than for *tert*-butyl formate in the same solvent, in agreement with the results for the corresponding thiol esters and N-substituted formamides. The barriers for 2 are only slightly lower than 1, in keeping with the small difference in ^{17}O carbonyl chemical shifts for phenyl formate and methyl formate, as discussed above.

The rotational barriers for phenyl thiolformate (9.9 and 10.1 kcal/mol) are higher than for *tert*-butyl thiolformate (9.0 and 9.6 kcal/mol), and we have suggested[10] that the phenyl group in the former compound is twisted out of the plane of the HCO group and may be perpendicular to the rest of the molecule; in this conformation, little or no electron donation by the sulfur to the benzene ring is expected. However, for oxygen attached to a benzene ring, conjugation appears to be significant, even for large torsional angles, as found in molecular orbital calculations for phenol.[23] Also, $\sigma_R°$ of OCH_3 twisted 90° out of plane has been estimated as −0.23,[24] which is more than half the value for the planar conformation (−0.43),[18] and $\sigma_R°$ for the acetoxy group has been reported to be −0.24.[18] The lower barriers for 2 in comparison to the values for 1 are then expected to be a consequence of cross conjugation in 2 of the "ether" oxygen with the phenyl group.

Table II. Populations, Ground-State Free Energy Differences, Coalescence Temperatures, and Free Energy Barriers for Formate Esters 1-3

ester	P_E[a]	$\Delta G°$,[b] kcal/mol	T_c,[c] °C	$\Delta G^{\ddagger}_{Z\to E}$,[c] kcal/mol	$\Delta G^{\ddagger}_{E\to Z}$,[c] kcal/mol
1	0.14	0.57	−86	$9.0_9 \pm 0.2$	$8.5_2 \pm 0.2$
2	0.20	0.43	−98	$8.5_4 \pm 0.2$	$8.1_2 \pm 0.2$
3	0.03_5	1.14	−64	$10.6_3 \pm 0.2$	$9.4_9 \pm 0.2$

[a] Populations of the *E* isomers at −116 °C (1), −117 °C (2), or −100 °C (3). [b] Ground-state free energy differences for *E* and *Z* conformations at −116 °C (1), −117 °C (2), or −100 °C (3). [c] The coalescence temperatures and free energy barriers were determined from the carbonyl carbon signals for 1 and 3 and the peaks of C-1 of the ring for 2.

Nakanishi et al.[5] have taken low-temperature ^{13}C spectra of 2,6-dimethylphenyl formate (3) as a 10% solution by volume in dimethyl ether (60%), carbon disulfide (25%), and acetone-d_6 (5%), but no splitting of the signals was observed to −133 °C, although some line broadening was reported for the carbonyl carbon. The authors concluded that the coalescence temperature was below −133 °C and suggested that the barriers for 3 are considerably lower than for 1. However, we have found that coalescence occurs at −64 °C for 3, and the barriers are actually higher than for 1 or 2 (Table II).

The population of the *E* isomer is only 0.03_5 at −100 °C in acetaldehyde/acetone solvent, and probably the population would be even lower in the less polar solvent mixture used by Nakanishi et al.;[5] as a consequence, the authors failed to observe coalescence, and the broadening at lower temperatures was caused by the increasing viscosity of the sample.

Molecular mechanics calculations indicate[16] that replacement of the ortho hydrogens of phenyl acetate by methyl groups results in an increase in the torsional angle from 64° to 73°. The effects of the out-of-plane methyl groups of 3 in changing the conformational properties of 2 have a parallel in the results[25,26] for acetanilide and 2,4,6-trialkylacetanilides. Acetanilide has a population of the *Z* isomer of greater than 99%, apparently as the consequence of a larger steric interaction in the *E* conformation between the phenyl and methyl groups than occurs in the *Z* conformation between the carbonyl oxygen and the phenyl group. The 2,4,6-trialkylacetanilides have larger populations of the *E* isomers, with the percentages of this conformation increasing for the larger alkyl groups, up to 45% for *tert*-butyl. Similarly, substitution of the ortho hydrogens of 2 by methyl groups causes a shift in 3 to the conformation in which the larger group (carbonyl oxygen) is closer to the aromatic ring. The amide rotational barriers for the trialkylacetanilides increase as the ortho substituents become larger, and the barriers for 2 and 3 show a comparable increase with ortho substitution of methyl groups for hydrogens.

$\Delta H°$ and $\Delta S°$ for the $E \to Z$ conversion at −100 °C have been estimated[5] for 1 (1.22 ± 0.09 kcal/mol and 1.8 ± 0.3 eu) and for 1,1-diethylpropyl formate (0.76 ± 0.09 kcal/mol and 0.1 ± 0.3 eu), but the enthalpy and entropy contributions to the free energy differences have not been determined for the other alkyl and aryl formates. True and co-workers[27,28] obtained $\Delta H°$ and $\Delta S°$ for a series of alkyl nitrites, in both the gas phase and solution, and

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showed that $\Delta S°$ favors the E conformation for most of the compounds, including methyl nitrite and the primary nitrites. The higher entropy of (E)-methyl nitrite ($\Delta S°$ = 1.6 eu)[28] is related to the lower methyl top barrier of this conformation (29 cal/mol[29a] vs 1912 cal/mol[29b] for the Z isomer) and contributes −0.28 kcal/mol to $\Delta G°$ at −100 °C. The methyl rotational barrier of (Z)-methyl formate (1.19 kcal/mol)[30] is lower than the barrier for this conformation of methyl nitrite (1.91 kcal/mol),[29b] but the E conformation of methyl formate may also be stabilized by a favorable $\Delta S°$ term resulting from a lower methyl top barrier. The calculated barrier of 0.23 kcal/mol[11] for rotation of the phenyl group of (Z)-**2** through 90° is smaller than the corresponding barrier of 0.72 kcal/mol for the E isomer and suggests that the Z conformation may be favored by $\Delta S°$ in this case.

Conclusions

The large population (0.20) of the E isomer of phenyl formate is evidence for a significant contribution of "aromaticity" to the stabilization of the Z conformation of most esters. Because the Z conformation still predominates, other factors must also be important in determining the conformations of these compounds, as discussed above. "Aromaticity" is expected to have an important influence on the conformational equilibria in many related compounds, including secondary amides, alkyl nitrites,[31] and alkyl vinyl ethers.

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Registry No. Phenyl formate, 1864-94-4; 2,6-dimethylphenyl formate, 1865-00-5.

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A Comparative Study of the Kinetics of Selenol/Diselenide and Thiol/Disulfide Exchange Reactions

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Abstract: The kinetics of symmetrical selenol/diselenide and thiol/disulfide exchange reactions involving selenocysteamine/selenocystamine and cysteamine/cystamine have been studied in D_2O solution by NMR spectroscopy. The rate of selenol/diselenide exchange is so fast that resonances for the selenol and diselenide forms are coalesced in ^1H NMR spectra of millimolar selenocysteamine/selenocystamine mixtures at pD >2–3. In contrast, the rate of thiol/disulfide exchange is so slow that separate, sharp resonances are observed for both cysteamine and cystamine in mixtures at concentrations up to at least 0.2 M from pD <1 to >13. Rate constants for the selenol/diselenide exchange reaction were determined by line shape analysis of exchange-broadened resonances, while those for thiol/disulfide exchange were determined by an inversion-transfer method. The rate constants at 25 °C for exchange by reaction of $D_3N^+CH_2CH_2X^-$ with $D_3N^+CH_2CH_2XXCH_2CH_2ND_3^+$ are as follows: X = Se, $k = 1.65 \times 10^7$ L/mol·s; X = S, $k = 68.0$ L/mol·s. When the differences in the acidities of the selenol and thiol groups are accounted for, selenocysteamine/selenocystamine exchange is 1.2×10^7 times faster than cysteamine/cystamine exchange at physiological pH.

Selenium in the form of selenocysteine residues is an essential component of glycine reductase, certain formate dehydrogenases, and a hydrogenase of bacterial origin and of glutathione peroxidase in mammals and birds. Of these, glutathione peroxidase is the most studied.[1-3] Glutathione peroxidase catalyzes the reduction of hydroperoxides by glutathione by a mechanism thought to involve first the oxidation of the selenium and then its reduction, all by a sequence of nucleophilic displacement reactions.[2,3] In these reactions, the selenium, in its various oxidation states, is either the nucleophile, the central atom, or the leaving group, depending on the step in the catalytic cycle. Although the proposed mechanism is consistent with experimental results, it has not been proven. For example, it has not yet been possible to determine unequivocally the oxidation state of selenium in the various oxidized forms of glutathione peroxidase.[4]

As part of a project to characterize the chemistry of selenium in glutathione peroxidase, we have initiated a study of the kinetics and equilibria of nucleophilic displacement reactions involving model organoselenium compounds. In this paper, we report the results of a study of the kinetics of the selenol/diselenide exchange reaction

$$R^*SeH + RSeSeR \rightleftarrows R^*SeSeR + RSeH \qquad (1)$$

where R is $H_3N^+CH_2CH_2^-$ and the asterisk serves to label otherwise identical R groups. We also report the results of a study of the thiol/disulfide exchange reaction of the analogous sulfur compounds for comparison. Rate constants were determined for

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