Tetrahedron Letters, Vol.31, No.33, pp 4685-4688, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A New NMR Technique for Measuring the Ground State Populations of Formate Esters: Polar Aprotic Solvents Favor the s-cis (*E*)-Isomer of *t*-Butyl Formate

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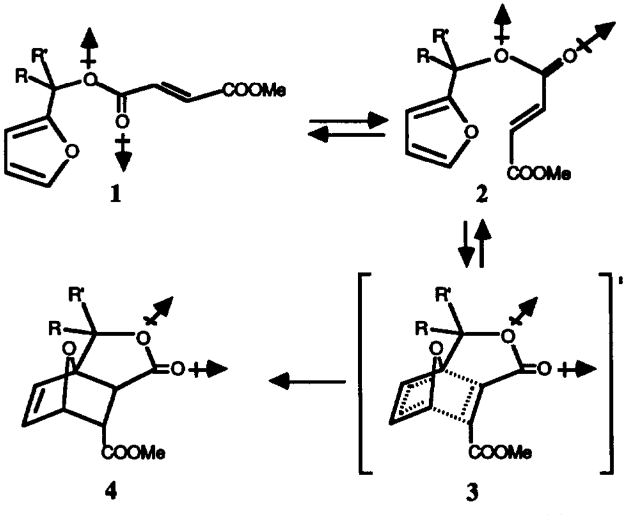
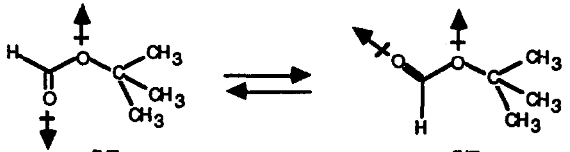
Abstract: A new NMR technique for measuring the conformational population of *t*-butyl formate in a rapidly equilibrating mixture ($^3J_{CH}$ averaging) has been developed and used to show that polar aprotic solvents favor the *E*-isomer.

Recently we reported[2] a dramatic and synthetically quite useful solvent effect on the rate of the intramolecular Diels-Alder cycloaddition of substituted furfuryl methyl fumarates **1**. Polar solvents increased the rate of cyclization significantly, e.g., the ratio of the rates of cyclization of the dihydrido compound **1** (R=R'=H) in DMSO vs. toluene at 25° C is 3200. We attributed this effect to the fact that due to dipole overlap, the transition state **3** is more polar than the s-trans or *Z* ground state ester conformation **1** and thus polar solvents would be expected to lower the energy of activation and thereby increase the rate. We now report the use of a new NMR technique which shows that this polar effect applies to ground state conformations as well, namely, that polar solvents stabilize the less stable but more polar s-cis or *E* ground state ester conformation such as **2**. By proper choice of polar solvent, as much as 33% of the less stable s-cis or *E* conformation can be present in equilibrium at 25° C.



Most esters exist almost completely in the s-trans or *Z* conformation with little or none of the s-cis or *E* conformation present at room temperature ($\Delta G° > 4$ kcal/mole).[3] The most common explanations for this preference for the Z conformation are dipole-dipole interactions,[4] lone pair-σ^* interactions,[5] and aromatic stabilization.[6] Bulky alkyl formates, e.g., *t*-butyl formate **5**, generally have the highest percentage of the *E* isomer because the steric interaction of the *t*-butyl group with the carbonyl oxygen is greater than that with the formyl hydrogen and thus this steric interaction mitigates the preference for the *Z* isomer due to dipole interactions. For example, Ōki and Nakanishi reported that the ^1H NMR spectrum of a 50% solution of 5 in dimethylformamide (DMF) at -94° C showed two singlets (at 8.0 and 8.9 ppm, respectively) due to the *Z* and *E* isomers in a ratio of 86:14.[7] We reasoned that since the *E* isomer is more polar than the Z due to dipole overlap,[7] this isomer should be favored in polar solvents and therefore its percentage should increase. This is indeed the case!



5Z 5E

However, since the free energy of activation for the Z to *E* isomerization is only about 9-11 kcal/mole,[8] a method had to be developed to study this equilibrium in certain polar solvents that could not be cooled to the very low temperatures (ca.-100° C) where the equilibrium is slow enough for the individual isomers to be seen. Drakenberg and Forsén[9] had published a method based on a 5-bond coupling between the formyl and methyl hydrogens of 5 at 60 MHz, in which they made several assumptions in order to estimate the $^5J_{HH}$ for each isomer. Their indirectly estimated values were $^5J_{trans} = 0.42$ Hz and $^5J_{cis} = 0.11$ Hz. We had trouble in obtaining well-split spectra at very low temperatures where the $^5J_{HH}$ could be measured experimentally for each isomer and therefore decided to develop a new technique to determine the percentages of both isomers at higher temperatures. We expected that the 3-bond coupling between the formyl hydrogen and the quaternary *t*-butyl carbon, $^3J_{CH}$ would be significantly different in each isomer and therefore could be used in a *J* averaging method to determine the isomeric composition.[10] The 125 MHz ^{13}C NMR spectrum of a 10% solution of *t*-butyl formate 5 in several solvents at temperatures of -100° C to -122° C[11] (with selective decoupling of the singlet due to the methyls of the *t*-butyl group) showed a large downfield doublet for the Z isomer in all solvents and a much smaller upfield signal for the *E* isomer. This upfield peak could be resolved into a clean doublet in only two solvent mixtures, dimethyl ether/10% acetone-d_6 at -111° C and acetaldehyde/10% acetone-d_6 at -121° C (the acetone-d_6 was added for a deuterium lock). From these spectra, the measured coupling constants were Z isomer, $J = 4.4$ Hz; *E* isomer, $J = 1.3$ Hz. Integration of the absorptions in the ^{13}C spectra gave the isomeric composition shown in **Table 1**. As expected, as the polarity of the solvent is increased from carbon disulfide and toluene to acetone and DMF, the percentage of the more polar *E* isomer increases (from ~ 0 to 17%). It is reassuring to note that the percentages derived from the ^{13}C integration for the sample in DMF-d_7 matches well those calculated by Ōki and Nakanishi[7] by the ^1H integration (83:17 vs. 86:14). A variable temperature study was carried

Table 1: Isomeric Composition of *t*-Butyl Formate 5 at Low Temperature[a]

Solvent	Temperature	% Z	% E
DMF-d_7	-100°C	83	17
Acetone-d_6	-95°C	86	14
Acetaldehyde + 10% Acetone-d_6	-121°C	87	13
Dimethyl ether + 10% Acetone-d_6	-111°C	95	5
Ethanol + 10% Acetone-d_6	-101°C	95	5
Tetrahydrofuran-d_8	-122°C	96	4
Toluene-d_8	-106°C	~ 100	~ 0
Carbon disulfide + 10% CD_2Cl_2	-100°C	~ 100	~ 0

a) A 10% solution of 5 in the indicated solvent was used in all cases except DMF where a 50% solution was used (in order to be able to cool to -100° C without freezing).

out in several solvents and the $^3J_{CH}$ for the single peak observed for the ethereal carbon measured carefully in each. The percentage of the *E* isomer of **5**, calculated by the *J* averaging method, is given in **Table 2** along with the dielectric constant ε and E_T parameter for each solvent (the solvents are listed in order of decreasing dielectric constant). Inspection of the results at 24° C shows that with the exception of the protic solvents, ethanol and *N*-methylformamide (NMF), the population of the *E* isomer increases linearly with dielectric constant (and with E_T except also for DMSO, which seems to be more polar than its E_T value would indicate).[12] Thus, as predicted, as the polarity of the solvent increases, the percentage of the more polar conformation increases. The ground state free energy difference at 24° C for the *Z* to *E* equilibration is given in **Table 3**. Examination of the numbers in **Tables 1** and **2** for various solvents shows that, in general, the percentage of the minor *E* isomer first increases and then decreases with increasing temperature. The initial increase is readily explained since one would normally expect that the percentage of the minor isomer of an equilibrium would be increased at higher temperatures. However, here an additional effect is operative, namely that the polarity of solvents (especially very polar solvents) decreases with increasing temperature.[13] Therefore at higher temperatures, the solvent is less polar, the stabilization of the polar *E* isomer is lessened and its percentage decreases. The crossover point for these two opposing effects differs depending on the solvent but in nearly all cases an initial increase and then a decrease in the percentage of the *E*-isomer is seen. For aprotic solvents, then, the effect is clear: higher polarity causes a higher percentage of the *E* isomer.

Table 2: Percentage of *E* isomer of t-Butyl Formate 5 with Changes in Solvent[a]

Solvent	-25°C	24°C	77°C	110°C	$\varepsilon_{25°}$[b]	E_T[c]	E_T[b]
NMF + 10% Acetone-d_6	16.0	6.0	~ 0	~ 0	166.2	-----	52.9
DMSO-d_6	-----	32.9	31.6	25.5	48.9	45.0	45.0
CD_3CN	30.0	27.4	28.7	-----	37.5	47.5	46.0
DMF-d_7	31.9	26.4	26.4	19.4	36.7	43.7	43.8
Ethanol	6.5	16.1	-----	-----	24.3	51.2	51.9
Acetone-d_6	23.5	21.0	-----	-----	20.5	42.0	42.2
CCl_4 + 20% $CDCl_3$	14.6	-----	-----	-----	2.72	37.8	33.8
Toluene-d_8	11.6	12.3	11.0	8.4	2.38	35.7	33.9

a) A 10% solution of **5** in the indicated solvent was used.

b) The dielectric constants and reported E_T values for the pure solvents are from reference 12. The values for the mixtures were calculated by using a weighted average.

c) The E_T values were obtained by dissolving Reichardt's dye in the actual sample used for the NMR study and recording the UV absorbance.

Table 3: *Z* to *E* Equilibration of *t*-Butyl Formate 5 at 24° C

Solvent	% E Isomer	K_{eq}	$\Delta G°_{297}$ (kcal/mole)
DMSO-d_6	32.9	0.49	0.42
CD_3CN	27.4	0.38	0.58
DMF-d_7	26.4	0.36	0.61
Acetone-d_6	21.0	0.27	0.78
Toluene-d_8	12.3	0.14	1.17

However, at this time, we have no explanation for the very low percentages of the *E* isomer in the very polar protic solvents ethanol and NMF. With these solvents, one would expect other factors such as hydrogen bonding to be important.[14] However, recent theoretical calculations[15] (Monte Carlo simulations on ester stability in protic solvents) show clearly that the *E* isomer would be expected to be stabilized to a greater degree by hydrogen bonding than the *Z* isomer and thus one would predict more, not less, of the more polar *E* isomer in these solvents. Further studies, both experimental and theoretical, are underway to try to explain this discrepancy.

In summary, for the first time the $^3J_{CH}$ of the *Z* and *E* conformers of *t*-butyl formate **5** have been determined and used to calculate the isomeric composition of **5** in various solvents at different temperatures. Polar aprotic solvents cause an increase in the percentage of the minor more polar *E* isomer to a maximum of 33% in DMSO at 24° C.

Acknowledgement: We thank the National Institutes of Health (GM-31349) for financial support and Frank Anet, Ken Houk, Jane Strouse, Nazim Jaffer, Dan O'Leary, Jeff Evanseck, and Julie Bartley, all at UCLA, for helpful advice and discussions. We thank Prof. Jay Siegel of UC San Diego for pointing out an earlier use of $^3J_{CH}$ for the conformational analysis of acetaldehyde and its oxime *O*-methyl ether by Karabatsos and coworkers.[16]

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10. We assume here that the coupling constant for both isomers is both solvent- and temperature-independent. Our measured values for J_{trans} in several solvents at -100 to -121° C was more sensitive to the shimming of the NMR instrument than anything else and varied less than 10% in all experiments, so that we think these assumptions are fair. The usual *J* averaging method was used: $J_{obs} = J_E \rho_E + J_Z \rho_Z$, where ρ_X = mole fraction of x isomer.
11. Special precautions had to be taken to reach these temperatures. It was necessary to rigorously exclude water, to use new, high quality NMR tubes to avoid complications from uneven spinning or scratches on the inside wall of the tube, and to very gradually reduce the temperatures below -70° C.
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14. One factor affecting this discrepancy is the fact that in a hydrogen bonding solvent the $^3J_{CH}$ may change significantly since the effective hybridization of the carbonyl carbon is altered. Therefore the application of the *J* averaging method to the results in NMF, for example, would have to be modified to utilize the actual coupling constants, which we cannot measure in this system due to the freezing point of NMF (-40° C).
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(Received in USA 23 May 1990)