# Conformational Analysis of Organic Carbonyl Compounds. Part 4.[1-3] A $^{1}H$ and $^{13}C$ Nuclear Magnetic Resonance Study of Formyl and Acetyl Derivatives of Benzo[*b*]furan

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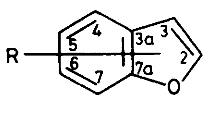
A conformational study of formyl and acetyl derivatives of benzo[*b*]furan provides evidence that in the case of 2- and 7-derivatives the *E,Z*-conformational mixture is solvent dependent, the *Z*-form prevailing in solvents with higher polarity. The presence of the same substituents in the 3- and 4-position gives compounds with predominantly *Z*-conformation and no change is caused by solvents. These results show an interestingly different behaviour by carbonyl derivatives of benzo[*b*]furan with respect to the same benzo[*b*]thiophene derivatives. The conformational analysis was carried out by the n.m.r. method by employing $^{1}H$ and $^{13}C$ chemical shifts, long-range proton–proton coupling constants, and lanthanide-induced shifts (LIS) simulation. For the derivatives substituted in position 7, the LIS method is not a suitable approach for the determination of conformer populations since, in solution, a chelate is formed where bonding of Eu to the oxygen atoms of the carbonyl and of the heterocyclic ring stabilizes the *Z*-form. A quantitative approach for determining the relative conformer populations of benzo[*b*]furan-7-carbaldehyde was set up by statistical manipulation of long-range proton–proton coupling constants, proton chemical shifts, and the classical theory of dielectrics.

Several studies have so far been reported[1-4] concerning the energy barrier restricting internal rotation and the relative conformer stability of the carbonyl derivatives, formyl and acetyl, of unsaturated, aromatic, and heteroaromatic compounds. In these conformational studies the answers given by both $^{1}H$ and $^{13}C$ n.m.r. spectroscopy have revealed the most exhaustive experimental approach to the problem. From variable-temperature experiments, direct information on energy barriers and conformer populations are obtained, while an indirect estimate of the latter quantities may sometimes be gained through the employment of chemical shifts and spin–spin coupling constants. In addition, the lanthanide-induced shift (LIS) method,[5-8] widely accepted as a reliable method for determining the relative isomer population in the case of the fast internal rotation (on the n.m.r. time scale), may often be employed.

In previous papers[1-3] we have reported studies on the practical applicability of MO semi-empirical and *ab initio* methods in the predictions of energy barriers and relative isomer stability[1] and on the conformational analysis of a number of derivatives of condensed hydrocarbons[2] and of benzo[*b*]thiophene.[3] In these latter derivatives[3] the preferred conformation both of the acetyl and formyl groups is of the *Z*-type, representing, for the 4- and 2-substituted compounds, situations respectively close to that of $\alpha$-naphthalene derivatives and 2-substituted thiophenes, while for the 7-carbonyl derivatives the conformation predominates where the carbonyl oxygen faces the heterocyclic sulphur atom. The presence of these conformations seems to be determined mostly by the mesomeric interaction originating in the *trans*-arrangement of the C=O bond and the C=C bond having the higher double bond character. In principle, the same situation should apply also for the formyl and acetyl derivatives of benzo[*b*]furan, if other effects are not operating, such as interaction between the oxygen atom of the carbonyl group and that of the heterocyclic ring which could influence the conformation of 2- and 7-carbonyl substituted derivatives. For 2-substituted carbonyl derivatives of furan it is known[9,10] that the two planar conformations exist in almost equimolecular amounts with a tendency to increase the *Z*-conformer population in polar solvents.[11]

We have thus undertaken a study on derivatives (**1**)—(**4**) with the aim of analysing the conformational properties of the formyl and acetyl groups in the benzo[*b*]furan system. The conformational analysis of these molecules was carried out by employing their $^{1}H$ and $^{13}C$ chemical shifts, long-range proton–proton coupling constants, the LIS method, and the classical theory of dielectrics.[12] For a quantitative estimate of conformer populations a critical comparison between the results obtained from the employment of the different experimental and empirical approaches was also performed.



(**1a**) R = 2–CHO (**1b**) R = 2–MeCO
(**2a**) R = 3–CHO (**2b**) R = 3–MeCO
(**3a**) R = 4–CHO (**3b**) R = 4–MeCO
(**4a**) R = 7–CHO (**4b**) R = 7–MeCO

## Results and Discussion

The $^{1}H$ chemical shifts ($\delta$ values) and proton–proton coupling constants (Hz), obtained by analysing the experimental spectra with the use of the LAOCOON 3 program,[13] are reported in Table 1. $^{13}C$ Chemical shifts ($\delta$ values) are collected in Table 2. These data refer to [$^{2}H$]chloroform solutions. In the $^{1}H$ n.m.r. spectra the inter-ring coupling constants $J_{26}$, $J_{37}$, and $J_{24}$ were measured, and, of these, $J_{37}$ was reported previously.[14-18] $J_{37}$ and $J_{24}$ show the highest and smallest values and involve a coupling mechanism over five bonds: these constants were also measured for benzo[*b*]thiophene derivatives[18] where they show slightly smaller values. The $J_{26}$ coupling constant, which is close to the values measured in benzo[*b*]thiophene derivatives,[18,19] extends over six bonds. The remaining coupling constants are in the range of those reported for the unsubstituted molecule.[14,15] A long-range coupling constant involving the formyl proton and one of the ring protons was measured only in compound (**4a**) and the ring proton is 5-H. This coupling constant over five bonds should account for a zig-zag path coupling mechanism and amounts[2] to 0.4—0.5 Hz for the *E*-conformer of the $\alpha$-formyl derivative of naphthalene; it also indicates that a consistent amount of this conformer should be present even in compound (**4a**). This long-range coupling

**Table 1.** $^1$H Chemical shifts (δ values) and proton–proton coupling constants (Hz) in formyl and acetyl derivatives of benzo[*b*]furan (in [$^2$H]chloroform solution)

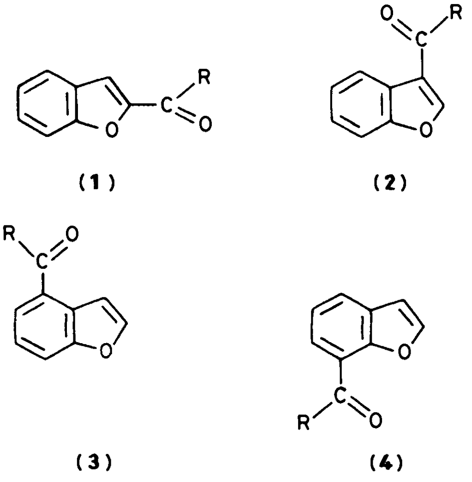
| Compound | 2-H | 3-H | 4-H | 5-H | 6-H | 7-H | CHO or $CH_3$ | $J_{23}$ | $J_{24}$ | $J_{26}$ | $J_{37}$ | $J_{45}$ | $J_{46}$ | $J_{47}$ | $J_{56}$ | $J_{57}$ | $J_{67}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **(1a)** | | 7.56 | 7.74 | 7.34 | 7.51 | 7.60 | 9.86 | | | | 1.078 | 7.979 | 1.256 | 0.708 | 7.206 | 0.838 | 8.492 |
| **(2a)** | 8.02 | | 8.19 | 7.39 | 7.41 | 7.55 | 10.17 | | | 0.303 | | 7.710 | 1.404 | 0.716 | 7.317 | 0.878 | 8.414 |
| **(3a)** | 7.79 | 7.51 | | 7.72 | 7.44 | 7.74 | 10.19 | 2.157 | | 0.406 | 0.962 | | | | 7.455 | 0.913 | 8.235 |
| **(4a)** | 7.77 | 6.86 | 7.86 | 7.38[a] | 7.79 | | 10.43 | 2.255 | 0.273 | 0.391 | | 7.715 | 1.290 | | 7.592 | | |
| **(1b)** | | 7.49 | 7.70 | 7.30 | 7.47 | 7.57 | 2.60 | | | | 0.921 | 7.925 | 1.248 | 0.792 | 7.211 | 0.851 | 8.464 |
| **(2b)** | 8.23 | | 8.23 | 7.36 | 7.37 | 7.52 | 2.55 | | | | | 8.090 | 1.103 | 0.771 | 7.239 | 1.194 | 8.168 |
| **(3b)** | 7.74 | 7.53 | | 7.79 | 7.34 | 7.68 | 2.67 | 2.171 | | 0.365 | 0.960 | | | | 7.677 | 0.862 | 8.196 |
| **(4b)** | 7.74 | 6.85 | 7.80 | 7.32 | 7.90 | | 2.84 | 2.227 | 0.200 | 0.354 | | 7.622 | 1.265 | | 7.680 | | |
| Benzo[*b*]furan[b] | 7.52 | 6.66 | 7.49 | 7.14 | 7.20 | 7.42 | | 2.1 | | | 0.8 | 7.8 | 1.2 | 0.8 | 7.2 | 0.9 | 8.4 |

[a] This proton shows a coupling constant of 0.414 Hz with the formyl proton. [b] Ref. 14: $CCl_4$ solution.

**Table 2.** $^{13}$C Chemical shifts (δ values) in formyl and acetyl derivatives of benzo[*b*]furan ([$^2$H]chloroform solution)

| Compound | $\delta_2$ | $\delta_3$ | $\delta_4$ | $\delta_5$ | $\delta_6$ | $\delta_7$ | $\delta_{3a}$ | $\delta_{7a}$ | $\delta_{C=O}$ | $\delta_{CH_3}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **(1a)** | 152.69 | 117.70 | 123.64 | 124.18 | 129.18 | 112.68 | 126.64 | 156.23 | 179.69 | |
| **(2a)** | 155.94 | 123.69 | 122.57 | 124.83 | 126.24 | 111.64 | 122.91 | 155.94 | 184.70 | |
| **(3a)** | 147.93 | 106.66 | 129.45 | 128.72 | 123.93 | 117.14 | 126.18 | 155.40 | 191.89 | |
| **(4a)** | 146.30 | 106.40 | 127.69 | 122.99 | 126.27 | 121.26 | 129.14 | 153.70 | 188.89 | |
| **(1b)** | 152.56 | 113.07 | 123.27 | 123.87 | 128.24 | 112.39 | 127.00 | 155.60 | 188.54 | 26.40 |
| **(2b)** | 151.19 | 122.65 | 122.87 | 124.51 | 125.60 | 111.44 | 124.16 | 155.65 | 192.88 | 28.06 |
| **(3b)** | 147.23 | 108.02 | 130.23 | 125.16 | 123.51 | 116.15 | 126.69 | 155.49 | 198.36 | 27.52 |
| **(4b)** | 145.44 | 106.65 | 126.47 | 122.78 | 125.32 | 122.37 | 129.00 | 153.20 | 196.24 | 30.69 |
| Benzo[*b*]furan[a] | 144.8 | 106.50 | 121.15 | 122.70 | 124.25 | 111.45 | 127.45 | 155.0 | | |

[a] Ref. 20: [$^2$H]chloroform solution.



**Scheme.** *Z*-Forms of the molecule examined (R = H, Me)

constant was not detected in derivative (**3a**), an indication in favour of a higher amount of *Z*-conformer in the case of this derivative.

Preliminary qualitative conclusions on conformer populations in derivatives (**1**)—(**4**) may also be reached by examining the $^1$H and $^{13}$C chemical shifts. The carbonyl substituents in the 2-position cause a low-field shift on 3-H of the same order of magnitude as those observed in the corresponding substituted furans;[11,14] for the 3-substituted derivatives this occurs only in the case of the formyl substituent, while the acetyl group causes a higher low-field shift on 2-H in benzo[*b*]furan than in furan. This is also found for the corresponding heterocycles[3] containing the sulphur atom and should probably reflect a larger amount of the *Z*-conformer in the condensed heterocycle or, alternatively, differences in the geometrical structure of the condensed rings. In the 3-substituted carbonyl derivatives even the low-field shift of 4-H with respect to the unsubstituted benzo[*b*]furan, of the order of 0.7 p.p.m., indicates that the oxygen atom of the carbonyl group should be preferentially directed toward this proton, in comparison also to the results obtained for the corresponding derivatives of benzo[*b*]thiophene.[3] When the carbonyl group is in position 4, compounds (**3a** and **b**), the low-field shift with respect to the unsubstituted compound is higher for 3-H (0.8—0.9 p.p.m.) than for 5-H (0.6 p.p.m.), and these results, compared with those relative to benzo[*b*]thiophene derivatives[3] and α-naphthalene derivatives,[2] indicate that the *Z*-conformer should be the most populated, even for compounds (**3a** and **b**). Less defined conclusions may be obtained from the low-field shift of 6-H in compounds (**4a** and **b**) with respect to the unsubstituted compound since they amount to 0.6 and 0.7 p.p.m., respectively, and in comparison with the results obtained for the corresponding benzo[*b*]thiophene derivatives[3] could indicate a predominant *Z*-conformer. This result is not in line with the conclusions reached from the long-range proton–proton coupling constant $^5J$(5-H, C*H*O) which indicates a prevailing *E*-conformer. Furthermore, the chemical shift of the methyl protons in compound (**4b**) is at lower field than in derivative (**3b**), while in the 4- and 7-acetyl derivatives of benzo[*b*]thiophene[3] having a preferred *Z*-conformation, these protons have very close chemical shift values (δ 2.72 and 2.75).

From the behaviour of the $^{13}$C chemical shifts these conclusions are confirmed from a qualitative point of view. In fact for C-3a a high-field shift is observed in derivatives (**2a**), (**3a**), (**2b**), and (**3b**), relative to benzo[*b*]furan[20] ($\Delta\delta_C$), in agreement with the results of the corresponding benzo[*b*]thiophene derivatives[3] and their preferred *Z*-type conformation. For the derivatives (**4a** and **b**) a high field shift $\Delta\delta_C$ is observed for C-7a, a result which is parallel, but quantitatively smaller with respect to that found in the corresponding derivatives of benzo[*b*]thiophene, which have a prevailing *Z*-type conformation.

**Table 3.** Experimental and calculated (in parentheses) LIS values, molecular geometry parameters of the complexes, and relative amounts of conformational isomers in formyl and acetyl derivatives of benzo[*b*]furan

| | | | | | | | | MOLA computer program[a] | | | | | LIRAS-3 computer program[b] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | 2-H | 3-H | 4-H | 5-H | 6-H | 7-H | CHO–CH$_3$ | *K* | φ(°) | ω(°) | A.F. | % *Z*-conformation | *R* | *r*(Å) | φ(°) | ψ(°) | Pop. | *f* | % *Z*-conformation |
| **(1a)** | | 4.37 | 1.38 | 0.93 | 0.99 | 1.98 | 9.30 | 848.55 | 25 | 50 | 0.008 52 | 88 | 0.021— | 2.8— | 45— | 125— | 100 | 784— | 90 |
| | | (4.38) | (1.36) | (0.90) | (1.00) | (1.99) | | | | | | | 0.022 | 3.05 | 50 | 130 | | 864 | |
| **(2a)** | 5.76 | | 13.31 | 2.71 | 2.19 | 2.68 | 17.28 | 1 108.77 | 45 | 10 | 0.011 | 100 | 0.015 | 3.0 | 75 | 135 | 100 | 1 117 | 100 |
| | (5.76) | | (13.30) | (2.86) | (2.13) | (2.63) | | | | | | | | | | | | | |
| **(3a)** | 2.63 | 13.31 | | 6.31 | 2.95 | 2.68 | 16.39 | 1 040.28 | 40 | 30 | 0.003 | 94 | 0.008 | 2.90 | 60 | 120 | 95 | 1 275 | 100 |
| | (2.60) | (13.32) | | (6.31) | (2.97) | (2.65) | | | | | | | | | | | | | |
| **(4a)** | 4.79 | 2.73 | 2.74 | 3.41 | 8.36 | | 9.76 | | | | | | | | | | | | |
| **(1b)** | | 8.47 | 1.57 | 0.99 | 1.08 | 2.30 | 11.23 | 1 570.72 | 0 | 50 | 0.010 | 59 | | | | | | | |
| | | (8.46) | (1.63) | (0.92) | (1.06) | (2.32) | | | | | | | | | | | | | |
| **(2b)** | 6.67 | | 12.09 | 1.04 | 1.52 | 2.32 | 12.97 | 1 100.03 | 65 | 0 | 0.007 | 100 | | | | | | | |
| | (6.68) | | (12.10) | (1.07) | (1.42) | (2.29) | | | | | | | | | | | | | |
| **(3b)** | 1.80 | 16.44 | | 8.71 | 3.64 | 3.06 | 15.86 | 1 313.49 | 45 | 50 | 0.007 | 89 | | | | | | | |
| | (1.94) | (16.44) | | (8.70) | (3.66) | (3.01) | | | | | | | | | | | | | |
| **(4b)** | 5.61 | 2.94 | 2.71 | 2.97 | 8.98 | | 8.82 | | | | | | | | | | | | |

[a] For the symbolism see ref. 6. [b] For the symbolism see ref. 23.

For benzo[*b*]furan-2-carbaldehyde the differences in chemical shift induced by the formyl substituent with respect to the unsubstituted derivative ($\Delta\delta_{2\text{-C}}$ and $\Delta\delta_{3\text{-C}}$) are of the same order of magnitude as those produced by this substituent on furan,[21] and this may be assumed to be a further indication that a similar conformational situation of the formyl group is present in both systems.[*]

More quantitative results on the conformational properties of the formyl and acetyl groups in compounds (**1**)—(**4**) may be obtained by applying the LIS method to the compounds. Analysis of the experimental results was performed by employing the McConnell–Robertson[22] equation and assuming the lanthanide–substrate interaction to be of a predominantly dipolar nature. Equimolecular 1:1 lanthanide–substrate complexes were considered and both the MOLA[6] and LIRAS-3[23] computer programs were employed. The complex was considered to have axial symmetry and a constant geometry was maintained in the different conformers. In the MOLA approach the one-site model for complexation was adopted and the population ratio was determined according to Montaudo and his co-workers.[7] The procedure and the symbols employed for describing the molecular geometry parameters are collected in a previous paper of this series.[3] In the approach contained in the LIRAS-3 computer program[23] the two-site model is introduced while the use of any normalising atom is also avoided.

The molecular geometry of the benzo[*b*]furan ring was obtained[24a] from those of naphthalene and furan, while for the formyl and acetyl groups the following bond distances were employed: C=O, 1.22; C–H, 1.085; C–C(exocyclic), 1.485; C–C($H_3$), 1.515 Å; the bond angles were chosen to be perfectly trigonal. The formyl proton and the methyl group were excluded from LIS simulation since their $\Delta\delta_{\text{lim.}}$ are affected by contact contributions.

The experimental $\Delta\delta_{\text{lim.}}$ referring to the protons of compounds (**1**)—(**4**), the pseudo-contact constant *K*, the molecular geometry parameters of the complexes, and relative amounts of the conformers are reported in Table 3. According to the MOLA symbolism,[6] φ and ω are the molecular geometry parameters of the complexes, and A.F. the Hamilton agreement factor, while in the LIRAS-3 convention[23] *R* is the agreement factor, *r*(Å) the La–O distance,[†] φ and ψ the molecular geometry parameters of the complexes, expressed in a different reference system with respect to the MOLA program, Pop. the *exo–endo* lanthanide population (% value) on the two-site C=O binding model, and *f* a normalising factor which minimizes the *R*-value. The two approaches were applied to the conformational analysis of the compounds only in the case of formyl derivatives (**1a**)—(**3a**), while for the remaining derivatives only the MOLA procedure was employed. The two models provide equivalent results since only one oxygen lone-pair, the less hindered (*exo*) one, appears to be bonded to a lanthanide atom.

For compound (**1a**) the amount of the *Z*-conformation corresponding to the lowest A.F. value in the MOLA procedure is 88%, but considering that the minimum is rather flat and a value of the A.F. of the order of 0.01 may still be considered acceptable, the calculated amount of the *Z*-conformer ranges over 80—90%.

In the LIRAS-3 approach, applied according to the procedure described by Abraham,[23] for the agreement factor *R* the minima are found in an interval of *r* values (La–O distance) which leaves this quantity undetermined within the interval 2.8—3.05 Å: the corresponding intervals of definition of the φ, ψ, and *f* parameters are also reported in Table 3. Within the range of variation of the above quantities, the % of *Z*-stereoisomer is almost unchanged and amounts to 90%. The conformational composition of benzo[*b*]furan-2-carbaldehyde is thus very similar to that of the corresponding furan derivative,[10,23,26,27] confirming that conclusions advanced on a qualitative ground on the basis of $^1H$ and $^{13}C$ chemical shifts.

Even for the 2-acetylbenzo[*b*]furan, compound (**1b**), the conformer population found from the LIS study is similar to that of the corresponding derivative of furan.[10,26,28–30]

For derivative (**2a**) the LIS method indicates an amount of *Z*-stereoisomer close to 100% both from the MOLA and LIRAS-3 approaches. These results show that the situation is comparable with that of furan-3-carbaldehyde[31,32] and benzo[*b*]thiophene-3-carbaldehyde[3] and the stable conformer should thus correspond to the *trans*-arrangement of the C=O and C=C bond of the heterocyclic ring. Even for compound (**2b**) the amount of *Z*-stereoisomer is close to 100%, thus showing the same behaviour by the acetyl and formyl groups when bonded in the 3-position. For derivative (**3a** and **b**) the LIS approach provides amounts of *Z*-conformer corresponding to 94 and 89%, respectively, and the results may be compared with those obtained for the corresponding derivatives of benzo[*b*]thiophene[3] and naphthalene-1-carbaldehyde.[2] In derivative (**3a**) the $^5J$ coupling constant of the formyl proton with 6-H was not observed and this is also in agreement with a high amount of the *Z*-conformer.

For compounds (**4a** and **b**) the LIS simulation shows that the *Z*-conformer should be present in amounts close to 100%. We have seen that from $^1H$ chemical shifts no conclusive information was derived, while both long-range $^5J$(5-H, C*H*O) and $^{13}C$ chemical shifts measured in chloroform solution are in line with a prevailing *E*-type conformation.

Considering the relative positions of the oxygen atoms in the *Z*-conformer it seems reasonable to suppose that the Eu atom stabilizes the conformation in which it is bonded to both the oxygen atoms. In fact the calculated $\Delta\delta_{\text{lim.}}$ for compounds (**4a** and **b**) differ consistently from the experimental values as may be expected from the fact that complexation to two sites of the same molecule is not in line with the model employed for LIS simulation.

In the case of compounds (**4a** and **b**) the lanthanide atom seems thus to change the conformer equilibrium in solution as a consequence of bidentate complex formation.

Further information on the conformational equilibria for the compounds here examined may be obtained from solvent effects. In Table 4 the $^1H$ chemical shifts in different solvents are reported for compoumds (**1a** and **b**) and (**4a** and **b**): for these derivatives only are significant changes in conformer populations expected as a function of the polarity of the solvent.

For compound (**1a**) the chemical shifts of the formyl proton in different solvents show behaviour parallel to that of the same proton in 2-formylfuran[27] and, quantitatively, they are reproduced quite satisfactorily by a linear correlation. Since it has been proved[27,33–35] that the *E*/*Z* ratio for 2-formylfuran is strongly solvent dependent, the same, reasonably, should also occur in the corresponding benzo[*b*]furan derivative. Quantitative information on conformer populations in different solvents may be gained, in the case of derivative (**4a**), by

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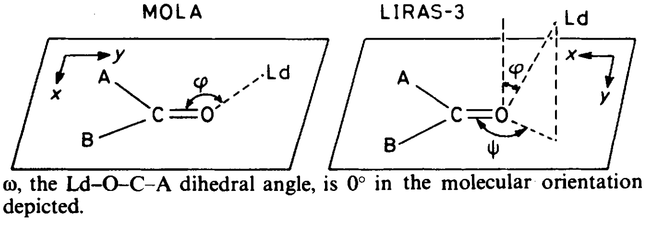
[*] The $^{13}C$ chemical shifts of the furan derivatives[21] refer to a 1,4-dioxane solution.

[†] This distance is kept fixed and assumed[25] to be 3 Å for the Eu atom in the LIS simulation with the MOLA program. The lanthanide coordinates differ in the two approaches as follows, according to different reference systems:



ω, the Ld–O–C–A dihedral angle, is 0° in the molecular orientation depicted.

**Table 4.** $^1$H Chemical shifts (δ values) for compounds (**1a** and **b**) and (**4a** and **b**) in different solvents

| Compound | Solvent | 2-H | 3-H | 4-H | 5-H | 6-H | 7-H | CHO or $CH_3$ | $J_{23}$ | $J_{24}$ | $J_{26}$ | $J_{37}$ | $J_{45}$ | $J_{46}$ | $J_{47}$ | $J_{56}$ | $J_{57}$ | $J_{67}$ | $J$(5H-CHO) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (**1a**) | $C_6D_{12}$ | | 7.32 | 7.60 | 7.20 | 7.36 | 7.45 | 9.82 | | | | 0.997 | 7.959 | 1.260 | 0.778 | 7.271 | 0.894 | 8.473 | |
| | $(CDCl_2)_2$ | | 7.60 | 7.77 | 7.37 | 7.55 | 7.62 | 9.83 | | | | 0.896 | 7.936 | 1.213 | 0.735 | 7.303 | 0.861 | 8.427 | |
| | $CD_3OD$ | | 7.73 | 7.78 | 7.33 | 7.57 | 7.57 | 9.79 | | | | 0.924 | 7.984 | 1.276 | 0.756 | 7.272 | 0.897 | 8.504 | |
| | $(CD_3)_2SO$ | | 7.95 | 7.88 | 7.38 | 7.56 | 7.72 | 9.85 | | | | 1.045 | 7.935 | 1.307 | 0.753 | 7.235 | 0.891 | 8.479 | |
| | $C_6D_6$ | | 6.75 | 7.27 | 6.97 | 7.06 | 7.21 | 9.44 | | | | 0.980 | 7.944 | 1.290 | 0.808 | 7.246 | 0.906 | 8.476 | |
| (**4a**) | $C_6D_{12}$ | 7.59 | 6.72 | 7.68 | 7.23 | 7.74 | | 10.54 | 2.233 | 0.254 | 0.414 | | 7.676 | 1.297 | | 7.621 | | | 0.677 |
| | $(CDCl_2)_2$ | 7.80 | 6.90 | 7.90 | 7.41 | 7.80 | | 10.41 | 2.201 | 0.296 | 0.399 | | 7.714 | 1.258 | | 7.593 | | | 0.412 |
| | $(CD_3)_2CO$ | 8.02 | 7.05 | 8.00 | 7.45 | 7.84 | | 10.45 | 2.150 | 0.249 | 0.416 | | 7.757 | 1.243 | | 7.579 | | | 0.477 |
| | $CD_3OD$ | 7.89 | 6.94 | 7.90 | 7.37 | 7.77 | | 10.36 | 2.260 | 0.210 | 0.410 | | 7.689 | 1.288 | | 7.620 | | | 0.457 |
| | $(CD_3)_2SO$ | 8.17 | 7.10 | 8.01 | 7.46 | 7.83 | | 10.33 | 2.250 | 0.250 | 0.405 | | 7.713 | 1.288 | | 7.612 | | | 0.337 |
| | $C_6D_6$ | 7.08 | 6.23 | 7.31 | 6.91 | 7.59 | | 10.37 | 2.226 | 0.291 | 0.388 | | 7.707 | 1.292 | | 7.589 | | | 0.507 |
| (**1b**) | $C_6D_{12}$ | | 7.29 | 7.56 | 7.18 | 7.32 | 7.42 | 2.45 | | | | 0.964 | 7.927 | 1.279 | 0.825 | 7.249 | 0.921 | 8.465 | |
| | $(CD_3)_2CO$ | | 7.71 | 7.81 | 7.35 | 7.53 | 7.62 | 2.56 | | | | 0.962 | 7.954 | 1.264 | 0.804 | 7.258 | 0.841 | 8.474 | |
| | $(CD_3)_2SO$ | | 7.88 | 7.82 | 7.35 | 7.52 | 7.69 | 2.54 | | | | 1.002 | 7.899 | 1.259 | 0.778 | 7.249 | 0.935 | 8.482 | |
| (**4b**) | $(CD_3)_2SO$ | 8.13 | 7.07 | 7.80 | 7.35 | 7.91 | | 2.73 | 2.16 | *a* | *a* | | 7.612 | 1.293 | | 7.637 | | | |
| | $C_6D_6$ | 7.01 | 6.25 | 7.34 | 6.99 | 8.08 | | 2.58 | 2.22 | 0.29 | 0.394 | | 7.690 | 1.317 | | 7.684 | | | |

$^a$ The multiplets are poorly resolved.

employing the long range $^5J$(5-H, C*H*O). This coupling constant has its maximum value for the *E*-conformer and changes as a function of the *E*/*Z*-conformer ratio, according to the equation (1). By assuming that the values of the coupling

$$J = n_EJ_E + (1 - n_E)J_Z \tag{1}$$

constants in the individual conformers are not solvent dependent[12,33,36] the *J* values should change in the different solvents as a function of conformer populations.

To solve equation (1) and obtain the molar fractions of the conformers, the $J_E$ and $J_Z$ values are needed. As regards $J_E$, this was set equal to 0.7 Hz, the value found in *o*-hydroxybenzaldehyde,[37] while $J_Z \leqslant 0.1$ Hz was assumed. An estimate from semi-empirical calculations, employing extended Hückel wave functions,[38] gives for these constants $J_E$ 0.673 and $J_Z$ −0.158 Hz, in reasonable agreement with the assumed values. The results are collected in Table 5, in column A.

$^1$H Chemical shifts may be also affected by conformer composition,[27] and in derivative (**4a**) the changes of δ(6-H) and δ(CHO) may be assumed to depend mainly on this factor. We may thus set up equation (2) containing the δ values for 6-H or

$$\delta = n_E\delta_E + (1 - n_E)\delta_Z \tag{2}$$

for the formyl proton in the individual rotamers which are almost independent of solvent (if one excludes the aromatic media) as found for the formyl porton of furfural.[27] By solving equations (1) and (2) simultaneously referring to the different solvents, the conformer populations reported in Table 5 in columns B and C were found (B refers to the chemical shifts of the formyl proton and C to those of 6-H).

From previous studies it has been evident that the conformer ratio depends[33,34,36] on solvent polarity: the conformer having higher polarity prevails in the solvents with higher dielectric constant, in the absence of specific solute–solvent interactions (aromatic solvents, hydrogen bonding, and other similar effects). The results in Table 5 columns A—C show anomalous behaviour for compound (**4a**) in halogenoalkane solvents. In these solvents the conformer populations are much higher than expected from their dielectric constants according to the classical theory of dielectrics[12] applied to the study of conformer populations. By employing the empirical procedure suggested by Abraham[12,34] and the coupling constant $^5J$(5-H, C*H*O) in the different solvents, we were able to calculate the conformer ratio in the solvents employed and in the vapour phase, by combining equations (1) and (3): in the latter equation $\Delta E^S = \Delta E^V - H$, where $\Delta E^S$ and $\Delta E^V$ are the energy differences between the isomers in the vapour (V) and any solvent (S), while

$$(1 - n_E)/n_E = \exp(-\Delta E^S/RT) \tag{3}$$

*H* is a term containing[12,34,36] functions* of the dipole and quadrupole moments of the isomers, of the dielectric constant of the solution, and of the solute polarizability. The dipole moment of the conformers, obtained from bond-moment combination, indicate that the *E*-form has higher polar character. According to the small value of the dipole moment of the benzo[*b*]furan ring, 0.79 D,[24b] the direction of the dipole moment of the whole molecule may be assumed to be very close to that of the carbonyl bond.

**Table 5.** *E*-conformer population ($n_E$) in benzo[*b*]furan-7-carbaldehyde in solvents with different dielectric constant (ε), obtained through different empirical approaches

| Solvent | ε | A | B | C | D | E |
|---|---|---|---|---|---|---|
| $C_6D_{12}$ | 2.007 | 0.961 | 0.977 | 1 | 0.982 | 0.972 |
| $CDCl_3$ | 4.632 | 0.523 | 0.495 | 0.524 | | |
| $(CDCl_2)_2$ | 8.20 | 0.520 | 0.486 | 0.494 | | |
| $(CD_3)_2CO$ | 20.22 | 0.628 | 0.609 | 0.518 | 0.695 | 0.594 |
| $CD_3OD$ | 32.63 | 0.595 | 0.553 | 0.628 | 0.607 | 0.499 |
| $(CD_3)_2SO$ | 46.60 | 0.395 | 0.337 | 0.323 | 0.532 | 0.422 |

A By employing equation (1) and $J_E$ 0.7, $J_Z$ 0.1 Hz. B By solving simultaneously equation (1) and (2), where the chemical shifts are those of the formyl proton; the following limiting values were also obtained: $\delta_E$ 10.56 ± 0.04, $\delta_Z$ 10.24 ± 0.08 p.p.m., $J_E$ 0.688 ± 0.05 Hz, $J_Z$ 0.154 ± 0.04 Hz. C With the same procedure as under B, where the chemical shifts are those of 6-H; the following limiting values were found: $\delta_E$ 7.74 ± 0.01, $\delta_Z$ 7.87 ± 0.02 p.p.m., $J_E$ 0.669 ± 0.08, $J_Z$ 0.174 ± 0.10 Hz. D With the classical theory of dielectrics and equation (1) the following limiting values were found: $J_E$ 0.692 ± 0.08, $J_Z$ 0.00 ± 0.06 Hz, $\Delta E^V$ 13.81 ± 1.84 kJ mol$^{-1}$. E With the classical theory of dielectrics and employing $J_E$ and $J_Z$ obtained under B; $\Delta E^V$ 12.73 ± 0.67 kJ mol$^{-1}$.

The results reported in Table 5 are obtained by optimizing

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* For the calculation of the *H* term[12,34,36] the following molecular constants were employed: *d*, 1.295; $n_D$, 1.6022; $V_M$, 112.74; μ, 3.241 (*E*), 4.043 (*Z*); *k*, 3.382 (*E*), 5.262 (*Z*); *h*, 9.384 (*E*), 13.685 (*Z*); *l*, 0.686.

the quantities $\Delta E^V$, $J_E$, and $J_Z$ (column D) and by employing the $J_E$ and $J_Z$ values from method B (column E). The solvents containing chlorine were excluded since they give anomalous results. The conformer populations obtained in these approaches agree with those from methods A—C. From the calculated $\Delta E^V$ it is seen that in the vapour phase the *E*-form is the prevailing one (>99%), that is, the one having the lower polar character. By increasing the polarity of the solvent, the conformer mixture acquires a progressively higher content of *Z*-form, that having higher polar character. From the best fits for obtaining conformer populations the limiting values $^5J_E$ and $^5J_Z$ are also obtained, and they are very close in the different approaches as may be seen in the footnotes of Table 5.

For the solvents examined it appears that the change of conformer ratio for derivative (**4a**) is smaller than for compound (**1a**), if one assumes that the change of conformer populations in derivative (**1a**) should be parallel to that found for furfural according to the linear dependence of the chemical shift of the formyl proton of these two molecules in the different solvents. In fact, for the 7-CHO derivative (**4a**) the amount of *E*-conformer spans the interval 98—40% with a change in the solvent polarity, while for the 2-CHO derivative, according to the results found[34] for furfural the variation should be 93—19%.

Information on the conformation of the carbonyl group in organic compounds may also be obtained from the benzene solvent effect.[10] The solvent shift $\Delta\delta$ in benzene relative to carbon tetrachloride or cyclohexane solution was shown to be negative or positive according to the relative position of the observed proton with respect to the carbonyl group; according to the empirical law of aromatic-solvent-induced shifts, the *Z*-conformer should predominate, as found in furfural.[10,27] For 6-H of compound (**4a**) a small positive $\Delta\delta$ is observed, which is less conclusive, but, in any case, should indicate that a lower amount of the *Z*-form should be present in the conformational mixture. From the behaviour of proton 6-H of compound (**4b**) in benzene solution, the $\Delta\delta$ observed is negative, a prevailing *E*-conformation should be assumed. For this compound the behaviour in the presence of reagent shifts is close to that of derivative (**4a**).

The results are thus conclusive, from different points of view, namely, that in the case of 2- and 7-carbonyl derivatives of benzo[*b*]furan a conformational situation different from that of the corresponding benzo[*b*]thiophene derivatives is present. In non-polar solvents for benzo[*b*]furan derivatives the *E*-conformer is the more stable while the *Z*-form predominates in the sulphur heterocycle. According to an empirical interpretation which accounts for the stability of *Z*-forms in benzo[*b*]thiophene derivatives[3] on the basis of mesomeric interactions generated by the *trans*-arrangement of the C=O and the shorter C=C bond in the ring, it could be argued that in the case of benzo[*b*]furan derivatives in the vapour phase or in solvents having low dielectric constant, the repulsive electrostatic interaction[34,39] between the oxygen atoms of the carbonyl group and the heterocyclic ring should overcome the mesomeric stabilizing effects. For the 7-substituted benzo[*b*]furans significant hydrogen bonding may also contribute to the stability of the *E*-conformer.

## Experimental

The n.m.r. spectra of compounds (**1**)—(**4**) were recorded in solution of the selected solvent (0.2M) at 200 MHz for $^1$H and 53.3088 MHz for $^{13}$C using a Varian XL200 spectrometer. The shift reagent employed is Eu(fod)$_3$ purified by sublimation *in vacuo* and kept in a dry atmosphere and added in known amounts to solutions of the substrate examined. All calculations were performed on a Cyber 76 CDC computer.

*Compounds*.—Benzo[*b*]furan-2-[40] and, -3-carbaldehyde[41] were prepared according to known methods.

4-*Aminobenzo*[b]*furan*. Reduction of 4-nitrobenzo[*b*]furan[42] (12 g) in methanol (150 ml) with 2 atm. hydrogen using 10% Pd–C catalyst, gave the *amino-derivative* (8.5 g, 87%), b.p. 85—86 °C at 0.3 mmHg, $n_D^{21}$ 1.6260 (Found: C, 72.1; H, 5.2; N, 10.35. $C_8H_7NO$ requires C, 72.2; H, 5.3; N, 10.5%).

*Benzo*[b]*furan*-4-*carbonitrile*. 4-Aminobenzo[*b*]furan (4 g, 0.03 mol) was diazotized[43] at 0—5 °C in dilute $H_2SO_4$ (4 ml of conc. $H_2SO_4$ in 40 ml $H_2O$). The neutralized solution was added dropwise at 40—50 °C to an aqueous solution of $Cu_2(CN)_2$. The nitrile was extracted with ether and the solvent removed to leave a yellow oil which was chromatographed on silica gel (light petroleum–diethyl ether 9:1) and crystallized from light petroleum to give *benzo*[b]*furan*-4-*carbonitrile* (2.3 g, 53%), m.p. 44—45 °C (Found: C, 75.5; H, 3.4; N, 9.6. $C_9H_5NO$ requires C, 75.5; H, 3.5; N, 9.8%).

*Benzo*[b]*furan*-4-*carbaldehyde* (**3a**). The aldehyde was obtained (80% yield) from the nitrile according to a known method[44] by employing sodium hypophosphite and Raney nickel in aqueous acetic acid–pyridine, b.p. 55—56 °C at 0.1 mmHg, $n_D^{20}$ 1.6130 (Found: C, 73.8; H, 4.0. $C_9H_6O_2$ requires C, 74.0; H, 4.1%).

2-*Methylphenoxyacetaldehyde dimethyl acetal*. A mixture of *o*-cresol (54 g, 0.5 mol) and 2-bromoacetaldehyde dimethyl acetal (84.5 g, 0.5 mol) in sodium ethoxide solution (11.5 g Na in 200 ml ethanol) was refluxed for 20 h. The solvent was evaporated and the residue was poured into water and extracted with ether. The extract was washed with 5% aqueous sodium hydroxide and evaporated. Distillation of the residue afforded 2-*methylphenoxyacetaldehyde dimethyl acetal* (61 g, 62%), b.p. 133—134 °C at 14 mmHg, $n_D^{22}$ 1.4996 (Found: C, 67.3; H, 8.0. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%).

7-*Methylbenzo*[b]*furan*. A mixture of phosphorus pentaoxide (24 g) and phosphoric acid (80 ml, 85%) was added slowly (1 h) to a solution of 2-methylphenoxyacetaldehyde dimethyl acetal (64 g) in chlorobenzene (600 ml) heated at 125—130 °C. After cooling to room temperature, the chlorobenzene layer was decanted and the inorganic layer poured into water–ice and extracted with chloroform. The chlorobenzene and chloroform layers were combined, washed with water, evaporated under reduced pressure, and the residue was distilled to give 7-methylbenzo[*b*]furan (30 g, 90%), b.p. 73 °C at 10 mmHg, $n_D^{25.5}$ 1.5583 (lit.,[16] b.p. 74 °C at 10 mmHg) (Found: C, 81.7; H, 5.9. Calc. for $C_9H_8O$: C, 81.8; H, 6.1%).

7-*Bromomethylbenzo*[b]*furan*. A solution of benzoyl peroxide (1.8 g) and 7-methylbenzo[*b*]furan (23.7 g, 0.179 mol) in dry carbon tetrachloride (560 ml) was heated to reflux while being irradiated by two 120 W electric lamps. *N*-Bromosuccinimide (32 g, 0.179 mol) was added in small portions during 20 min. The mixture was heated under reflux for an additional 8 h, cooled, and filtered from succinimide. The solvent was evaporated and the residue was distilled to give 7-*bromomethylbenzo*[b]*furan* (21.6 g, 48%), b.p. 88—90 °C at 0.9 mmHg (Found: C, 51.1; H, 3.2; Br, 37.75. $C_9H_7BrO$ requires C, 51.2; H, 3.35; Br, 37.9%).

*Benzo*[b]*furan*-7-*carbaldehyde* (**4a**). A mixture of 7-bromomethylbenzo[*b*]furan (26.8 g, 0.127 mol) and hexamethylenetetramine (35.6 g, 0.254 mol) in chloroform (350 ml) was heated to reflux for 4 h. On cooling, the crystalline hexamine salt was isolated and refluxed in aqueous acetic acid (250 ml, 50%) for 3 h. After being cooled at 0 °C, the product was extracted with chloroform. The extract was washed with 10% sodium carbonate and evaporated. The residue was distilled to afford *benzo*[b]*furan*-7-*carbaldehyde* (139 g, 70%), b.p. 75 °C at 0.5 mmHg, $n_D^{16}$ 1.6022 (Found; C, 73.9; H, 3.9. $C_9H_6O_2$ requires C, 74.0; H, 4.1%).

2-Acetylbenzo[*b*]furan (**1b**) is a commercial product from EGA Chemie, purified by crystallization from cyclohexane.

*Benzo*[b]*furan-3-carboxylic acid.* To an aqueous mixture of silver oxide (0.79 g, 0.042 mol) in water (90 ml) cooled in an ice-bath was added benzo[*b*]furan-3-carbaldehyde[41] (**2a**) (6 g, 0.041 mol) in small portions with stirring. The black silver suspension was removed by suction filtration and washed with several portions of hot water. The cold combined filtrate was acidified with conc. hydrochloric acid and the precipitate collected. Recrystallization from benzene gave *benzo*[b]*furan-3-carboxylic acid* (5 g, 75%) as prisms, m.p. 161—162 °C (lit.,[45] 162 °C) (Found: C, 66.6; H, 3.6. Calc. for $C_9H_6O_3$: C, 66.7; H, 3.7%).

Benzo[*b*]furan-7-carboxylic acid was prepared (77% yield) from benzo[*b*]furan-7-carbaldehyde (**4a**) by the procedure described for the synthesis of the above acid, m.p. 162—163 °C (from benzene) (lit.,[46] 162—163 °C) (Found: C, 66.6; H, 3.6. Calc. for $C_9H_6O_3$: C, 66.7; H, 3.7%).

3- and 7-Acetylbenzo[*b*]furan (**2b**) and (**4b**) were prepared from the corresponding carboxylic acids by employing the method for the synthesis of ketones through the diethyl acylmalonate derivatives.[47] 3-Acetylbenzo[*b*]furan (**2b**) had b.p. 85 °C at 0.3 mmHg, m.p. 35 °C (lit.,[48] b.p. 120—135 °C at 14 mmHg, m.p. 35 °C) (Found: C, 74.9; H, 4.9. Calc. for $C_{10}H_8O_2$: C, 75.0; H, 5.0%). 7-Acetylbenzo[*b*]furan (**4b**) had m.p. 61—62 °C (from pentane) (Found: C, 74.9; H, 4.9%).

*4-Acetylbenzo*[b]*furan* (**3b**). A solution of benzo[*b*]furan-4-carbonitrile (3.57 g, 0.025 mol) in dry toluene (5 ml) was added dropwise to a solution of methylmagnesium iodide in dry toluene (30 ml) obtained by removing nearly all the ether from a solution of the Grignard reagent from methyl iodide (10.57 g, 0.074 mol) and Mg (1.8 g) in dry ether (35 ml). The mixture was heated at 60 °C for 1 h and poured into an ammonium chloride aqueous solution. After acidification with dil. hydrochloric acid, the mixture was refluxed for 1 h, cooled, and extracted with benzene. The solvent was evaporated and the residue was distilled to give 4-acetylbenzo[*b*]furan (2.2 g, 55% yield), b.p. 67—68 °C at 0.1 mmHg, $n_D^{20}$ 1.5948 (Found: C, 74.9; H, 4.9. $C_{10}H_8O_2$ requires C, 75.0; H, 5.0%).

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