HETEROCYCLES, Vol. 5, 1976

# $^{1}H$ NMR SOLVENT SHIFTS INDUCED BY HEXAFLUOROBENZENE IN LACTONES, LACTAMS, ACID ANHYDRIDES AND IMIDES

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Aromatic solvent-induced shifts (ASIS) with hexafluorobenzene in 60-MHz $^{1}H$ nmr spectra of lactones including sesquiterpenic ones, lactams, carboxylic acid anhydrides and imides were examined to demonstrate that the ASIS method becomes more useful in signal assignments and structure elucidation of lactones and lactams when hexafluorobenzene is employed as a solvent rather than benzene or pyridine.

In previous papers,[1] we proposed the use of aromatic solvent-induced shifts (ASIS)[2] with hexafluorobenzene ($C_6F_6$) in $^{1}H$ nmr spectroscopy as an aid in assigning signals and elucidating structures of terpenic ketones. The ASIS method is sometimes more useful than the shift reagent method;[3] besides, the former is more convenient in view of its simple procedure and easy recovery of samples. The direction of ASIS with $C_6F_6$ observed for some polar solutes is known to be opposite to that of ASIS with benzene-$d_6$

($C_6D_6$).[4] We also confirmed that a carbonyl reference plane rule[1,5a] holds good for the ASIS with $C_6F_6$ as well as those with $C_6D_6$ and pyridine-$d_5$ ($C_5D_5N$) (see Figs. a-c).[1]

Since Connolly and McCrindle's paper,[5b] a number of ASIS studies have been published on lactones, lactams, acid anhydrides and imides.[1,6] ASIS with $C_6D_6$ or $C_5D_5N$ does not seem very useful for these kinds of molecules. However, examining 60-MHz $^1$H nmr spectra of several compounds in $CCl_4$, $CDCl_3$, $C_6D_6$, $C_5D_5N$ and $C_6F_6$, we found that the ASIS with $C_6F_6$ is more useful than that with $C_6D_6$ or $C_5D_5N$ because a modified reference plane rule holds better than with $C_6D_6$ and $C_5D_5N$ for lactones and lactams (see Fig. d). Thus, we wish to report the results promptly.

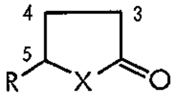
Examinations of ASIS values listed in the Table and molecular models of lactonic compounds 1-13 show a general trend for the $C_6F_6$ effects as represented in Fig. d. This modified reference plane rule is similar to that proposed for coumarins in $C_6D_6$ earlier,[7] the shift direction being opposite. The ASIS with $C_6D_6$ does not seem to be clearly characterized for the lactones though the magnitudes are much larger than those of $C_6F_6$. The ASIS behavior of $C_5D_5N$ seems to resemble that of $C_6F_6$ with the opposite shift direction, but is less clearly characterized. The large downfield shift by $C_5D_5N$ for 6-H of mevalonic lactone (3) is due to the presence of a hydroxy group.

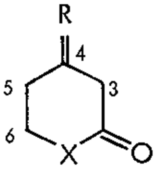
In the ASIS with $C_6F_6$, high-field shifts were clearly observed for the signals of 3c-H in isolinderalactone (6),[8] 14-H in both dihydroisoalantolactone (7) and dihydroalantolactone (8), and 13c-H in costunolide (9),[8] because these protons are situated in front of the reference plane (the carbonyl side); slight or no shifts were observed for the signals of 3- and 10-H in menthofurolactone (4), 6- and 13-H in saussurealactone (5), 6-H in both 6 and 9, 13-H in dihydrocostunolide (10),[8] 8- and 13-H in compound 11,[9] and 6-H in both linderalactone (12)[8] and linderane (13),[8] because these protons are located near the reference plane. It should be emphasized that the downfield shift of the 14-H signal in 12 arises from the conformation of its ten-membered ring[8] in which the 14-H (Me) lies in front of the reference plane. In molecules 6, 12 and 13, some effects due to the furan rings were discernible, and in 13 that due to the epoxy ring was exerted on neighboring protons, particularly 1-H.

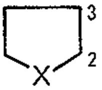
The ASIS results with several lactams, 14-18, resemble those with the lactones (see the Table and Fig. d). The N-methyl signals in 16 and 18 shifted upfield in $C_6F_6$, which is consistent with the rule.

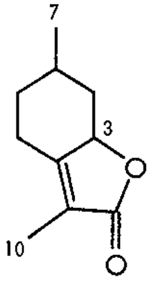
ASIS behavior was also examined for some simple heterocyclic compounds, 19-22, for comparison. In these cases, $C_5D_5N$ appears to be the best solvent for an ASIS study. Furthermore, ASIS for some simple cyclic carboxylic acid anhydrides 23-27 and imides 30-33 was similarly investigated but no useful rule was obtained; in particular, the ASIS with $C_5D_5N$ behaves strangely for these molecules (see the Table). However, endo-exo stereoisomers of maleic anhydride adducts, 28 and 29,[10] were assessed by ASIS with $C_6F_6$ better than those with $C_6D_6$ or $C_5D_5N$, because the $C_6F_6$-ASIS value for b-H is much larger in 29 (+0.24 ppm) than in 28 (+0.09). Therefore, ASIS observations in $C_6F_6$ are sometimes of value and thus are recommended for these kinds of molecules also.

In conclusion, we propose that as an ASIS solvent, $C_6F_6$ is sometimes superior to $C_6D_6$ or $C_5D_5N$.







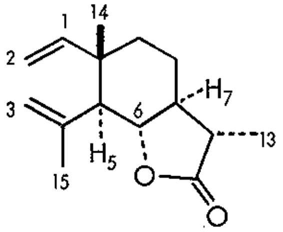


**1**: X = O, R = H
**2**: X = O, R = Me
**14**: X = NH, R = H
**15**: X = NH, R = Me
**16**: X = NMe, R = H

**3**: X = O, $\text{R} = \,<^{\text{Me}}_{\text{OH}}$
**17**: X = NH, R = $H_2$
**18**: X = NMe, R = $H_2$

**19**: X = O
**20**: X = NH
**21**: X = S
**22**: X = $SO_2$

**4**



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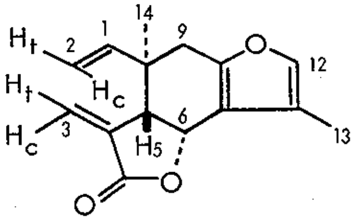

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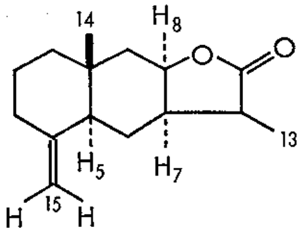

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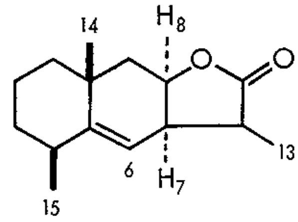

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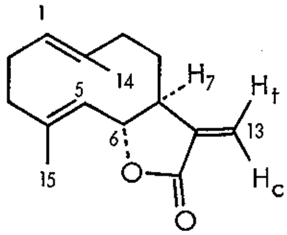

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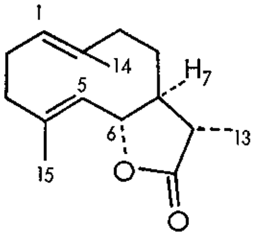

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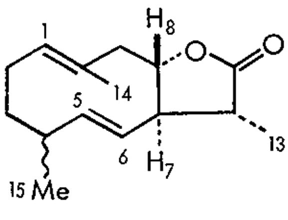

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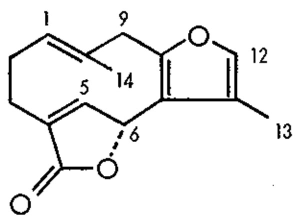

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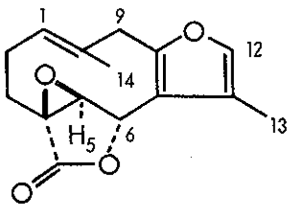

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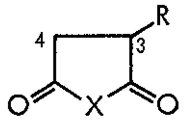
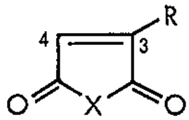
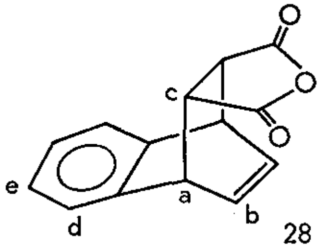


23: X = O, R = H
24: X = O, R = Me
30: X = NH, R = H
31: X = NMe, R = H



25: X = O, R = H
26: X = O, R = Me
32: X = NH, R = H
33: X = NMe, R = H



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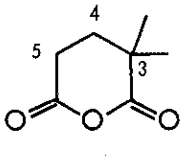

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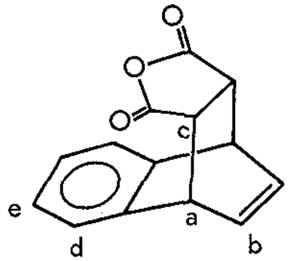

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TABLE. $^1$H Chemical Shifts (δ) and ASIS Data[a] on Heterocyclic Compounds Examined[b]

| Proton | δ | ASIS (ppm)[c] | | | δ |
|---|---|---|---|---|---|
| | $CCl_4$ | $C_6F_6$ | $C_6D_6$ | $C_5D_5N$ | $CDCl_3$ |
| (1) | | | | | |
| 5-H | 4.26 | +0.10 | -0.61 | -0.13 | 4.34 |
| (2) | | | | | |
| 5-H | 4.57 | +0.07 | -0.62 | -0.08 | 4.66 |
| 5-Me | 1.38 | +0.11 | -0.42 | -0.19 | 1.41 |
| (3) | | | | | |
| 4-Me | 1.35 | +0.14 | -0.32 | +0.04 | 1.38 |
| 6-H | 4.29 | +0.10 | -0.42 | +0.02 | 4.32 |
| | 4.47 | +0.17 | -0.12 | +0.24 | 4.59 |
| (4) | | | | | |
| 3-H | 4.51 | +0.04 | -0.44 | +0.04 | 4.63 |
| 7-H | 1.02 | +0.17 | -0.41 | -0.23 | 1.02 |
| 10-H | 1.75 | -0.02 | -0.14 | 0.00 | 1.80 |
| (5) | | | | | |
| 1-H | 5.81 | +0.15 | -0.13 | +0.06 | 5.85 |
| 3-H | 4.67 | +0.05 | +0.05 | +0.13 | 4.71 |
| | 4.97 | +0.05 | +0.08 | +0.09 | 5.02 |
| 5-H | 2.18 | +0.05 | -0.19 | +0.07 | 2.24 |
| 6-H | 4.02 | +0.08 | -0.35 | +0.21 | 4.13 |
| 13-H | 1.16 | +0.06 | -0.13 | +0.03 | 1.23 |
| 14-H | 1.07 | +0.12 | -0.23 | -0.03 | 1.09 |
| 15-H | 1.77 | +0.06 | -0.03 | +0.01 | 1.78 |
| (6) | | | | | |
| 1-H | 5.86 | +0.20 | -0.44 | +0.03 | 5.88 |
| (6) | | | | | |
| 2c-H | 5.04 | +0.16 | -0.35 | -0.07 | 5.02 |
| 2t-H | 5.17 | +0.16 | -0.29 | -0.04 | 5.21 |
| 3c-H | 6.19 | -0.06 | 0.00 | +0.16 | 6.31 |
| 3t-H | 5.54 | +0.16 | -0.37 | +0.05 | 5.65 |
| 5-H | 2.95 | +0.12 | -0.60 | +0.07 | 3.03 |
| 6-H | 5.14 | 0.00 | -0.42 | +0.14 | 5.28 |
| 9-H | 2.57 | -0.05<br>+0.13 | -0.31 | -0.01 | 2.61 |
| 12-H | 7.04 | -0.04 | -0.15 | +0.25 | 7.12 |
| 13-H | 2.08 | +0.03 | -0.14 | -0.03 | 2.08 |
| 14-H | 0.97 | -0.03 | -0.21 | -0.04 | 0.99 |
| (7) | | | | | |
| 8-H | 4.35 | +0.11 | -0.51 | +0.03 | 4.48 |
| 13-H | 1.17 | +0.04 | -0.16 | +0.01 | 1.23 |
| 14-H | 0.82 | -0.04 | 0.00 | -0.01 | 0.82 |
| 15-H | 4.73 | 0.00 | +0.02 | +0.07 | 4.79 |
| | 4.48 | 0.00 | -0.07 | +0.02 | 4.49 |
| (8) | | | | | |
| 6-H | 5.13 | +0.18 | -0.20 | 0.00 | 5.18 |
| 8-H | 4.67 | +0.06 | -0.53 | +0.03 | 4.77 |
| 13-H | 1.16 | +0.08 | -0.14 | -0.11 | 1.14 |
| 14-H | 1.23 | -0.03 | +0.02 | +0.03 | 1.25 |
| 15-H | 1.16 | +0.03 | +0.03 | +0.05 | 1.22 |

TABLE (Continued)

| Proton | δ | ASIS (ppm)[c] | | | |
|---|---|---|---|---|---|
| | $CCl_4$ | $C_6F_6$ | $C_6D_6$ | $C_5D_5N$ | $CDCl_3$ |
| (9) | | | | | |
| 5-H | 4.70 | 0.00 | -0.26 | +0.07 | 4.79 |
| 6-H | 4.41 | 0.00 | -0.30 | +0.19 | 4.53 |
| 13c-H | 6.10 | -0.05 | +0.12 | +0.23 | 6.25 |
| 13t-H | 5.38 | +0.15 | -0.35 | +0.13 | 5.52 |
| 14-H | 1.41 | +0.16 | -0.29 | -0.07 | 1.43 |
| 15-H | 1.69 | +0.15 | -0.34 | -0.08 | 1.69 |
| (10) | | | | | |
| 13-H | 1.18 | +0.03 | -0.07 | +0.07 | 1.25 |
| 14-H | 1.40 | +0.13 | -0.25 | -0.05 | 1.43 |
| 15-H | 1.66 | +0.15 | -0.24 | -0.06 | 1.69 |
| (11) | | | | | |
| 1-H | 5.18 | +0.16 | -0.23 | +0.01 | 5.23 |
| 5-H | 5.80 | +0.20 | -0.41 | -0.06 | 5.84 |
| 6-H | 4.99 | +0.20 | -0.38 | +0.01 | 5.01 |
| 8-H | 3.87 | +0.03 | -0.36 | +0.13 | 3.97 |
| 13-H | 1.09 | +0.01 | -0.21 | -0.08 | 1.07 |
| 14-H | 1.63 | +0.14 | -0.29 | -0.09 | 1.63 |
| 15-H | 1.12 | +0.12 | -0.01 | +0.07 | 1.17 |
| (12) | | | | | |
| 1-H | 4.85 | +0.15 | -0.35 | +0.11 | 4.94 |
| 5-H | 6.70 | +0.15 | -0.63 | +0.25 | 6.82 |
| 6-H | 5.70 | +0.04 | -0.32 | +0.22 | 5.83 |
| 9-H | {3.33 | +0.11 | -0.23 | +0.10 | 3.40 |
| | 3.56 | -0.12 | -0.07 | +0.05 | 3.60 |
| 12-H | 7.05 | -0.03 | -0.20 | +0.24 | 7.12 |
| 13-H | 2.09 | +0.07 | -0.26 | -0.05 | 2.09 |
| 14-H | 1.26 | -0.14 | -0.04 | +0.02 | 1.26 |
| (13) | | | | | |
| 1-H | 5.31 | -0.01 | -0.50 | -0.13 | 5.37 |
| 5-H | 3.73 | +0.17 | -0.48 | +0.60 | 3.92 |
| 6-H | 5.16 | 0.00 | -0.04 | +0.37 | 5.30 |
| 9-H | 3.46 | 0.00 | -0.23 | +0.08 | 3.51 |
| 12-H | 7.06 | 0.00 | -0.27 | +0.25 | 7.13 |
| 13-H | 2.02 | 0.00 | -0.44 | -0.09 | 2.01 |
| 14-H | 1.56 | 0.00 | -0.06 | -0.03 | 1.58 |
| (14) | | | | | |
| 5-H | 3.40 | +0.04 | -0.53 | -0.19 | 3.40 |
| (15) | | | | | |
| 5-H | 3.74 | +0.04 | -0.46 | -0.09 | 3.79 |
| 5-Me | 1.21 | +0.06 | -0.33 | -0.13 | 1.22 |

| Proton | | ASIS (ppm)[c] | | | δ |
|---|---|---|---|---|---|
| | $CCl_4$ | $C_6F_6$ | $C_6D_6$ | $C_5D_5N$ | $CDCl_3$ |
| (16) | | | | | |
| 5-H | 3.33 | +0.13 | -0.65 | -0.28 | 3.38 |
| N-Me | 2.75 | -0.04 | -0.22 | +0.04 | 2.83 |
| (17) | | | | | |
| 6-H | 3.26 | -0.01 | -0.43 | -0.10 | 3.31 |
| (18) | | | | | |
| 6-H | 3.28 | +0.14 | -0.69 | -0.29 | 3.29 |
| N-Me | 2.84 | -0.04 | -0.15 | +0.01 | 2.94 |
| (19) | | | | | |
| 2-H | 3.63 | -0.11 | -0.05 | +0.04 | 3.75 |
| 3-H | 1.79 | -0.12 | -0.34 | -0.15 | 1.85 |
| (20) | | | | | |
| 2-H | 2.78 | -0.06 | -0.12 | +0.02 | 2.87 |
| 3-H | 1.62 | -0.01 | -0.21 | -0.10 | 1.73 |
| (21) | | | | | |
| 2-H | 2.75 | -0.03 | -0.19 | -0.05 | 2.82 |
| 3-H | 1.91 | +0.09 | -0.40 | -0.20 | 1.93 |
| (22) | | | | | |
| 2-H | 2.92 | -0.01 | -0.54 | +0.08 | 3.02 |
| 3-H | 2.19 | +0.21 | -0.89 | -0.24 | 2.22 |
| (23) | | | | | |
| 3-H | 2.89 | +0.24 | -1.38 | +0.17 | 2.98 |
| (24) | | | | | |
| 3-Me | 1.43 | +0.19 | -0.78 | -0.11 | 1.44 |
| (25) | | | | | |
| 3-H | 6.96 | +0.23 | -1.31 | +0.25 | 7.04 |
| (26) | | | | | |
| 3-Me | 2.19 | +0.21 | -0.89 | -0.01 | 2.21 |
| 4-H | 6.61 | +0.13 | -1.17 | 0.24 | 6.66 |
| (27) | | | | | |
| 3-Me | 1.33 | +0.15 | -0.56 | -0.09 | 1.36 |
| 4-H | 1.86 | +0.21 | -1.06 | -0.12 | 1.87 |
| 5-H | 2.76 | +0.14 | -0.74 | +0.12 | 2.83 |
| (28) | | | | | |
| a-H | 4.47 | +0.05 | -0.48 | +0.14 | 4.49 |
| b-H | 6.65 | +0.09 | -0.57 | -0.02 | 6.63 |
| c-H | 3.17 | +0.12 | -0.74 | +0.47 | 3.26 |
| d-H | 7.15 | +0.03 | -0.34 | +0.11 | 7.18 |
| e-H | 7.15 | +0.03 | -0.34 | +0.03 | 7.18 |
| (29) | | | | | |
| a-H | 4.41 | +0.07 | -0.49 | +0.12 | 4.47 |

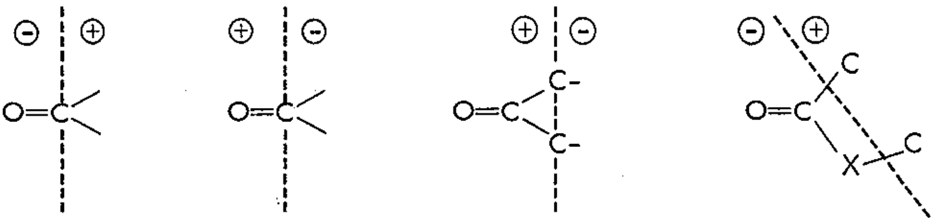
TABLE (Continued)

| Proton | δ | ASIS (ppm)[c] | | | δ |
|---|---|---|---|---|---|
| | $CCl_4$ | $C_6F_6$ | $C_6D_6$ | $C_5D_5N$ | $CDCl_3$ |
| (29) | | | | | |
| b-H | 6.66 | +0.24 | -0.67 | -0.05 | 6.70 |
| c-H | 3.29 | +0.15 | -0.81 | +0.47 | 3.42 |
| d-H | 7.16 | +0.02 | -0.20 | +0.10 | 7.19 |
| e-H | 7.16 | +0.02 | -0.31 | -0.02 | 7.19 |
| (30) | | | | | |
| 3-H | 2.67 | +0.15 | -1.00 | -0.01 | 2.74 |
| (31) | | | | | |
| 3-H | 2.11 | +0.09 | -0.44 | +0.11 | 2.18 |
| N-Me | 2.52 | +0.09 | -0.39 | +0.20 | 2.63 |
| (32) | | | | | |
| 3-H | 6.61 | +0.13 | -0.92 | +0.13 | 6.73 |
| (33) | | | | | |
| 3-H | 6.65 | +0.05 | -0.84 | +0.08 | 6.70 |
| N-Me | 2.98 | -0.01 | -0.43 | -0.10 | 3.00 |

[a] We chose $CCl_4$ and TMS as a reference solvent and an internal standard, respectively. We should like to claim that $CCl_4$ and $CDCl_3$ have wide applicability in organic chemistry, although cyclohexane might be recommended for both references;[1] and therefore, we have also included δ values in $CDCl_3$ in the TABLE. ASIS values are indicated by δ (aromatic solvent) − δ ($CCl_4$); the plus sign represents a downfield shift.

[b] $^1H$ NMR spectra were taken with a Varian A-56/60D spectrometer at 40°. Sample concentrations were about 5% (w/v) or less. Accuracies of chemical shifts (δ) are within ±0.01.

[c] Only our data are given though many appear in literature.[1,5,6]



(a) $C_6F_6$  (b) $C_6D_6$  (c) $C_5D_5N$  $F_6$ (X = O, N)

Figure. Carbonyl reference plane rules. Dotted line shows a reference plane; ⊖, shielding zone; ⊕, deshielding zone.

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Received, 26th July, 1976