

¹H 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 ¹H 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 (C₆F₆) in ¹H 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 C₆F₆ observed for some polar solutes is known to be opposite to that of ASIS with benzene-d₆

(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 1H 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.

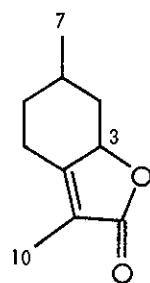
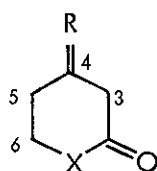
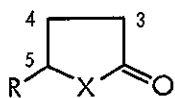
In the ASIS with C_6F_6 , high-field shifts were clearly observed for the signals of 3c-H in isolinderalactone (6),⁸ 14-H in both dihydroisoalantolactone (7) and dihydroalantolactone (8), and 13c-H in costunolide (9),⁸ because these protons are situated in front of the reference plane (the carbonyl side); 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 ring⁸ 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, R = $\begin{matrix} \text{Me} \\ \diagup \\ \text{OH} \end{matrix}$

17: X = NH, R = H₂

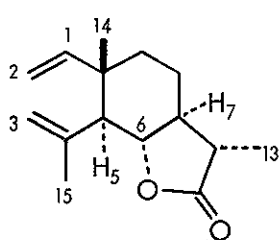
18: X = NMe, R = H₂

19: X = O

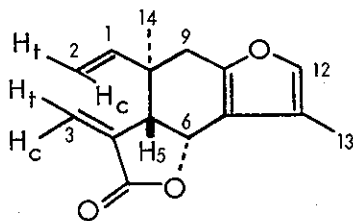
20: X = NH

21: X = S

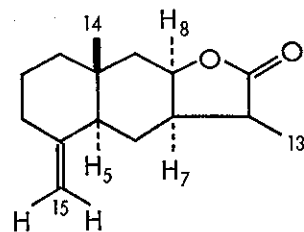
22: X = SO₂



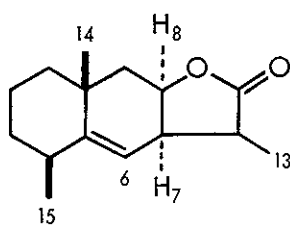
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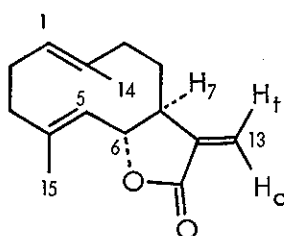
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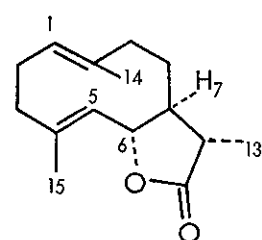
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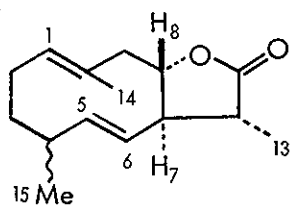
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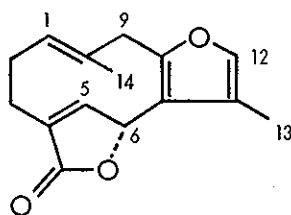
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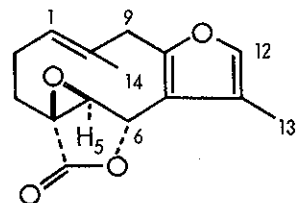
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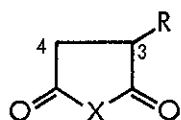
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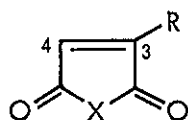


23: X = O, R = H

24: X = O, R = Me

30: X = NH, R = H

31: X = NMe, R = H

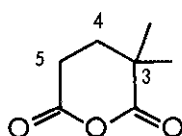


25: X = O, R = H

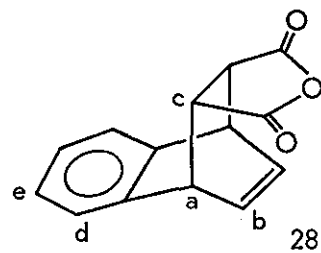
26: X = O, R = Me

32: X = NH, R = H

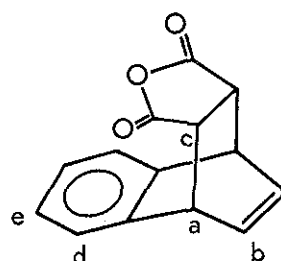
33: X = NMe, R = H



27



28



29

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

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

TABLE (Continued)

Proton	δ					Proton	δ				
	CCl ₄	ASIS (ppm) ^c					CCl ₄	ASIS (ppm) ^c			
	C ₆ F ₆	C ₆ D ₆	C ₅ D ₅ N	CDCl ₃			C ₆ F ₆	C ₆ D ₆	C ₅ D ₅ N	CDCl ₃	
(9)						(16)					
5-H	4.70	0.00	-0.26	+0.07	4.79	5-H	3.33	+0.13	-0.65	-0.28	3.38
6-H	4.41	0.00	-0.30	+0.19	4.53	N-Me	2.75	-0.04	-0.22	+0.04	2.83
13c-H	6.10	-0.05	+0.12	+0.23	6.25	(17)					
13t-H	5.38	+0.15	-0.35	+0.13	5.52	6-H	3.26	-0.01	-0.43	-0.10	3.31
14-H	1.41	+0.16	-0.29	-0.07	1.43	(18)					
15-H	1.69	+0.15	-0.34	-0.08	1.69	6-H	3.28	+0.14	-0.69	-0.29	3.29
(10)						N-Me	2.84	-0.04	-0.15	+0.01	2.94
13-H	1.18	+0.03	-0.07	+0.07	1.25	(19)					
14-H	1.40	+0.13	-0.25	-0.05	1.43	2-H	3.63	-0.11	-0.05	+0.04	3.75
15-H	1.66	+0.15	-0.24	-0.06	1.69	3-H	1.79	-0.12	-0.34	-0.15	1.85
(11)						(20)					
1-H	5.18	+0.16	-0.23	+0.01	5.23	2-H	2.78	-0.06	-0.12	+0.02	2.87
5-H	5.80	+0.20	-0.41	-0.06	5.84	3-H	1.62	-0.01	-0.21	-0.10	1.73
6-H	4.99	+0.20	-0.38	+0.01	5.01	(21)					
8-H	3.87	+0.03	-0.36	+0.13	3.97	2-H	2.75	-0.03	-0.19	-0.05	2.82
13-H	1.09	+0.01	-0.21	-0.08	1.07	3-H	1.91	+0.09	-0.40	-0.20	1.93
14-H	1.63	+0.14	-0.29	-0.09	1.63	(22)					
15-H	1.12	+0.12	-0.01	+0.07	1.17	2-H	2.92	-0.01	-0.54	+0.08	3.02
(12)						3-H	2.19	+0.21	-0.89	-0.24	2.22
1-H	4.85	+0.15	-0.35	+0.11	4.94	(23)					
5-H	6.70	+0.15	-0.63	+0.25	6.82	3-H	2.89	+0.24	-1.38	+0.17	2.98
6-H	5.70	+0.04	-0.32	+0.22	5.83	(24)					
9-H	3.33	+0.11	-0.23	+0.10	3.40	3-Me	1.43	+0.19	-0.78	-0.11	1.44
	3.56	-0.12	-0.07	+0.05	3.60	(25)					
12-H	7.05	-0.03	-0.20	+0.24	7.12	3-H	6.96	+0.23	-1.31	+0.25	7.04
13-H	2.09	+0.07	-0.26	-0.05	2.09	(26)					
14-H	1.26	-0.14	-0.04	+0.02	1.26	3-Me	2.19	+0.21	-0.89	-0.01	2.21
(13)						4-H	6.61	+0.13	-1.17	0.24	6.66
1-H	5.31	-0.01	-0.50	-0.13	5.37	(27)					
5-H	3.73	+0.17	-0.48	+0.60	3.92	3-Me	1.33	+0.15	-0.56	-0.09	1.36
6-H	5.16	0.00	-0.04	+0.37	5.30	4-H	1.86	+0.21	-1.06	-0.12	1.87
9-H	3.46	0.00	-0.23	+0.08	3.51	5-H	2.76	+0.14	-0.74	+0.12	2.83
12-H	7.06	0.00	-0.27	+0.25	7.13	(28)					
13-H	2.02	0.00	-0.44	-0.09	2.01	a-H	4.47	+0.05	-0.48	+0.14	4.49
14-H	1.56	0.00	-0.06	-0.03	1.58	b-H	6.65	+0.09	-0.57	-0.02	6.63
(14)						c-H	3.17	+0.12	-0.74	+0.47	3.26
5-H	3.40	+0.04	-0.53	-0.19	3.40	d-H	7.15	+0.03	-0.34	+0.11	7.18
(15)						e-H	7.15	+0.03	-0.34	+0.03	7.18
5-H	3.74	+0.04	-0.46	-0.09	3.79	(29)					
5-Me	1.21	+0.06	-0.33	-0.13	1.22	a-H	4.41	+0.07	-0.49	+0.12	4.47

TABLE (Continued)

Proton	δ CCl ₄	ASIS (ppm) ^c				δ CDCl ₃	Proton	δ CCl ₄	ASIS (ppm) ^c				δ CDCl ₃
		C ₆ F ₆	C ₆ D ₆	C ₅ D ₅ N					C ₆ F ₆	C ₆ D ₆	C ₅ D ₅ N		
(29)							(31)						
b-H	6.66	+0.24	-0.67	-0.05	6.70		3-H	2.11	+0.09	-0.44	+0.11	2.18	
c-H	3.29	+0.15	-0.81	+0.47	3.42		N-Me	2.52	+0.09	-0.39	+0.20	2.63	
d-H	7.16	+0.02	-0.20	+0.10	7.19		(32)						
e-H	7.16	+0.02	-0.31	-0.02	7.19		3-H	6.61	+0.13	-0.92	+0.13	6.73	
(30)							(33)						
3-H	2.67	+0.15	-1.00	-0.01	2.74		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 CCl₄ and TMS as a reference solvent and an internal standard, respectively. We should like to claim that CCl₄ and CDCl₃ have wide applicability in organic chemistry, although cyclohexane might be recommended for both references;¹ and therefore, we have also included δ values in CDCl₃ in the TABLE. ASIS values are indicated by δ (aromatic solvent) - δ (CCl₄); 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}

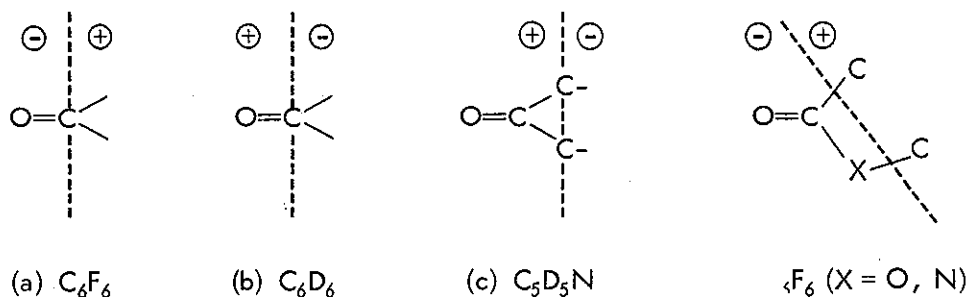


Figure. Carbonyl reference plane rules. Dotted line shows a reference plane; $\ominus$, shielding zone; $\oplus$, deshielding zone.

References

- 1 K. Tori, I. Horibe, H. Shigemoto, and K. Umemoto, Tetrahedron Lett., 1975, 2199; I. Horibe, H. Shigemoto, and K. Tori, ibid., 1975, 2849.
- 2 For reviews, see P. Laszlo, Progr. NMR Spectroscopy, 1967, 3, 231; J. Ronayne and D. H. Williams, Ann. Rev. NMR Spectroscopy, 1969, 2, 83; E. M. Engler and P. Laszlo, J. Amer. Chem. Soc., 1971, 93, 1317.
- 3 For a review, see B. C. Mayo, Chem. Soc. Rev., 1973, 2, 49.
- 4 R. D. Bertrand, R. D. Compton, and J. G. Verkade, J. Amer. Chem. Soc., 1970, 92, 2702; R. S. Armstrong, M. J. Aroney, R. K. Duffin, H. J. Stootman, and R. J. W. Le Fèvre, J.C.S. Perkin II, 1973, 1362; K. Nikki and N. Nakagawa, Chem. Lett., 1974, 699.
- 5 (a) J. D. Connolly and R. McCrindle, Chem. & Ind., 1965, 379; (b) Idem., ibid., 1965, 2066.
- 6 For example, see G. di Maio, P. A. Tardella, and C. Iavarone, Tetrahedron Lett., 1966, 2825; Y. Ichikawa and T. Matsuo, Bull. Chem. Soc. Japan, 1967, 40, 2030; C. R. Narayanan and N. K. Venkatasubramanian, J. Org. Chem., 1968, 33, 3156; T. Ledaal, Tetrahedron Lett., 1968, 1683; D. Bryce-Smith and M. A. Hems, J. Chem. Soc. (B), 1968, 812; R. M. Moriarty and J. M. Kliegman, J. Org. Chem., 1966, 31, 3007.
- 7 R. Grigg, J. A. Knight, and P. Roffey, Tetrahedron, 1966, 22, 3301.
- 8 For a review, see K. Takeda, ibid., 1974, 30, 1525.
- 9 K. Takeda and I. Horibe, J.C.S. Perkin I, 1975, 870.
- 10 K. Takeda, K. Kitahonoki, M. Sugiura, and Y. Takano, Ber., 1962, 95, 2344.

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