Pergamon

Tetrahedron Letters 40 (1999) 3591–3594

TETRAHEDRON LETTERS

Is the Magnetic Shielding Effect of a Lactone Group the Simple Sum of Those of a Ketone and an Ether?

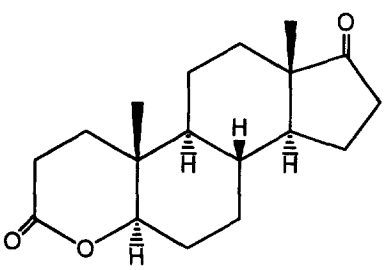
Yoshimasa Fukazawa,* Takeharu Haino, and Yoshiaki Kondoh

Department of Chemistry, Hiroshima University, Higashi-Hiroshima 739-8526, Japan

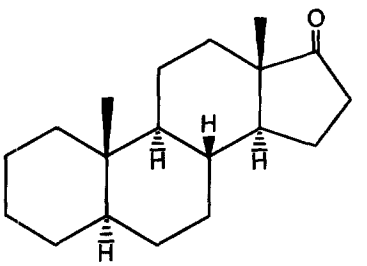
Received 15 February 1999; revised 8 March 1999; accepted 12 March 1999

Abstract: 3-Oxo-4-oxa-5α-androstanone (**1**) was synthesized in order to obtain the NMR shielding parameters for lactone group. The assignment of ^{1}H-NMR and substituent-induced shifts (SIS) from the corresponding androstanone (**2**) are presented. A simple sum of the magnetic shieldings of ketone and ether can satisfactorily reproduce the observed SIS values due to the lactone group of **1**. © 1999 Elsevier Science Ltd. All rights reserved.

It is well known that NMR chemical shifts reflect molecular structure. Thus, variation in the local environment affects chemical shieldings, and the change in chemical shifts of nuclei caused by adjacent substituents provides valuable information about the relative arrangement of the nuclei under study with respect to these nearby substituents.[1] The chemical shift changes caused by secondary induced magnetic fields due to aromatic ring currents[2] have proven effective for the conformational analysis of flexible macrocyclophanes.[3] However, the quantification of such shielding effects[4] has been rather limited, and this situation has restricted the broad application of the technique. In a previous paper we have reported new parameters associated with the shielding effect of carbonyl groups[5] and by using them succeeded in determining the preferred conformers of [3.3]metacyclophanedione,[6] a twelve-membered ring compound having two benzenes and two carbonyl groups.



1



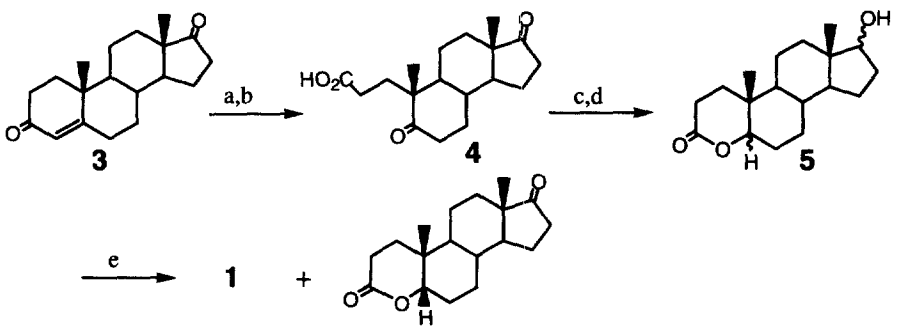
2

In order to extend the applicability of the method of chemical shift simulation to heteroatom-containing compounds, it is necessary to obtain the shielding parameters for other functionalities such as the

PII: S0040-4039(99)00580-8

lactone group which is ubiquitous in organic compounds. In order to obtain reliable shielding parameters for this group, the steroid skeleton was chosen because of its rigidity and well defined geometry. Hence, we synthesized 3-oxo-4-oxa-5α-androstanone (**1**) and compared the chemical shifts of the associated protons with those of the corresponding reference compound (**2**).

Scheme 1.



a) O_3, AcOH-AcOEt. b) 30%H_2O_2,79%. c) $NaBH_4$. d) H_3O^+,54%. e) CrO_3,Py, 73%

The synthesis of compound **1** is shown in Scheme 1. Thus, ozonolysis[7] of 4-androstene-3,17-dione (**3**) and subsequent *in situ* treatment of the resulting ozonide with H_2O_2 yielded keto-acid (**4**). Reduction of compound **4** with $NaBH_4$ in EtOH and subsequent acid treatment gave a mixture of the four diastereomers of lactone (**5**). This mixture was oxidized using Collins reagent so as to give the corresponding mixture of keto-lactone **1** and its 5β-isomer. HPLC separation of the mixture afforded target **1** and 3-oxo-4-oxa-5β-androstan-17-one in a ratio of 2:1. The preparation of the reference compound (**2**) was carried out by a reported procedure.[8] The structure of model compound **1** was confirmed by X-ray crystallographic analysis (Figure 1).[9] Assignments of the ^{1}H-NMR signals for **1** in $CDCl_3$ solution were made using a combination of COSY, NOESY, HMBC, and phase-sensitive DQF-COSY experiments. The observed substituent-induced shift (SIS), which is defined as the change in chemical shift of a proton produced by the substituent, can be obtained by the chemical shift differences between structures **1** and **2**.

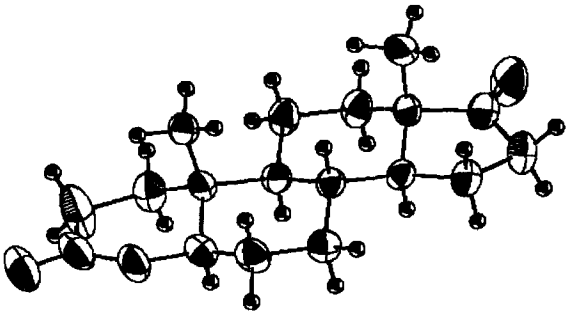


Figure 1. ORTEP drawing of **1**

The observed SIS values can be reproduced by calculation if the correct set of shielding parameters

and relative geometry of a proton with respect to the substituent are known and in the present case the precise geometrical factors associated with these protons were obtained from the X-ray crystallographic analysis mentioned above.

In our previous paper, we have found that the SIS values in [3.3]metacyclophanedione can be correctly obtained by the addition of the SIS values due to the benzene ring and those of carbonyl group within the molecules.[6] Of course, these functional groups are mutually independent because they are not in sufficiently close proximity to have an electronic interaction, and hence, the observed additivity of SIS values is readily explained.

Table 1. ^{1}H-NMR Chemical Shifts for Compound **1** and **2** Together with their Observed and Calculated SIS Values

position	**1**	**2**	Obs.	Calc.		
			SIS	SIS lactone	SIS C-O-C	SIS C=O
1α	1.56	0.89	0.67	0.62	0.12	0.50
2α	2.61	1.50	1.11	1.16	0.01	1.15
2β	2.63	1.41	1.22	1.19	0.05	1.14
6α	1.94	1.25	0.69	0.51	0.28	0.23
6β	1.66	1.25	0.41	0.54	0.36	0.18
7α	1.05	0.97	0.08	-0.01	-0.11	0.10
7β	1.92	1.78	0.14	0.14	0.02	0.12
8	1.56	1.55	0.01	0.12	0.03	0.09
9	0.83	0.72	0.11	0.02	-0.14	0.16
11α	1.62	1.67	-0.05	0.12	0.04	0.08
11β	1.43	1.27	0.16	0.13	0.05	0.08
12α	1.25	1.23	0.02	0.05	0.00	0.05
12β	1.85	1.79	0.06	0.08	0.02	0.06
14	1.26	1.27	-0.01	-0.01	-0.05	0.04
15α	1.96	1.91	0.05	0.02	-0.01	0.03
15β	1.54	1.60	-0.06	0.03	0.00	0.03
16α	2.09	2.03	0.06	0.04	0.01	0.03
16β	2.47	2.45	0.02	0.03	0.01	0.02

It is important to determine whether or not there is an additivity associated with the SIS values of two moieties that are interacting electronically. In order to examine these matters in a functional group such as a lactone, we calculated the SIS values of protons in compound **1** due to the magnetic shielding effect of the ketone and ether individually (Table 1). As can be clearly seen, the magnitude of SIS values obtained from the ketone are closer to the observed ones than those of the ether[10] group. Correlation analysis of the observed and calculated SIS values clearly shows that the carbonyl group (correlation coefficient, R^2 = 0.88) contributes more significantly than the ether group (correlation coefficient, R^2 = 0.17). To our surprise, the observed SIS value of the lactone group can be reproduced when we assume that the shielding effect of

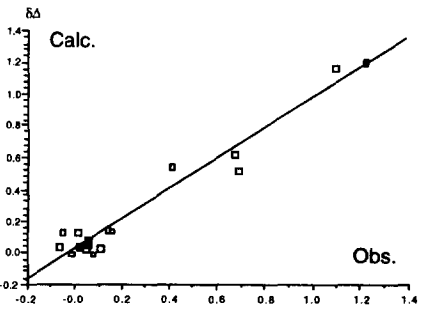


Figure 2. Observed and Calculated SIS Values of **1**

the lactone is a simple sum of those due to the ketone and ether. This is clearly shown by correlation analysis (Figure 2) [a set of 18 data (range of the observed data -0.06 ~ 1.22 ppm) $\Delta\delta_{calc} = a \cdot \Delta\delta_{obs} + b$; a = 0.953, b = 0.018, $R^2 = 0.953$].

REFERENCES

1. (a) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, W. B. Whalley, *Tetrahedron*, **1967**, *23*, 2339, 2357, and 2375. (b) J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders, W. B. Whalley, *Tetrahedron*, **1970**, *26*, 119. (c) J. W. ApSimon, H. Beierbeck, *Can. J. Chem.* **1971**, *49*, 1328. (d) J. W. ApSimon, H. Beierbeck, D. K. Todd, *Can. J. Chem.* **1972**, *50*, 2351. (e) T. Asakura, Y. Niizawa, M. P. Williamson, *J. Magn. Res.*. **1992**, 98, 646. (f) K. Osapay, D. A. Case, *J. Am. Chem. Soc.* **1991**, *113*, 9436. (g) D. Sitkoff, D. A. Case, *J. Am. Chem. Soc.* **1997**, *119*, 12262.
2. (a) J. S. Waugh, R. W. Fessenden, *J. Am. Chem. Soc.* **1957**, *79*, 846; **1958**, *80*, 6697. (b) C. E. Johnson, F. A. Bovey, *J. Chem, Phys.*, **1958**, *29*, 1012. (c) H. C. Longuet-Higgins, L. Salem, *Proc. Roy. Soc. (London)*, **1960**, *A257*, 445. (d) R. B. Mallion, *Mol. Phys.* **1973**, *25*, 1415.
3. (a) Y. Fukazawa, K. Ogata, S. Usui, *J. Am. Chem. Soc.* **1988**, *110*, 8692. (b) Y. Fukazawa, K. Ogata, S. Usui, *J. Am. Chem. Soc.* **1988**, *110*, 8692. (c) T. Okajima, Z.-H. Wang, Y. Fukazawa, *Tetrahedron Lett.* **1989**, *30*, 1551. (d) T. Okajima, Z.-H. Wang, Y. Fukazawa, *Chem. Lett.* **1991**, 37. (e) Y. Fukazawa, K. Deyama, S. Usui, *Tetrahedron Lett.* **1992**, *33*, 5803. (f) Wang, Z.-H.; Usui, S. Fukazawa, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1239. (g) Y. Fukazawa, S. Usui, K. Tanimoto, Y. Hirai, *J. Am. Chem. Soc.* **1994**, *116*, 8169.
4. (a) R. F. Zürcher, *Progr. NMR Spectrosc.* **1967**, *2*, 205. (b) H. –J. Schneider, U. Buchheit, N. Becker, G. Schmidt, U. Siehl, *J. Am. Chem. Soc.* **1985**, *107*, 7027.
5. Y. Fukazawa, Y. Yang, T. Hayashibara, S. Usui, *Tetrahedron* **1996**, *52* 2847.
6. Y. Fukazawa, T. Hayashibara, Y. Yang, S. Usui, *Tetrahedron Lett.* **1995**, *36*, 3349.
7. (a) R. B. Turner, *J. Am. Chem. Soc.* **1950**, *72*, 579. (b) G. I. Fujimoto, *J. Am. Chem. Soc.* **1951**, *73*, 1856.
8. L. Ruzicka, A. C. Muhr. *Helv. Chim. Acta*, **1944**, *27*, 503.
9. The crystal data for **1** are as follows; **1**: Orthorhombic; space group $P2_12_12_1$ with a = 11.701 (2), b = 12.806 (2), c = 10.431 (2) Å, V = 1563.0 (4) $Å^3$, and Z = 4; Of 1437 total unique reflections, 1430 were considered observed at the level of $|Fo|>3.0\sigma|Fo|$. The structures were solved by the direct method (Sir92). Full-matrix least squares refinements converged to a conventional R factor of 0.051, wR = 0.063.
10. Y. Yang, T. Haino, S. Usui, Y. Fukazawa, *Tetrahedron*, **1996**, *52*, 2325.