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Magnetic Resonance in

¹H and ¹³C NMR spectral study of some 3-aryl-5*r*-aryl-6*t*-carbethoxycyclohex-2-enones – a study of four-bond ¹H–¹H couplings

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Nine 3-aryl-5*r*-aryl-6*t*-carbethoxycyclohex-2-enones 2a–2i have been synthesized. For all these compounds, ¹H and ¹³C NMR spectra have been recorded. For two compounds, 2D spectra have been recorded. The spectral data suggest that these compounds adopt sofa conformation in solution with H-5, H-6 and H-4*t* occupying axial-like positions and H-4*c* occupying equatorial-like positions. In 3-phenyl-5*r*-(*o*-chlorophenyl)-6*t*-carbethoxycylohex-2-enone (2b), the *o*-chlorophenyl group is oriented such that the chlorine atom is in between H-4*c* and H-5. Allylic coupling of H-2 is observed only with H-4*t*. Evidence has been obtained for four-bond coupling between 1,3-diaxial and 1,3-axial–equatorial protons. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: cyclohex-2-enones; ¹H NMR; ¹³C NMR; four-bond ¹H–¹H coupling

Introduction

Cyclohex-2-enones are useful in the synthesis of organic compounds.^[1-5] Cyclohex-2-enone derivatives exhibit antifungal^[6] and anticancer^[7] activities. However, to our knowledge only two NMR spectral studies^[8,9] have been reported on cyclohex-2-enones. Though it has been established by theory and experiments that the *vicinal* coupling between two protons depend on the torsional angle between them, the dependence of allylic coupling with the relative positions of the coupling protons has not been investigated. This is probably due to the lack of suitable compounds for this study. In the ¹H NMR spectra of 5-aryl-3-methylcyclohex-2-enones ($\mathbf{1}$)^[9] the olefinic proton H-2 has been found to give rise to a singlet though there can be allylic coupling with the methyl protons and protons at C-4. Probably, the signal of H-2 is not well resolved due to too many small couplings.

Four-bond coupling between 1,3-diequatorial protons, which are in W conformation, has been well demonstrated.^[9–11] However, such couplings involving 1,3-diaxial protons and 1,3-equatorial – axial protons have not been demonstrated. Herein we report the NMR spectral study of nine 3-aryl-5*r*-aryl-6*t*-carbethoxycyclohex-2-enones **2a**–**2i**. This study reveals that allylic coupling preferentially occurs with proton parallel to the *p*-orbitals involved in the formation of the π -bond. Also evidence has been obtained for 1,3-diaxial and 1,3-equatorial – axial ¹H–¹H couplings.

Results and Discussion

Compounds **2a–2i** were synthesized as racemates using the reaction shown in Scheme 1. The physical and analytical data are given in Table 1. The numbering of the carbon atoms is also shown in the scheme. The protons are numbered accordingly. Thus, protons at C-2 is denoted as H-2 and that at C-2' is denoted as H-2'. Among the two methylene protons at C-4, proton *cis* to H-5 is denoted as H-4*c* and that *trans* to H-5 is denoted as H-4*t*.



In the IR spectra, the C=O stretching of the ester carbonyl group is observed in the range $1734-1739 \text{ cm}^{-1}$ and that of the keto carbonyl group is observed in the range $1654-1600 \text{ cm}^{-1}$. All compounds gave molecular ion peaks corresponding to their molecular formulae. For the chloro compounds, **2b**, **2c** and **2d** (M + 2)⁺ peak also was observed. For **2a-2f** the experimental values of elemental analysis are in good agreement with those calculated for the molecular formulae. The structures of **2b** and **2g** have been determined using X-ray crystallography.^[12,13]

The ¹H NMR signals were assigned based on their positions, multiplicities and integral values. The ¹³C NMR signals were assigned based on their positions and intensities. In **2b**-**2i** the signals for the aromatic carbons and protons were assigned using known effects of substituents.^[14] The assignments were confirmed for **2b** using ¹H-¹H COSY, HSQC and HMBC spectra and for **2c** using ¹H-¹H COSY and HSQC spectra. Though the methylene protons of the COOCH₂CH₃ group are diastereotopic only for **2b** and **2c**, a multiplet was observed for them. In all other cases only a quartet was observed for them. However, in all cases only the center of the signal was taken as chemical shift of these protons.

The methylene protons at C-4 form an AB system and their chemical shifts were calculated using second-order analysis.^[15] The chemical shifts of H-5 and H-6 were determined by first-order analysis in **2b**. Since H-5 and H-6 from an XY system in

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Scheme 1. Synthesis of compounds 2a-2i.

Table 1. Physical and analytical data of 2a – 2i										
			IR (cm ⁻¹)		Found		Calculated			
Compound	Yield (%)	m.p. (°C)	Ester C=0	Keto C=O	% C	% H	% C	% H		
2a	65	103	1735	1659	78.66	6.25	78.73	6.29		
2b	70	116	1739	1654	70.98	5.35	71.08	5.40		
2c	69	112	1736	1659	70.99	5.32	71.08	5.40		
2d	73	130	1737	1660	71.00	5.30	71.08	5.40		
2e	72	146	1738	1660	78.94	6.56	79.08	6.63		
2f	63	112	1734	1659	74.47	5.59	74.54	5.66		
2g	65	86	1736	1657	_	_	_	-		
2h	71	108	1739	1662	_	_	_	-		
2i	72	115	1739	1659	-	-	-	-		

2c, **2d** and **2f** their chemical shifts were calculated using secondorder analysis in these cases. In the other cases, H-5 and H-6 probably form an XX' system and their chemical shifts were taken as the center of the two most intense lines observed for them. In **2c**, **2e**, **2f**, **2h** and **2i** the chemical shifts of the 5aryl protons were calculated using second-order analysis. The ¹H chemical shifts and ¹H-¹H coupling constants are given in Tables 2 and 3, respectively. The ¹³C chemical shifts are furnished in Table 4.

The chemical shifts and coupling constants are quoted to two decimal points less than those obtained directly from the spectral data. Thus, ¹³C chemical shifts were obtained to three decimal points but are rounded off and quoted to one decimal point. When the coupling constants could be determined from several spacings the reported values are the average of all the observed spacing. For example, the value of $J_{4c,4t}$ can be obtained from the spacing between lines 1 and 3 and that between lines 2 and 4 in the signal for H-4c. This value can also be obtained from the signal for H-4t. The reported $J_{4c,4t}$ values are the averages of the several values obtained from the signals of H-4c and H-4t. The individual values differ from the average value by 1–3% when $J_{obs} > 6$ Hz and by 2–5% when $J_{obs} < 6$ Hz.

X-ray crystallographic studies^[12,13] have shown in **2b** and **2g** that the torsional angles about C(1)-C(2) and C(2)-C(3) bonds are in the range $0.3-3.8^{\circ}$. Since *m*- or *p*-substituents cannot have a significant effect on the ring torsional angles in compounds



Figure 1. Conformation of 2a-2i.

2a–**2i** the torsional angles about C(1)-C(2) and C(2)-C(3) bonds should be in this range. Thus, atoms C(1), C(2), C(3), C(4) and C(6) should be almost coplanar, whereas atom C(5) can be above or below this plane. These two arrangements represent the sofa conformations of the two possible enantiomers. The conformation of one enantiomer with C-5 above the plane containing the other carbon atoms is shown in Fig. 1.

For **2b** the *vicinal* coupling constants $J_{4c,5}$ and $J_{4t,5}$ were calculated using second-order analysis and are true values. These values are characteristics of equatorial-axial and diaxial couplings. Also the value of $J_{5,6}$ is the characteristic of diaxial coupling. In the earlier studies,^[12,13] the torsional angle for segments involving hydrogens has not been reported. From X-ray crystallographic data we have found that in **2b** the torsional angles H(4c)-C(4)-C(5)-H(5), H(4t)-C(4)-C(5)-H(5) and H(5)-C(5)-C(6)-H(6) are -56.05, 173.66 and 177.86°, respectively. These torsional angles and the *vicinal* ¹H-¹H coupling constants

Table 2. ¹ H NMR chemical shifts (ppm) of 2a – 2i									
	Compound								
	2a	2b	2c	2d	2e	2f	2g	2h	2i
H-2	6.57	6.57	6.56	6.57	6.56	6.56	6.54	6.53	6.51
H-4c	3.11 ^a	3.20	3.07	3.08	3.08	3.08	3.05	3.04	3.04
H-4 <i>t</i>	3.00 ^a	2.86	2.96	2.97	2.97	2.96	2.97	2.94	2.94
H-5	3.81	4.39	3.80	3.78	3.77	3.80	3.79	3.75	3.75
H-6	3.81	3.97	3.74	3.75	3.77	3.76	3.79	3.75	3.75
C(8)H ₂	4.06	4.08	4.08	4.09	4.07	4.07	4.05	4.07	4.07
C(9)H ₃	1.03	1.07	1.09	1.09	1.07	1.07	1.04	1.07	1.07
H-2′, H-6′	7.55	7.55	7.55	7.55	7.55	7.55	7.55	7.55	7.55
H-3′, H-5′	7.43	7.42	7.43	7.42	7.42	7.43	7.41	7.40	7.10
H-4′	7.43	7.42	7.43	7.42	7.42	7.43	_	_	-
H-2", H-6"	7.33	7.41	7.33	7.33	7.21	7.20	7.21	7.20	7.20
				7.22					
H-3″, H-5″	7.33	7.37	7.26	7.27	7.15	7.04	7.28	7.15	7.15
		7.29							
H-4″	7.33	7.23	_	7.22	_	_	7.21	_	_
^a Calculated assuming J _{4c 4t} as 18.0 Hz.									

Table 3. ${}^{1}H - {}^{1}H$ coupling constants (Hz) of **2a - 2i**

		Compound									
	2a	2b	2c	2d	2e	2f	2g	2h	2i		
J _{2,4t}	2.18	1.96	2.25	2.24	2.34	2.23	2.27	2.24	2.29		
$J_{4c,4t}$	а	18.12	18.10	18.37	18.15	18.29	18.09	18.13	18.32		
^d J _{4c,5}	3.28	4.52	4.20	3.98	3.00	4.26	4.00	3.04	3.03		
^d J _{4t,5}	а	11.02	10.16	9.58	6.99	10.41	6.68	6.46	6.39		
J _{5,6}	b	12.97	13.24	13.09	b	12.69	b	b	b		
е Ј _{6,4t}	а	с	1.18	2.01	4.26	0.81	4.46	4.66	4.92		
^е Ј _{6,4с}	с	с	с	с	0.84	с	0.33	0.85	0.94		

^a The frequencies of only four lines of the AB part where given by the computer and these values could not be determined.

^b Could not be determined since H-6 and H-5 form an XX' system.

^c Not observed.

^d Except for **2b** the reported values are only apparent values.

^e Apparent values.

suggest that the positions of H-5, H-6 and H-4t are equivalent to the axial positions of the chair conformations of cyclohexanone. Also, the positions of Ar', COOEt and H-4c are equivalent to equatorial positions of the chair conformation of cyclohexanone.

In **2b** H-5 and H-4*c* are deshielded but C-4, C-5 and H-4*t* are shielded relative to the other compounds. These observations suggest that the chlorine atom of the *o*-chlorophenyl group lies in between H-4*c* and H-5. In such a conformation, the chlorine atom can interact with the C-H(4*c*) and C-H(5) bonds so that H-4*c* and H-5 get partial positive charge, whereas C-4 and C-5 get partial negative charge. Interestingly, X-ray crystallographic study^[12] has shown that in **2b** the *o*-chlorophenyl group adopts such a conformation.

In all cases, H-2 appeared only as a doublet. In the ${}^{1}H{-}{}^{1}H$ COSY^[16] spectra of **2b** and **2c** there was correlation between H-2 and H-4t. The AB part of the ${}^{1}H$ NMR spectrum of **2b**, containing the signals for H-4c and H-4t, is shown in Fig. 2. The signal due to H-4c is a double-doublet, whereas that of H-4t contain eight lines.

Obviously, H-4*c* couples with H-4*t* and H-5 whereas H-4*t* couples with H-4*c*, H-5 and H-2.

In all the other cases, the signal for H-4t showed additional splittings due to coupling with H-6 also. In **2c**, **2d** and **2f** the value of this coupling varies from 0.81 to 2.01 Hz. In these compounds H-4t, H-6 and H-5 form an AXY system. The values of $J_{4t,6}$ and $J_{4t,5}$ obtained directly from the spectral data are only apparent values. The observed value of $J_{4t,6}$ should be greater than the real value and the observed value of $J_{4t,5}$ should be less than the real value. In **2e**, **2g**, **2h** and **2i** the observed value of $J_{4t,6}$ is greater than 4 Hz. In these compounds H-4t, H-6 and H-5 form an AXX' system causing an increase in the observed value of $J_{4t,6}$ and a decrease in the observed value of $J_{4t,6}$.

In the cases of **2e**, **2h** and **2i** additional splitting occurs in the B part also. The AB part of **2e** is also shown in Fig. 2. The apparent value for the four bond coupling $J_{4c,6}$ is around 0.84–0.94 Hz. The real value of this coupling should be small. Indeed in these cases the value of $J_{4c,5}$ decreases apparently to 3.00–3.04 Hz.

Table 4. ¹⁴ C NMR chemical shifts (ppm) of 2a – 2i										
	Compound									
	2a	2b	2c	2d	2e	2f	2g	2h	2i	
C-1	194.0	193.6	193.4	193.5	194.0	193.6	193.8	193.8	193.8	
C-2	124.1	124.1	124.0	124.1	124.1	124.2	124.3	124.4	124.0	
C-3	158.6	158.3	158.3	158.3	158.5	158.3	157.1	157.1	157.2	
C-4	36.1	34.5	35.8	35.8	36.2	36.2	36.0	36.0	36.3	
C-5	44.1	40.2	43.4	43.7	43.7	43.5	44.0	43.6	43.7	
C-6	59.6	58.1	59.3	59.3	59.7	59.8	59.5	59.6	59.6	
C-7	169.2	168.8	168.9	168.9	169.2	169.1	169.0	169.0	169.1	
C-8	60.9	61.0	60.9	61.1	60.8	61.0	61.0	60.9	60.8	
C-9	13.9	13.9	13.9	14.0	13.9	14.0	13.9	13.9	13.9	
C-1′	137.7	137.7	137.5	137.5	137.8	137.8	136.5	137.2	134.0	
C-2′, C-6′	126.2	126.2	126.1	126.2	126.1	126.2	128.8	129.5	128.2	
C-3′, C-5′	128.8	128.8	128.8	128.9	128.7	128.9	132.1	132.1	115.9 (21 Hz) ^a	
C-4′	130.5	130.5	130.5	130.6	130.4	130.5	124.9	124.9	164.1 (250 Hz) ^a	
C-1″	141.0	138.4	139.5	143.0	138.0	136.9	140.8	137.9	138.0	
C-2″, C-6″	127.3	134.0, 127.3	128.6	127.6, 125.5	127.1	128.9	127.3	127.1	129.5	
C-3″, C-5″	128.8	128.5, 127.6	128.8	134.6, 130.1	129.4	115.7 (21 Hz) ^a	127.7	127.7	127.1	
C-4″	127.5	130.3	133.2	127.7	137.0	162.1 (245 Hz) ^a	127.6	136.7	137.1	
CH ₃	-	-	-	-	20.9	-	-	20.9	20.9	
^a Values of ¹³ C– ¹⁹ F coupling constants.										

The real value of $J_{4t,6}$ can be calculated from the spectral data of **2c**, **2d** and **2f** using second-order analysis. However, the frequencies of all the lines of the XY part were given by the computer only for **2c**. Calculations suggested that the real value of $J_{4t,6}$ in 0.33 Hz. In **2c**, **2d** and **2f** the observed values of $J_{4t,6}$ are greater than this real value due to second-order effect. Since no such second-order effect is in **2b**, the long-range coupling between H-4t and H-6, being really small, is not observed in it.

In **2c** the value of J_{AY} ($J_{4t,5}$) was calculated as 11.01 Hz. However, this cannot be the real value of $J_{4t,5}$ because H-4t, H-4c and H-5 form an ABY system. Further second-order analysis suggested that in **2c** the real values of $J_{4t,5}$ and $J_{4c,5}$ are 11.24 and 3.98 Hz, respectively. Thus, in compounds **2a** – **2i** the real values of $J_{4t,5}$ should be around 11.0 Hz and that of $J_{4c,5}$ should be around 4.0 Hz. Hence, all these compounds must adopt sofa conformation shown in Fig. 1.

Conclusions

In solution 3-aryl-5*r*-aryl-6*t*-carbethoxycyclohex-2-enones adopt sofa conformation with H-4*t*, H-5 and H-6 occupying axial-like positions and the 5-aryl group, carbethoxy group and H-4*c* occupying equatorial-like positions. In 3-phenyl-5*r*-(*o*-chlorophenyl)-6*t*-carbethoxycyclohex-2-enone, the *o*-chlorophenyl group is oriented such that the chlorine atom is in between H-4*c* and H-5. Allylic coupling occurs preferentially with a proton parallel to the *p*-orbitals involved in the formation of π -bond. Evidence is obtained for four-bond coupling between 1,3-diaxial and 1,3-axial–equatorial protons.

Experimental

Preparation of cyclohex-2-enones 2a-2i

A mixture of chalcone ArCOCHCHAr' (0.015 mol), ethyl acetoacetate (0.015 mol) and sodium ethoxide (0.015 mol) in absolute alcohol (50 ml) was refluxed for 14 h. After cooling, the reaction mixture was neutralized with 0.1 N HCl. It was then extracted with diethyl ether (3 \times 20 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed in a rotary evaporator. The solid mass obtained was recrystallized from ethanol.

IR spectra

IR spectra were recorded on an Avatar Nicholet FT-IR spectrometer in KBr pellets.

Mass spectra

Mass spectra were recorded on a VARIAN SATURN 2200 GC – MS/MS spectrometer.

Elemental analysis

Elemental analyses were performed on an Elemental Vario EL III CHNS/O analyzer.

NMR spectra

¹H and ¹³C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400.23 MHz for ¹H and 100.62 MHz for ¹³C. Solutions were prepared by dissolving 10 mg of the compound in 0.5 ml of CDCl₃. All NMR measurements were made in 5 mm NMR tubes. The spectral parameters for ¹H were as follows: spectral width 8223.6859 Hz; acquisition time 3.98 s; number of data points 16K; digital resolution 0.3 Hz; number of scans 16. For ¹³C the spectral parameters were as follows: spectral width 25 000 Hz; acquisition time 1.31 s; number of data points 32K; digital resolution 5 Hz and number of scans 80. 2D NMR spectra of **2b** and **2c** were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. The number of data points were 1K.



Figure 2. ¹H NMR spectra of 2b and 2e (inset – expanded spectra of H-4c and H-4t).

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References

- [1] R. Hernandez, E. Suarez, J. Org. Chem. **1994**, 59, 2766.
- [2] W. Cocker, D. H. Grayson, P. V. R. Shannon, J. Chem. Soc. Perkin Trans. 1 1995, 1153.
- [3] A. Sobolev, M. Vos, H. T. Zuilhof, F. C. E. Saraber, B. J. M. Jansen, A. de Groot, ARKIVOC 2005, 29.
- [4] E. Lewandowska, Tetrahedron 2007, 63, 2107.
- [5] S. C. Pandey, S. S. Singh, B. Patro, A. C. Ghosh, *Indian J. Chem. B* 2004, 43, 2705.
- [6] M. Friedrich, W. Meichle, H. Bernhard, G. Rihs, H.-H. Otto, Arch. Pharm. Med. Chem. 1996, 329, 361.
- [7] B. Rebacz, T. O. Larsen, M. H. Clausen, M. H. Ronnest, H. Loffler, A. D. Ho, A. Karamber, *Cancer Res.* **2007**, *67*, 6342.
- [8] S. Sivasubramanian, A. Ponnuswamy, S. Muthusubramanian, Indian J. Chem. B 1995, 34, 825.
- [9] S. Kamatchi, R. T. Sabapathy Mohan, R. Gomathi, K. Pandiarajan, Indian J. Chem. B 2009, 48, 553.
- [10] K. Pandiarajan, R. T. Sabapathy Mohan, R. Gomathi, G. Muthukumaran, Magn. Reson. Chem. 2005, 43, 430.
- [11] D. Devanathan, K. Pandiarajan, Spectrosc. Lett. 2009, 42, 147.
- [12] N. Anuradha, A. Thiruvalluvar, K. Pandiarajan, C. Yuvaraj, Acta Crystallogr. E 2009, 65, o191.
- [13] N. Anuradha, A. Thiruvalluvar, C. Yuvaraj, K. Pandiarajan, R. J. Butcher, Acta Crystallogr. E 2010, 66, o1896.
- [14] R. M. Silverstein, F. X. Webster, Spectrometric Identification of Organic Compounds (6th edn), Wiley: New York, 2007, p. 209.
- [15] J. A. Pople, H. J. Bernstein, W. G. Schneider, *Can. J. Chem.* **1957**, *35*, 65.
 [16] D. M. Silverstein, F. Y. Webster, *Constant on the information of the second seco*
- [16] R. M. Silverstein, F. X. Webster, Spectrometric Identification of Organic Compounds (6th edn), Wiley: New York, 2007, p. 255.