


Trends in NMR Structural Elucidation Of Polycyclic Cages, Namely: Adamantane, Pentacycloundecane and Trishomocubane

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ABSTRACT

Advances in Nuclear Magnetic Resonance (NMR) spectroscopy is a cornerstone in structure elucidation of polycyclic ‘cage’ scaffolds. Due to the compactness of these compounds, much overlap, as well as unique through-space and bond NMR interactions are frequently observed. This review serves as a guide for the NMR elucidation of future derivatives by providing some of the typical and relevant aspects of the characteristic trends, substituent patterns and chemical shift behaviour for the identification of the polycyclic structures, namely adamantane, pentacycloundecane and trishomocubane derivatives.

KEYWORDS

adamantane, NMR elucidation, pentacycloundecane, polycyclic compounds, trishomocubane

1. Introduction

The chemistry of polycyclic ‘cage’ scaffolds has fascinated organic chemists for over six decades.^{1–8} These compounds include adamantane, pentacycloundecane, trishomocubane, pentacyclodecane, cubane, basketane (Figure 1).

These molecules have played a significant role in synthetic, theoretical and medicinal chemistry. The effect of the unusual cage geometries on chemical reactivity,⁹ and more importantly, its role in pharmacological profiles have been and still are investigated. Application of these compounds in drug discovery stems from the polycyclic cage compounds ability to increase drug lipophilicity¹⁰, thus serving as a transport aid to carry such drug pharmacophores across cellular membranes, including the blood-brain barrier (BBB) and the central nervous system (CNS).^{8, 11–16} Furthermore, polycyclic cage based compounds have been reported to possess antifungal/antibacterial,^{17–18} anti-tuberculosis^{19–23} and anti-viral properties.^{24–28} Research on the chemistry and medicinal applications of this class of polycyclic cage derivatives is ongoing.^{9, 29–32}

In terms of their chemistry, these cage moieties exhibit unique features such as strained bonds/angles due to their rigid nature. The result is broad overlapping of ¹H NMR resonances for long-range proton-proton interactions due to through-space effects, geminal/vicinal proton-proton coupling and long-range proton-proton interactions, making the spectral data assignments quite challenging.^{31, 33} Over the years, with advances in NMR spectroscopy, there has been much progress in the elucidation of these types of compounds, which has been vital in contributing to a better understanding of the chemistry of these fascinating molecules. However, despite the great importance of polycyclic cage compounds, a review of these important NMR spectroscopic data for cage compounds highlighting general

trends and unusual observations appears to be absent in literature. Accordingly, this review summarises the ¹H and ¹³C NMR data of 20 adamantane, 69 pentacycloundecane and 8 trishomocubane derivatives in the bid to establish tendencies; this will be a useful tool for future structural elucidation of these classes of polycyclic compounds. Herein we provide an account on the progress in the NMR elucidation using two-dimensional NMR techniques for the most commonly reported polycyclic cage families, namely: adamantane, pentacycloundecane and trishomocubane.

2. Discussion

The NMR data are arranged into seven tables and three figures to enable easy interpretation of the collated data and as a guide for the elucidation of newer derivatives. There are a few cases where more than one reference for the NMR data of the same compound are documented. Here we used the data that best described the NMR elucidation or pattern. Information on the references, solvents, and magnetic field strength in which the NMR data were obtained for each compound are provided in Table 1.

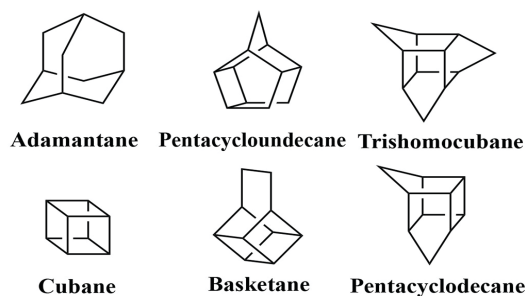


Figure 1. Representative polycyclic cages

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Table 1 Solvent, magnetic field strength and literature references for ¹H and ¹³C NMR data of reported adamantane, pentacycloundecane and trishomocubane derivatives.

Compound #	Solvent/MHz	Ref. ¹ H	Solvent/MHz	Ref. ¹³ C	Compound #	Solvent/MHz	Ref. ¹ H	Solvent/MHz	Ref. ¹³ C
1	CDCl ₃ /400	35	CDCl ₃ /100	35	39	CD ₃ OD/400	45	CD ₃ OD/100	45
2	CDCl ₃ /600	35	CDCl ₃ /150	35	40	(CD ₃) ₂ SO/400	46	(CD ₃) ₂ SO/100	46
3	CDCl ₃ /400	35	CDCl ₃ /100	35	41	CD ₃ OD/600	46	CD ₃ OD/150	46
4	CDCl ₃ /600	35	CDCl ₃ /150	35	42	CD ₃ OD/400	46	CD ₃ OD/100	46
5	CDCl ₃ /400	35	CDCl ₃ /100	35	43	CD ₃ OD/400	46	CD ₃ OD/100	46
6	CDCl ₃ /600	35	CDCl ₃ /150	35	44	(CD ₃) ₂ SO/400	46	(CD ₃) ₂ SO/100	46
7	(CD ₃) ₂ SO/400	36	(CD ₃) ₂ SO/100	36	45	CDCl ₃ /400	47	CDCl ₃ /100	47
8a	CDCl ₃ /300	37	CDCl ₃ /75	37	46	CDCl ₃ /400	47	CDCl ₃ /100	47
8b	CDCl ₃ /300	37	CDCl ₃ /75	37	47	CD ₃ OD/400	47	CD ₃ OD/100	47
9a–9k (<i>syn</i>)	CDCl ₃ /300MHz	38	CDCl ₃ /75MHz	38	48	(CD ₃) ₂ SO/600	48	(CD ₃) ₂ SO/150	48
9a–9k (<i>anti</i>)	CDCl ₃ /300MHz	38	CDCl ₃ /75MHz	38	49	(CD ₃) ₂ SO/400	48	(CD ₃) ₂ SO/100	48
10a	CDCl ₃ /400	39-40	CDCl ₃ /100	39-40	50	(CD ₃) ₂ SO/600	48	(CD ₃) ₂ SO/150	48
10b	CDCl ₃ /600	40	CDCl ₃ /150/175	40	51	(CD ₃) ₂ SO/400	48	(CD ₃) ₂ SO/100	48
10c	CDCl ₃ /600	40	CDCl ₃ /150/175	40	52	(CD ₃) ₂ SO/600	48	(CD ₃) ₂ SO/150	48
10d	CDCl ₃ /600	40	CDCl ₃ /150/175	40	53	(CD ₃) ₂ SO/600	48	(CD ₃) ₂ SO/150	48
10e	CDCl ₃ /600	40	CDCl ₃ /150/175	40	54	(CD ₃) ₂ SO/400	48	(CD ₃) ₂ SO/100	48
10f	CDCl ₃ /600	40	CDCl ₃ /150/175	40	55	(CD ₃) ₂ SO/400	48	(CD ₃) ₂ SO/100	48
10g	CDCl ₃ /600	40	CDCl ₃ /150/175	40	56	CDCl ₃ /400	39	CDCl ₃ /100	39
11	CDCl ₃ /400	39	CDCl ₃ /100	39	57	(CD ₃) ₂ SO/400	45	(CD ₃) ₂ SO/100	45
12	CDCl ₃ /400	39	CDCl ₃ /100	39	58	CDCl ₃ /400	45	CDCl ₃ /100	45
13	CDCl ₃ /400	41	CDCl ₃ /100	41	59	CD ₃ OD/400	45	CD ₃ OD/100	45
14	CDCl ₃ /400	41	CDCl ₃ /100	41	60	CDCl ₃ /400	49	CDCl ₃ /100	49
15	CDCl ₃ /400	42	CDCl ₃ /100	42	61	CDCl ₃ /400	49	CDCl ₃ /100	49
16	CDCl ₃ /400	42	CDCl ₃ /100	42	62	CDCl ₃ /400	49	CDCl ₃ /100	49
17	CDCl ₃ /400	42	CDCl ₃ /100	42	63	(CD ₃) ₂ SO/500	50	(CD ₃) ₂ SO/125	50
18	CDCl ₃ /400	42	CDCl ₃ /100	42	64	CDCl ₃ /500	50	CDCl ₃ /125	50
19	CDCl ₃ /400	42	CDCl ₃ /100	42	65	CD ₃ OD/600	51	CD ₃ OD/150	51
20	CDCl ₃ /400	42	CDCl ₃ /100	42	66	CD ₃ OD/600	51	CD ₃ OD/150	51
21	CDCl ₃ /600	43	CDCl ₃ /150	43	67	CDCl ₃ /500	52	CDCl ₃ /125	52
22	CDCl ₃ /600	43	CDCl ₃ /150	43	68	CDCl ₃ /400	53	CDCl ₃ /100	53
23	CDCl ₃ /600	43	CDCl ₃ /150	43	69	CDCl ₃ /300	54	CDCl ₃ /75	54
24	D ₂ O/400	43	D ₂ O/100	43	70	CDCl ₃ /600	54	CDCl ₃ /125	54
25	CDCl ₃ /600	43	CDCl ₃ /150	43	71	CDCl ₃ /600	54	CDCl ₃ /125	54
26	CDCl ₃ /600	43	CDCl ₃ /150	43	72	CDCl ₃ /400	55	CDCl ₃ /100	55
27	CDCl ₃ /400	44	CDCl ₃ /100	44	73	(CD ₃) ₂ SO/400	56	(CD ₃) ₂ SO/100	56
28	CDCl ₃ /600	45	CDCl ₃ /150	45	74	CDCl ₃ /400	56	CDCl ₃ /100	56
29	CDCl ₃ /400	45	CDCl ₃ /100	45	75	CDCl ₃ /400	56	CDCl ₃ /100	56
30	CDCl ₃ /400	44	CDCl ₃ /100	44	76	CDCl ₃ /400	57	CDCl ₃ /100	57
31	CDCl ₃ /400	41	CDCl ₃ /100	41	77	CDCl ₃ /400	57	CDCl ₃ /100	57
32	CDCl ₃ /400	41	CDCl ₃ /100	41	78	CDCl ₃ /400	57	CDCl ₃ /100	57
33	D ₂ O/400	43	D ₂ O/100	43	79	(CD ₃) ₂ SO/600	36	(CD ₃) ₂ SO/100	36
34	D ₂ O/400	43	⁴³ D ₂ O/100	43	80	CDCl ₃ /400	57	CDCl ₃ /100	57
35	CDCl ₃ /400	44	CDCl ₃ /100	44	77	CDCl ₃ /400	57	CDCl ₃ /100	57
36	CDCl ₃ /400	44	CDCl ₃ /100	44	78	CDCl ₃ /400	57	CDCl ₃ /100	57
37	CDCl ₃ /400	45	CDCl ₃ /100	45	79	(CD ₃) ₂ SO/600	36	(CD ₃) ₂ SO/100	36
38	CDCl ₃ /400	45	CDCl ₃ /100	45	80	CDCl ₃ /400	57	CDCl ₃ /100	57

2.1. Adamantane

Adamantane, a naturally occurring substance, was first isolated in 1933 from petroleum fractions.^{5-6, 34} The synthesis of adamantane was first reported in 1941³⁰ with subsequent reports aimed at improving the reaction yield.⁶ Although scientists have focused extensively on the synthesis⁶ and pharmacological importance of adamantane and its derivatives, great strides have been made recently in the attempt to elucidate adamantane scaffolds when compared to the early 1970s.

From literature, a general trend was observed in the elucidation of monosubstituted (positions 1 or 2) adamantane compounds (1–6) (Figure 2). Free rotation along the C-1 or C-2 (of the adamantane scaffold) with the substituent (X = N, O etc.) amplifies the plane of symmetry of the adamantyl moiety.

For instance, for substituents at position 1 of the adamantane group (compounds 5 and 6), the following carbon groups are equivalent: C-2/C-8/C-9 (CH₂), CH-4/C-6/C-10 (CH₂) and C-3/C-5/C-7 (CH). Signals C-1/C-3 (CH), C-8/C-10 (CH₂), C-4/C-9 (CH₂), C-5 (CH), C-6 (CH₂) and C-7 (CH) are equivalent for substituents at position 2 (compounds 1–4) (see Table 2). The presence of a plane of symmetry on the adamantane moiety further simplifies the structural elucidation of these compounds. However, overlapping in the proton spectrum due to the symmetry and subtle differences of the often diastereotopic carbon skeleton of these derivatives still appears to sometimes obscure some assignments.

Compounds 1–4, reported by Onajole *et al.*³⁵, have the most de-shielded proton assigned to H-2, followed by H-4b/9b, H-1/3,

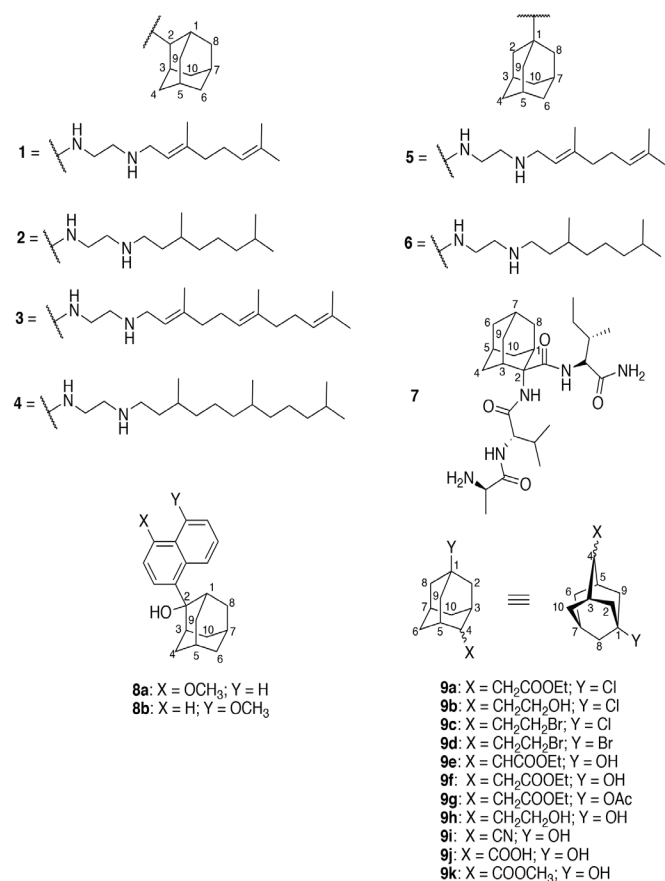


Figure 2 Structures of reported adamantane derivatives 1–9^{35–37}

H-8b/10b or H-7, H-5, H-6/8a/10a and H-4a/9a, consecutively. The de-shielding effect is expected due to the close proximity of the electronegative nitrogen atom.

Makatini *et al.*³⁶ reported di-substituents of compound 7 on C-2 with peptide linkages de-shielding the resonances of the neighbouring protons (Table 2), e.g. H-1/3 have chemical shifts around 2.66–2.74 ppm as compared to 1–6. Another di-substituted adamantane derivatives, **8a** and **8b**,³⁷ with naphthyl and hydroxyl groups attached to C-2 displayed neighbouring protons resonating in the lower field than normal occurrence, e.g. H-1 resonate at 2.48–2.54 ppm. This shift is attributed to the field-effect induced by the π -electron system and the steric hindrance of the bulk naphthyl group due to restricted rotation about the C-2 of adamantane and C-1' of the substituent.³⁷ Moreover, 1D and 2D NMR techniques at different temperatures, as well as computational density functional theory (DFT) studies and single X-ray analysis for **8a**, were used by Jelena *et al.*³⁷ to investigate the anomaly in the conformations of **8a** and of **8b**. Low-temperature NMR spectra (CDCl₃; ¹H and ¹³C) of compounds, **8a** and **8b** at 223 K showed well-resolved proton and carbon signals for both compounds accounting for fourteen chemically inequivalent aliphatic proton atoms and ten inequivalent carbon atoms, all belonging to the adamantane moiety. It is noteworthy, that low temperatures reduced the interconversion of **8a** and **8b** between their non-symmetrical conformations. However, this is not observed in the fast exchange (i.e. at room temperature) as only six different ¹³C chemical shifts corresponding to C5, C6, C7 and the diastereotopic atom pairs (C1, C3), (C4, C9) and (C8, C10) respectively and only eight signals were recorded for the protons (Table 3).

The methylene protons in the adamantane moiety are diastereotopic as a result of rigidity in the molecule, making these protons nonequivalent, therefore, exhibiting spin-spin

Table 2 ¹H NMR data for adamantane derivatives (chemical shift)

H	1 ³⁵	2 ³⁵	3 ³⁵	4 ³⁵	5 ³⁵	6 ³⁵	7 ³⁶	8a ³⁷	8b ³⁷
1	1.77	1.78	1.83	1.81	–	–	2.66–2.74	2.48	2.54
2	2.64	2.63	2.67	2.66	1.58	1.55	–	–	–
3	1.77	1.78	1.83	1.81	1.99	1.96	2.66–2.74	3.2	3.26
4	–	–	–	–	–	–	1.52–1.71/ 1.89–2.74	–	–
4a	1.41	1.43	1.47	1.45	1.56–1.61	1.48–1.57	–	1.68	1.69
4b	1.89	1.91	1.93	1.93	–	–	–	2.55	2.57
5	1.68	1.7	1.74	1.72	1.99	1.96	2.66–2.74	1.94	1.96
6	1.62	1.64	1.68	1.66	1.56–1.61	1.48–1.57	1.52–1.71/ 1.89–2.74	–	–
6a	–	–	–	–	–	–	–	1.73	1.74
6b	–	–	–	–	–	–	–	1.67	1.68
7	1.74	1.76	1.81	1.78	1.99	1.96	2.66–2.74	1.78	1.79
8	–	–	–	–	–	–	1.52–1.71/ 1.89–2.74	–	–
8a	1.62	1.64	1.68	1.66	1.58	1.55	–	1.94	1.9
8b	1.75	1.76	1.81	1.79	–	–	–	2.42	2.46
9	–	–	–	–	–	–	1.52–1.71/ 1.89–2.74	–	–
9a	1.41	1.43	1.47	1.45	1.58	1.55	–	1.75	1.77
9b	1.89	1.91	1.93	1.93	–	–	–	2.58	2.6
10	–	–	–	–	–	–	1.52–1.71/ 1.89–2.74	–	–
10a	1.62	1.64	1.68	1.66	1.56–1.61	1.48–1.57	–	1.5	1.51
10b	1.75	1.75	1.81	1.79	–	–	–	1.15	1.12

interactions. The protons (Ha) axial to each of the cyclohexyl rings show signals appearing at a lower frequency than the equatorial protons (Hb) due to the through-space effect. This effect is observed for compounds 1–4 as well as **8a** and **8b**. NOESY/ROESY interactions of Ha/Hb with neighbouring protons were used to distinguish between these two protons resulting from their orientation in space. Studies have shown that a class of 1,4-disubstituted adamantane derivatives (**9a–9k**) (Figure 2) containing electron-withdrawing groups at both positions C-1 and C-4 resulted in increased chemical shifts of adjacent protons.³⁸ This substituent pattern causes the resonances of the flanking carbons of the *cis*-isomers to be relatively closer together than the *anti*-isomers. These compounds, **9a–9k**, show large discrepancies in both proton and carbon resonance signals from the other classes stated above. In the carbon-13 spectra, compounds 1–4 with substituent attached to C-2 recorded the most de-shielded signal for C-2, followed by either C-6 or C-8/10, C-1/3, C-4/9, C-7, and C-5 consecutively, in decreasing order of chemical shift with C-5 being the most shielded (Table 3). The following class of compounds, **5**, **6**, **7**, including **8a** and **8b** isomers, displayed a definite pattern of chemical shifts of carbon-13 signals for each class as observed in their carbon spectra. The *syn*-isomers of compounds **9** registered C-1, C-8, C-2/9, C-4, C-6/10, in order of decreasing frequency except for **9f** and **9g** (**9k**), where the order of C-2/9 and C-4 (C-8 and C-2/9) are reversed, while the *anti*-isomers recorded C-1, through C-2/9, C-8, C-4, C-3/5, C-7, to C-6/10 in a definite order of decreasing chemical shift except for **9i** and **9k** with each displaying a different pattern. The combined effect of the 1,4-disubstituents on the adamantane skeleton causes the signals of C-2, 9 and C-6, 10 to be fairly close together in the *syn*-isomers while they are further apart in the *anti*-isomers.

The signals for the proton and carbon resonances fall within a similar region for equivalent positions for this class compounds with the same substituent pattern as displayed in Tables 2 and 3. The electron-withdrawing groups on either C-1, C-2 or C-4 have the effect of shifting the resonance signals of the adjacent protons towards the higher frequency region. So far,

Table 3. ¹³C NMR data for adamantane derivatives (chemical shift)

Atom	1 ³⁵	2 ³⁵	3 ³⁵	4 ³⁵	5 ³⁵	6 ³⁵	7 ³⁶	8a ³⁷	8b ³⁷	Atom	1 ³⁵	2 ³⁵	3 ³⁵	4 ³⁵	5 ³⁵	6 ³⁵	7 ³⁶	8a ³⁷	8b ³⁷
1	31.8	32.1	32.3	32.1	50.2	50.7	31.2	37.8	37.8	7	27.6	27.8	27.8	27.8	29.7	29.5	31.2	27.2	27.1
2	61.7	61.8	61.9	61.8	42.8	42.7	63.6	77.7	78.0	8							32.2/33.3	36.3	36.3
3	31.8	32.1	32.3	32.1	29.7	29.5	31.2	36.1	36.1	8a	37.4	37.5	37.6	37.5	42.8	42.5			
4							32.2/33.3	32.5	32.5	8b	37.4	37.5	37.6	37.5	–	–			
4a	31.1	31.3	31.3	31.3	36.8	36.6				9							32.2/33.3	33.7	33.8
4b	31.1	31.3	31.3	31.3	–	–				9a	31.1	31.3	31.3	31.3	42.8	42.5			
5	27.4	27.6	27.6	27.6	29.7	29.5	31.2	26.5	26.5	9b	31.1	31.3	31.3	31.3	–	–			
6	37.7	37.9	27.6	37.9	36.8	36.6	32.2/33.3	37.4	37.4	10							32.2/33.3	33.9	33.8
6a										10a	37.4	37.5	37.6	37.5	36.8	36.6			
6b										10b	37.4	37.5	37.6	37.5	–	–			

Atom	9a ³⁸ (syn)	9a ³⁸ (anti)	9b ³⁸ (syn)	9b ³⁸ (anti)	9c ³⁸ (syn)	9c ³⁸ (anti)	9d ³⁸ (syn)	9d ³⁸ (anti)	9f ³⁸ (syn)	9f ³⁸ (anti)	9g ³⁸ (syn)	9g ³⁸ (anti)	9h ³⁸ (syn)	9h ³⁸ (anti)	9i ³⁸ (syn)	9i ³⁸ (anti)	9k ³⁸ (syn)	9k ³⁸ (anti)
1	68.03	67.61	68.6	68.29	68.15	67.91	65.65	65.28	67.89	67.7	79.69	79.47	68.01	68.17	66.61	66.43	67.46	67.58
2	41.67	48.37	41.73	48.65	41.86	48.45	43.44	50.07	39.27	45.93	37.15	42.05	39.46	46.13	40.72	43.76	41.33	45.18
3	35.24	34.66	35.24	34.78	34.76	34.21	35.61	35.18	34.35	33.67	34.47	33.79	34.47	33.76	32.84	32.60	31.98	31.64
4	39.03	39.24	38.50		40.74	41.08	40.77	41.08	39.44	39.72	39.63	39.80	39.07	39.23	35.29	35.56	47.88	48.22
5	35.24	34.66	35.24	34.78	34.76	34.21	35.61	35.18	34.35	33.67	34.47	33.79	34.47	33.76	32.84	32.6	31.98	31.64
6	36.53	29.43	36.64	29.52	36.61	29.64	36.61	29.68	37.00	29.84	35.23	30.03	37.29	29.98	34.81	31.43	36.24	31.90
7	30.97	30.98	31.23	31.15	31.27	31.05	32.17	31.95	29.97	30.01	30.10	30.15	30.39	30.80	28.84	29.12	29.71	29.58
8	47.99	47.99	48.02	48.10	48.01	48.01	49.63	49.61	45.62	45.53	41.67	41.50	45.79	45.63	43.91	44.30	44.68	44.90
9	41.67	48.37	41.73	48.65	41.86	48.45	43.44	50.07	39.27	45.93	37.15	42.05	39.46	46.13	40.72	43.76	41.33	45.18
10	36.53	29.43	36.64	29.52	36.61	29.64	36.61	29.68	37.00	29.84	35.23	30.03	37.29	29.98	34.81	31.43	36.24	31.90

aromatic rings attached to an adamantane cage is expected to cause a large de-shielding effect of the adjacent proton resonances as compared to carbonyl, amino, hydroxyl, and other electron-withdrawing groups. The ¹³C Attach Proton Test (APT), Heteronuclear Single Quantum Coherence (HSQC), and Heteronuclear Multiple Bond Correlation (HMBC) spectra served as useful tools in resolving the overlapping signals of the proton and carbon signals observed mainly for the unsymmetrical derivatives.

2.2. Pentacycloundecane

The synthesis of the Cookson's dione, which is the starting material for all pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) derivatives, was first reported in 1964.⁴ It was not until 1993 that Cadd *et al.*³³ published the complete NMR assignment of the compound using ¹H and ¹³C NMR spectra. Although 1D NMR was found to be useful in the elucidation of various polycyclic cage compounds, 2D NMR proved to be a more effective tool for the PCU elucidation due to the geminal/vicinal proton-proton couplings along with long-range proton-proton interactions and the prevalence of overlapping of proton and carbon signals. The elucidation of PCU compounds becomes fairly straightforward for compounds with a plane of symmetry, therefore, making all of the atoms except for the protons on C-4 (H-4a and H-4s) to appear in pairs: H-1/H-7, H-2/H-6, H-3/H-5, H-9/H-10, determined from the ¹H-NMR data. It has been confirmed that the geminal protons at C-4 resonating as a pair of doublets display an AB spin-spin interaction around 1.5 and 1.8 ppm with a coupling constant of approximately 10 Hz.^{48, 58} Hence, Correlation Spectroscopy (COSY), Nuclear Overhauser Effect Spectroscopy (NOESY) and Rotating frame Overhauser Effect Spectroscopy (ROESY) interactions of H-4a (H-4s) with H-3/5 and H-2/6 (H-9/10), respectively, have been established as a starting point for the structural elucidation of PCU cage derivatives. In addition, HMBC, NOESY, and ROESY techniques are useful in determining the side "arm" with respect to the cage moiety.⁴⁸

Kenwright *et al.*,⁴⁰ reported a series of compounds, **10a–10g** (Figure 3), where the protons in the 2 and 6 positions of the

four-membered ring have the highest shift in frequency of all the methine protons in unsubstituted PCU derivatives. However, the chemical shift of position 2 appears de-shielded when position 1 is substituted by an alkyl or methoxy group. At least in most cases, it reduces to a frequency lower than any one of the bridgehead protons at position 3 or 5. H-6 is always the most de-shielded proton (Table 4) when there is no substituent attached to position 7, while H-2, H-3, or H-5 follow at the next highest frequency, but the order depends on the position and type of substituent at H-9 or H-10. A significant shift in the proton signal of H-9/H-10 is found in the derivatives where alkyl substituent is attached to either C-9 or C-10 than when alkyl substituent is attached to other positions and in unsubstituted PCU derivatives.

Generally, electron-withdrawing groups such as methoxy at C-1 and/or C-2 cause adjacent proton signals to be de-shielded but has no marked effect on protons farther away from the substituent. Furthermore, it is generally observed that the relative shifts in the signals of the methine protons are opposite to the trend for the carbon signals. Hence, the proton with the highest chemical shift value has its corresponding carbon appearing at the lowest frequency.

An asymmetric keto-ketal, **11**, reported by Kruger *et al.*,³⁹ recorded H-2 as the most de-shielded signal, followed next by H-3 and H-6 in decreasing order of frequency. At the same time, H-9 was registered as the most shielded signal among the methine protons. PCU ether with symmetrical substituents at positions 8 and 11 recorded the most de-shielded signal for H-2/6 of all the methine protons for **12–44** (Table 4). The next set of de-shielded signals is recorded for H-1/7 and H-9/10 consecutively, while the reverse is true for only **13**, but H-3/5 immediately follows H-1/7 in decreasing order of chemical shift for **41–44**. However, **27** and **31** are the only compounds where H-1/7 was recorded as the most de-shielded proton and followed next by H-9/10 and H-2/6 accordingly. The chiral side arm substituent of compound **27** induced diastereomeric character to the cage moiety. As a result of this effect, the cage protons are nonequivalent, thus making its elucidation challenging. Also, in compound **35**, the diastereomeric effect

Table 4 (continued) ¹H NMR data for pentacycloundecane derivatives (chemical shift and coupling constant)

Atom	24 ⁴³	25 ⁴³	26 ⁴³	27 ⁴⁴	28 ⁴⁵	29 ⁴⁵	30 ⁴⁴	31 ⁴¹	32 ⁴¹	33 ⁴³
H1	2.69	2.65	2.65	2.82	2.58	2.41	2.68	2.73	2.53	2.57
H2	2.73	2.69	2.68	2.64	2.6	2.5	2.71	2.61	2.56	2.59
H3	2.52	2.48	2.47	2.41	2.37	2.27	2.5	2.38	2.33	2.4
H4a	1.6, 10.6Hz	1.55, 10.5Hz	1.55, 7.0Hz	1.51, 10.5Hz	1.52, 10.4Hz	1.42, 10.4Hz	1.59, 10.5Hz	1.47, 10.4Hz	1.40, 10.6Hz	1.49, 10.6Hz
H4s	1.97, 10.6Hz	1.93, 10.5Hz	1.93, 7.0Hz	1.90, 10.5Hz	1.82, 10.4Hz	1.78, 10.4Hz	1.93, 10.5Hz	1.83, 10.4Hz	1.75, 10.6Hz	1.83, 10.6Hz
H5	2.52	2.48	2.47	2.41	2.37	2.27	2.5	2.38	2.33	2.4
H6	2.73	2.69	2.68	2.64	2.6	2.5	2.71	2.61	2.56	2.59
H7	2.69	2.65	2.65	2.82	2.58	2.41	2.68	2.73	2.53	2.57
H8										
H9	2.67	2.63	2.63	2.75	2.57	2.39	2.64	2.64	2.45	2.54
H10	2.67	2.63	2.63	2.75	2.57	2.39	2.64	2.64	2.45	2.54
H11										
Atom	34 ⁴³	35 ⁴⁴	36 ⁴⁴	37 ⁴⁵	38 ⁴⁵	39 ⁴⁵	40 ⁴⁶	41 ⁴⁶	42 ⁴⁶	43 ⁴⁶
H1	2.59	2.87	2.73	2.59	2.65	2.77	2.58	2.09/2.11	2.55	2.37
H2	2.61	2.87	2.73	2.57	2.62	2.74	2.47	2.48	2.62	2.51
H3	2.42	2.56	2.45	2.39	2.43	2.5	2.36	2.26/2.30	2.49/2.55	2.43
H4a	1.50, 10.6Hz	1.65, 10.5Hz	1.55, 10.5Hz	1.47, 10.5Hz	1.49, 10.5Hz	1.59, 10.4Hz	1.02, 10.4Hz	1.04, 10.6Hz	1.18, 10.8 Hz	1.10, 10.8Hz
H4s	1.85, 10.6Hz	1.98, 10.5Hz	1.90, 10.5Hz	1.82, 10.5Hz	1.85, 10.5Hz	1.97, 10.4Hz	1.49, 10.4Hz	1.39, 10.5Hz	1.60, 10.7Hz	1.50, 10.7Hz
H5	2.42	2.56	2.45	2.39	2.43	2.5	2.36	2.26/2.30	2.49/2.55	2.43
H6	2.61	2.87	2.73	2.57	2.62	2.74	2.47	2.48	2.62	2.51
H7	2.59	2.87	2.73	2.59	2.65	2.77	2.58	2.09/2.11	2.55	2.37
H8										
H9	2.56	2.87	2.73	2.58	2.62	2.73		1.67/1.89	2.33/2.40	2.15
H10	2.56	2.87	2.73	2.58	2.62	2.73		1.67/1.89	2.33/2.40	2.15
H11										
Atom	44 ⁴⁶	45 ⁴⁷	46 ⁴⁷	47 ⁴⁷	48 ⁴⁸	49 ⁴⁸	50 ⁴⁸	51 ⁴⁸	52 ⁴⁸	53 ⁴⁸
H1	2.67	2.76	2.58	2.81	2.75	2.77	2.72	2.76	2.73	2.73
H2	2.52	2.67	2.59	2.66	2.66	2.65	2.58	2.63	2.59	2.59
H3	2.42	2.51	2.42	2.5	2.52	2.51	2.45	2.47	2.44	2.46
H4a	1.04, 10.6Hz	1.57, 10.4Hz	1.52, 10.8Hz	1.56, 10.4Hz	1.47, d, 10.4Hz	1.47, d 10.1Hz	1.47, d 9.3Hz	1.48, d 10.2Hz	1.44, d 0.2Hz	1.45, d 10.1Hz
H4s	1.48, 10.5Hz	1.91, 10.4Hz	1.85, 10.8Hz	1.90, 10.4Hz	1.82/1.84, ^a d, 6.0Hz	1.83, d 10.1Hz	1.82, ^b t 9.3Hz	1.83, d 10.2Hz	1.79/1.80, ^a d, 6.1Hz	1.79/1.80, ^a d, 6.1Hz
H5	2.42	2.65	2.61	2.58	2.46	2.49	2.44	2.47	2.45	2.45
H6	2.52	2.78	2.74	2.74	2.68	2.66	2.64	2.65	2.65	2.67
H7	2.67	2.61	2.62	2.56	2.48	2.51	2.47	2.44	2.44	2.42
H8		-	-	-						
H9	2.1	2.62	2.59-2.62	2.57	2.52	2.55	2.49	2.47	2.47	2.48
H10	2.1	2.75	2.59-2.62	2.75	2.71	2.69	2.66	2.65	2.65	2.65
H11		-	-	-						
Atom	54 ⁴⁸	55 ⁴⁸	56 ³⁹	57 ⁴⁵	58 ⁴⁵	59 ⁴⁵	60 ⁴⁹	61 ⁴⁹	62 ⁴⁹	63 ⁵⁰
H1	2.71	2.72	2.44	2.41	2.46	2.6	2.86	2.68	2.71	2.268
H2	2.57	2.58	2.45	2.48	2.49	2.64	2.56	2.66	2.69	2.549
H3	2.43	2.45	2.36	2.4	2.38	2.56	2.35	2.62	2.66	2.569
H4a	1.44, d 10.2Hz	1.44, d 10.1Hz	1.07	1.05, 10.5Hz	1.06, 10.8Hz	1.20, 10.7Hz	0.99, 10.8Hz	1.08, 11.0Hz	1.10, 10.8Hz	1.336, 10.5Hz
H4s	1.78, 10.2Hz	1.79, 10.1Hz	1.5	1.50, 10.5Hz	1.52, 10.8Hz	1.65, 10.7Hz	1.51, 10.8Hz	1.51, 11.0Hz	1.54, 10.8Hz	1.660, 10.5Hz
H5	2.43	2.44	2.36	2.4	2.38	2.56	1.79	1.81	1.91	2.645
H6	2.66	2.64	2.45	2.48	2.49	2.64	2.58	2.6	2.64	2.723
H7	2.46	2.45	2.44	2.41	2.46	2.6	3.12	3.16	3.19	2.282
H8							5.10 (8-OH)			
H9	2.45	2.5	2.15	2.19	2.31	2.37	2.55	2.63	2.69	2.097
H10	2.66	2.64	2.15	2.19	2.31	2.37	2.59	2.33	2.35	2.066
H11							3.81, 1.62 (11-OH)			

^aTwo separate resonances potentially due to a side-chain conformational effect^bDue to the coalescence of the pair of doublets, the signal appears as a triplet

Table 4 (continued) ¹H NMR data for pentacycloundecane derivatives (chemical shift and coupling constant)

Atom	64 ⁵⁰	65 ⁵¹	66 ⁵¹	67 ⁵²	68 ⁵³	69 ⁵⁴	70 ⁵⁴	71 ⁵⁴	72 ⁵⁵
H1	2.966	2.73	2.75	2.838	2.85	3.37–3.41	2.75–2.78	2.40–2.46	2.33
H2	2.628	2.62	2.62	2.652	2.66	2.81–2.85	2.55–2.62	2.60–2.64	2.52
H3	2.535	2.26	2.3	2.273	2.33	2.19–2.23	2.49–2.53	2.55–2.59	2.27
H4a	1.489, 10.4 Hz	1.23, 10.35 Hz	1.26, 10.5 Hz	1.243, 10.8 Hz	1.23, 10.91 Hz	1.32 (d, 11.15 Hz)	1.42 (d, 10.84 Hz)	1.47 (d, 10.89 Hz)	1.15, 10.7 Hz
H4s	1.788, 10.4 Hz	1.71, 10.35 Hz	1.72, 10.5 Hz	1.64, 10.8 Hz	1.66, 10.91 Hz	1.37 (d, 11.15 Hz)	1.64 (d, 10.84 Hz)	1.90 (d, 10.89 Hz)	1.57
H5	2.878	2.57	2.15	2.989	2.98	2.19–2.23	2.33–2.36	2.55–2.59	2.27
H6	2.91	2.57	2.64	2.752, q, 7.1 Hz	2.77	2.81–2.85	2.68–2.73	2.60–2.64	2.52
H7	2.535	3.28	3.33	2.591, t, 6.6 Hz	2.6	3.37–3.41	2.86–2.90	2.40–2.46	2.53
H8									
H9	2.333	2.85	2.84	2.324	2.33	2.55–2.58	2.90–2.94	3.18–3.24	2.21
H10	2.794	2.46	2.47	2.528	2.53	2.55–2.58	2.78–2.81	3.18–3.24	2.31
H11		0.96 (11a)/ 2.06 (11s), 13.0 Hz	1.04(11a)/ 2.10 (11s), 12.8 Hz	1.267 (11a), dt, 8.4, 3.4 Hz/ 1.450 (11s), d, 13.7 Hz	1.28 (11a, 12.5 Hz)/ 1.40 (11s, 12.5 Hz)				

(induced by the chirality on the side arms) causes all the cage carbon signals to display a split pattern. High-temperature NMR experiments of **35** (333, 393 and 423 K) revealed that the C-1/7, C-9/10, and C-8/11 signals remained split even at the highest tested temperature (423 K) with the exception of C-4, an achiral methylene carbon, thus further confirming the diastereomeric effect experienced by these carbon atoms. This observed interaction illustrated a conformation of **35**, where one of the “arms” is positioned in front of the cage moiety while the other is at the back. As previously reported for related chiral PCU ligands,^{41–44, 48, 55, 59} the presence of heteroatoms on the side arms at close proximity to the cage induces a through-space de-shielding effect, which results in non-equivalence of atoms on the cage and that of the “arm” as observed in the ¹³C spectrum.

H-3/5 was registered as the most shielded proton of all the methine protons for the symmetrically substituted PCU ether at positions 8 and 11, except for **41–44**, where H-9/10 was recorded as the lowest frequency. The chemical shift of the carbon signals of compounds **12–44** follows a definite trend by decreasing from C-8/11 through C-9/10, C-1/7, C-3/5, C-4 to C-2/6. However, **31**, **32** and **40–44** show deviation from this regular pattern, where C-4 was registered as the lowest carbon frequency while C-2/6 takes the position of C-4, and that observed for **32** is given as follows, C-8/11, through C-9/10, C-1/7, C-2/6, C-3/5, to C-4. It is noteworthy that equivalent carbons resonate within a similar range of frequency. The electron-withdrawing effect induced by the oxo bridge of the ether functional group holding C-8 and C-11 together has an intense effect on these carbons; hence, they were recorded as the most de-shielded. Since C-1/7 and C-9/10 are both adjacent to the ether group, C-1/7 is expected to be

the next de-shielded because it is enclosed in a four-membered ring inducing strain effect. However, C-9/10 was recorded as the second most de-shielded carbon due to the high stretching strain exerted by the oxo bridge of the ether. This evidence is supported by single X-ray diffraction of certain PCU derivatives indicating shorter bond length for C9-C10 than normal value expected due to the stretching strain induced by the oxo bridge holding the cage “mouth” together by C8 and C11.⁶⁰

For the ether monosubstituted hydroxyl group at position 8, with position 11 substituted by an alkene functionality (**45** and **46**), methylene carboxylic acid (**47**) and the carbonyl group of peptide linkage (**48–55**), H-1 signal was attributed to the highest frequency, followed by H-10 and/or H-6. However, **45** and **46** registered the highest chemical shift value for H-6, followed by H-1 and H-10, and H-10 and H-1, respectively. The highest ppm was attributed to H-1 due to the electron-withdrawing effect induced by the carbonyl group attached to position 11. At the same time, there is little effect due to the alkene functionality compared to the carbonyl. H-3, H-5, and H-7 were recorded as the lowest frequency for **45–47**, **48–50/54–55** and **51–53**. H-3 and H-5 are farther away from the electron-withdrawing groups, hence experience little or no effect from these groups. This class of compounds exhibited a general pattern of carbon chemical shift decreasing from C-8, C-11, C-10, C-9, C-1, C-7 to C-3. The lowest frequency was registered for C-6 except for **45** and **46**, which recorded the lowest chemical shift for C-2. Simultaneously, the remaining two carbons, C-4 and C-5, show a very slight difference in ppm with C-4 slightly higher than C-5 or vice versa (see Table 5). C-8 was recorded as the most de-shielded carbon due to the hydroxyl group directly attached to

Table 5 ¹³C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	10a ⁴⁰	10b ⁴⁰	10c ⁴⁰	10d ⁴⁰	10e ⁴⁰	10f ⁴⁰	10g ⁴⁰	11 ³⁹	12 ³⁹	13 ⁴¹
C1	43.8	48.4	82.0	48.1	47.7	56.4	83.4 or 83.5	42.3	47.6	47.9
C2	38.7	45.0	43.3	44.3	43.9	40.2	41.1 or 41.2	41.5	41.4	41.6
C3	44.6	43.7	43.9	44.0	49.5	44.0	43.8	45.8	44.1	44.2
C4	40.5	40.9	41.9	39.5	39.9	39.7	41.3	38.7	43.5	43.5
C5	44.6	44.5	43.8	50.0	44.6	50.1	49.4	42.9	44.1	44.2
C6	38.7	36.2	34.6	34.9	35.5	35.5	41.1 or 41.2	36.3	41.4	41.6
C7	43.8	50.3	48.5	49.8	50.0	45.7	83.4 or 83.5	41.3	47.6	47.9
C8	212.1	212.2	209.6	213.9	212.4	214.6	211.0	215.4	96.4	95.0
C9	54.7	54.5	54.7	58.2	62.0	59.7	54.8	50.7	58.2	58.6
C10	54.7	54.7	50.8	61.4	58.4	63.3	58.5	53	58.2	58.6
C11	212.1	212.8	210.6	213.0	214.5	212.9	209.4	113.9	96.4	95.0

Table 5 (continued) ¹³C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	14 ⁴¹	15 ⁴²	16 ⁴²	17 ⁴²	18 ⁴²	19 ⁴²	20 ⁴²	21 ⁴³	22 ⁴³	23 ⁴³
C1	47.9	48	48.1	48	48	48.0	48.0	47.8	47.9	47.8
C2	41.6	41.8	41.8	41.8	41.8	41.8	41.8	41.5	41.6	41.5
C3	44.3	44.5	44.5	44.4	44.5	44.5	44.5	44.2	44.3	44.1
C4	43.4	43.4	43.5	43.5	43.4	43.4	43.4	43.5	43.5	43.4
C5	44.3	44.5	44.5	44.4	44.5	44.5	44.5	44.2	44.3	44.1
C6	41.6	41.8	41.8	41.8	41.8	41.8	41.8	41.5	41.6	41.5
C7	47.9	48	48.1	48	48	48.0	48.0	47.8	47.9	47.8
C8	95	94.9	94.8	94.7	94.8	94.9	94.9	95.6	95.4	95.2
C9	58.7	58.8	58.8	58.8	58.8	58.8	58.8	58.4	58.6	58.5
C10	58.7	58.8	58.8	58.8	58.8	58.8	58.8	58.4	58.6	58.5
C11	95	94.9	94.8	94.7	94.8	94.9	94.9	95.6	95.4	95.2
Atom	24 ⁴³	25 ⁴³	26 ⁴³	27 ⁴⁴	28 ⁴⁵	29 ⁴⁵	30 ⁴⁴	31 ⁴¹	32 ⁴¹	33 ⁴³
C1	47.3	47.2	47.2	48.67/48.58	45.9	47.7	48.57	48.5	47.5	48.3
C2	41.2	41.1	41.1	41.86/41.84	41.5	41.3	41.62	43.3	44.3	41.5
C3	44.1	44	44.1	44.64/44.61	41.5	44	44.16	44.5	43.9	44.1
C4	43.0	43	43	43.55	43.4	43.4	43.45	41.8	43.2	43.4
C5	44.1	44	44.1	44.64/44.61	41.5	44	44.16	44.5	43.9	44.1
C6	41.2	41.1	41.1	41.86/41.84	41.5	41.3	41.62	43.3	44.3	41.5
C7	47.3	47.2	47.2	48.67/48.58	45.9	47.7	48.57	48.5	47.5	48.3
C8	94.9	94.9	94.8	93.71/93.69	97.4	95.3	92.77	92.8	93.6	93.8
C9	57.9	57.9	57.9	59.26/59.16	56.4	58.3	59.21	59.2	58.4	58.6
C10	57.9	57.9	57.9	59.26/59.16	56.4	58.3	59.21	59.2	58.4	58.6
C11	94.9	94.9	94.8	93.71/93.69	97.4	95.3	92.77	92.8	93.6	93.8
Atom	34 ⁴³	35 ⁴⁴	36 ⁴⁴	37 ⁴⁵	38 ⁴⁵	39 ⁴⁵	40 ⁴⁶	41 ⁴⁶	42 ⁴⁶	43 ⁴⁶
C1	48.2	48.83/47.82	48.63/48.01	48	48.1	49.5	42.2	44.5/44.8	44.3	45.7
C2	41.4	41.50/41.44	41.54/41.39	41.3	41.4	42.8	38.8	39.4/39.7	40.6/40.7	40.6
C3	44.1	44.28/44.19	44.12/44.00	43.9	44	45.6	43.8	43.2/43.8	45.7	44.4
C4	43.4	43.35	43.48	43.3	43.4	44.3	33.4	33.9	34.8	34.8
C5	44.1	44.28/44.19	44.12/44.00	43.9	44	45.6	43.8	43.2/43.8	45.7	44.4
C6	41.4	41.50/41.44	41.54/41.39	41.3	41.4	42.8	38.8	39.4/39.7	40.6/40.7	40.6
C7	48.2	48.83/47.82	48.63/48.01	48	48.1	49.5	42.2	44.5/44.8	44.3	45.7
C8	93.9	94.21/94.16	94.14	93.6	94	95.2	76.4	77.2/77.8	78.5/78.6	78.7
C9	58.5	59.11/58.06	59.05/58.40	58.4	58.6	59.9	49.9	49.1/49.4	50.7/50.9	50.8
C10	58.5	59.11/58.06	59.05/58.40	58.4	58.6	59.9	49.9	49.1/49.4	50.7/50.9	50.8
C11	93.9	94.21/94.16	94.14	93.6	94	95.2	76.4	77.2/77.8	78.5/78.6	78.7
Atom	44 ⁴⁶	45 ⁴⁷	46 ⁴⁷	47 ⁴⁷	48 ⁴⁸	49 ⁴⁸	50 ⁴⁸	51 ⁴⁸	52 ⁴⁸	53 ⁴⁸
C1	42	49.39	48.03	49.52	48.9	48.7	48.2	48.4	48.1	48.2
C2	38.5	42.12	41.93	43.34	42.2	42.1	42.2	42.2	42.1	42.1
C3	43.9	45.36	45.2	46.38	46.1	46	46.2	46.1	46.2	46.1
C4	33.5	43.55	43.5	44.05	42.8	42.8	42.8	42.8	42.8	42.8
C5	43.9	43.96	44.03	45.14	42.7	42.7	42.8	42.7	42.7	42.7
C6	38.5	42.25	42.3	42.99	41.1	40.9	41	41	40.9	40.9
C7	42	47.92	47.75	48.49	46.3	46.2	46.4	46.3	46.2	46.3
C8	77.8	118.48	118.16	119.13	118.2	118.1	118.2	118.2	118.1	118.1
C9	50.3	57.74	58.13/58.17	58.78	56.2	56.4	56.2	56.2	56.1	56.1
C10	50.3	59.17	58.13/58.17	59.8	58.6	58.5	57.9	58.2	57.9	58.2
C11	77.8	91.84	91.46	89.89	89.8	89.6	89.7	89.5	89.6	89.5
Atom	54 ⁴⁸	55 ⁴⁸	56 ³⁹	57 ⁴⁵	58 ⁴⁵	59 ⁴⁵	60 ⁴⁹	61 ⁴⁹	62 ⁴⁹	63 ⁵⁰
C1	48.1	48.2	42.8	42.5	42.9	44.4	38.9	39.26	39.31	45.90
C2	42	42.1	40	38.9	39.3	40.7	39.01	39.42	39.48	40.30
C3	46	46.1	44	43.8	44.3	45.8	44.3	52.91	52.9	45.59
C4	42.8	42.8	33.9	33.5	34	34.8	34.11	34.58	34.63	36.58
C5	42.7	42.8	44	43.8	44.3	45.8	46.69	44.93	44.59	45.26
C6	41	41	40	38.9	39.3	40.7	41.52	40.68	40.71	41.43
C7	46.3	46.4	42.8	42.5	42.9	44.4	41.5	41.7	41.79	44.96
C8	118.1	118.2	72.2	76.6	77.3	78.6	79.4	78.7	78.62	79.86
C9	56.1	56.2	49.1	49.3	49.5	51	51.31	45.6	45.61	52.33
C10	58.2	57.9	49.1	49.3	49.5	51	46.7	47.5	47.55	53.78
C11	89.5	89.6	77.2	76.6	77.3	78.6	71.92	115.5	115.51	73.58

Table 5 (continued) ^{13}C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	64 ²⁰	65 ⁵¹	66 ⁵¹	67 ⁵²	68 ⁵³	69 ⁵⁴	70 ⁵⁴	71 ⁵⁴	72 ⁵⁵
C1	44.01	37.9	37.2	35.40	35.9	43.9 (49.1)	38.4 (40.6)	40.4 (41.7)	41.5
C2	39.96	43.0	43.1	41.30	41.5	40.4	41.1	38.1	39.2
C3	43.63	48.2	48.4	46.00	46.5	45.2	44.6	45.2	42.29
C4	37.59	35.3	35.4	33.82	34.3	38.1	38.1	38	35.1
C5	45.61	42.2/45.8	44.7	42.41	42.4	45.2	46	45.2	42.58
C6	42.19	42.2/45.8	43.1	41.19	41.4	40.4	39.9	38.1	39.6
C7	45.21	42.2	40.2	41.40	41.7	43.9 (51.4)	44.0 (49.1)	40.4 (45.4)	40.4
C8	80.31	67.1	67.5	68.52	68.1	169.4	169.5	167.5	84
C9	52.68	48.2	49.2	48.15	49	46.8 (49.6)	47.3 (51.3)	52.3 (55.1)	51.1
C10	51.88	44.1	44.2	42.06	43.2	46.8 (52.1)	52.4 (59.4)	52.3 (59.9)	49.5
C11	74.11	30.1	29.8	28.35	29.5	169.4	162.6	167.5	84.3

this position. The decreasing order of chemical shift ranging from C-10, through C-9, C-1, to C-7 is also supported by the evidence given above for **12–44**, except that there is no plane of symmetry; therefore, each carbon resonates at a different frequency. The unsymmetrical and non-separable diastereomeric nature of compounds **48–55** resulted in complicated ^1H NMR and splitting of ^{13}C signals.⁴⁸ However, despite the overlapping of signals observed in the proton spectra, 2D NMR spectroscopy proved to be a crucial tool towards the effective structural elucidation of these compounds.

Compounds **56–59** are symmetrically di-substituted at positions 8 and 11 with hydroxyl groups at these positions. These compounds all show similar patterns in chemical shifts, where H-2/6 was registered as the most de-shielded signal, followed by H-1/7 and H-3/5 consecutively, with H-9/10 being the least de-shielded of all the methine protons. The carbon-13 signals here show the following trend of chemical shift in decreasing order, from C-8/11, through C-9/10, C-3/5, C-1/7, C-2/6, to C-4. The hydroxyl groups attached to C-8 and C-11 cause a large de-shielding effect of these carbon signals.

The remaining compounds, **60–72**, lack a plane of symmetry except for compounds **69** and **71** with symmetrical di-substituents at positions 8 and 11. Compounds **69–71** are conformational isomers, while **70** proved to be the most stable isomer in solution. The observed ^{13}C NMR chemical shifts for **69–71** were also calculated using DFT⁵⁴ in order to compare the observed ^{13}C shifts with the calculated values to assess the reliability of the computational method. Nuclear shielding was observed for the calculated structures with the aliphatic cage carbons chemical shifts dependent on the orientation of imine nitrogen lone pairs. These shifts were not observed for the experimental spectrum for atoms C-1, C-7 and C-9, C-10; thus, it was attributed to replacing the phenyl groups with vinyl units in the computational model.⁵⁴ The calculated results suggested that **70** was energetically more stable, which agrees with the experimentally observed isomeric ratios. Here the shifts in the signals do not follow a regular pattern, while the through-space de-shielding effect plays a significant role in determining the shifts of signals. The carbon signals exhibited a definite pattern for the following pairs of compounds with similar functional groups, **63** and **64**, **65** and **66**, **67** and **68**.

In contrast, the remaining compounds do not follow a specified order of chemical shifts. Conclusively, in most cases, it can be proposed that H-2/6 seems to be the most de-shielded of the methine protons, followed by either H-1/7 or H-9/10 and H-3/5 being the most shielded proton for symmetrically substituted PCU ethers at positions 8 and 11 for **12–44**. The PCU ethers, **45–55**, with mono-substituent at position 11 and a hydroxyl group at position 8, lacking plane of symmetry, have H-1 and C-8 recorded at the highest ppm (for ^1H and ^{13}C NMR spectra, respectively). Simultaneously, the most shielded signal

is usually registered as H-3 and C-2 or C-6 in most cases and sometimes varies from H-5 to H-7 for ^1H NMR. The factors responsible for the shifts in the proton signals of the PCU derivatives include an inductive effect (comprising electron-withdrawing and electron-donating effect), ring strain and through-space de-shielding effect. Through-space de-shielding effect results from the proximity in space of bulky groups (such as carbonyl group, alkene, phenyl ring, etc.) possessing a high density of electrons which may lead to conformational isomers, hence, making elucidation difficult. The inductive effect and ring strain are the major factors responsible for the shifts in carbon frequencies. Corresponding carbons of protons were determined using HSQC and HMBC spectra. Therefore, 2D NMR techniques have been established to show a high level of significance towards the structural elucidation of PCU compounds.

In summary, the PCU family of compounds is quite intriguing, as it can exist in one of three forms (asymmetric, diastereomeric or mesomeric), which then dictate the protocol to be followed on its NMR elucidation. The mesomeric PCU cage becomes chiral upon attachment of a group that breaks the symmetry. In such cases, COSY and NOESY interactions, in particular, are required to supplement the 1D spectra in order to aid the elucidation. Next, the PCU cage can exist as diastereoisomers, i.e. when the side arm substituents are the same yet possess chirality. Here the carbon signals appear as pairs due to diastereomeric splitting. In both cases, the asymmetric and diastereomeric PCU derivatives experience conformational effects induced by the side arms (one arm pointing to the back whilst one arm points to the front of the cage) that influence the NMR spectra (NOESY interactions, splitting of carbons). When the side arms prove to be stable in a specific orientation relative to the cage, these isomers are referred to as configurational isomers. Finally, the PCU cage may have identical achiral side arms resulting in a mesomeric structure. In this instance, all the atoms on the PCU molecule, except for the methylene at the C-4 position, become equivalent resulting in much overlap in both the proton and carbon spectra. The carbon spectra, in particular, are somewhat simplified in these cases as an overlap of the equivalent signals occur. Generally, a convenient starting point in the elucidation of any of the above three forms of PCU is with the geminal bridge methylene protons (H-4) that register as an AB spin system around 1.1 and 1.5 ppm displaying a coupling constant of approximately 10 Hz. Essentially thereafter, the core PCU protons (i.e. H-1 through to H-11) are assigned using mainly COSY and NOESY spectra; the NOESY interactions are particularly important to confirm the cage methine protons with the substituents on the side arms due to the induction of different chemical environments. Typically, the COSY interaction of H-4a/s with H-3/5 is followed by the interaction of H2/6 and its connection with H-1/7. Thereafter,

the H-2/6 interaction with H-9/10 confirms the core handle to further the elucidation. The route to be followed is dependent on whether the arms make the cage asymmetric, diastereomeric (noting that configurational isomers can exist in these cases) or mesomeric.

2.3. Trishomocubane

The most stable of all the pentacycloundecane based cages, namely, the D₃-symmetrical trishomocubane, was first reported in 1970.⁶¹ It has become well known for its pharmacological properties.^{62–63} There are many publications on the synthesis and reactivity of these derivatives.^{1,62} Herein we highlight only the NMR elucidation reports on this intrinsically chiral, D₃ symmetric propeller-shaped cage made up of slightly twisted 5-membered rings (Figure 4). In earlier reports, simple chemical shift values, intensity ratios or only the ¹³C spectral data were used to characterise these cages since the ¹H spectra proved to be very complicated.^{61, 63–64} The NMR data was assigned using chemical shift values, double resonance ¹H NMR, off-resonance proton decoupled ¹³C NMR, Heteronuclear Correlation (HETCOR), nuclear overhauser enhanced (NOE) difference spectra, and previously reported data. The starting core structures, trishomocuban-4-ol and trishomocubanone, displayed much overlapping of the methine proton signals in the ¹H NMR spectra, which were overcome by adding lanthanide shift (LIS) reagents that resulted in some separation of the signals.⁶⁵

The trishomocubane hydantoin derivatives, **73–77**,^{56–57} reveal H-10 as the most de-shielded signal of all the methine protons followed by H-6 and H-9 or H-2 in most cases (Table 6) as evident from the DFT calculations⁵⁶. It shows H-10 being the closest in space to the carbonyl oxygen of the hydantoin group, therefore, experiences the largest through-space de-shielding effect. H-6, H-2, and H-9 are more likely to experience a small through-space de-shielding effect due to the carbonyl group of the t-Boc directly attached to the amide nitrogen of the hydantoin group in **75**.⁵⁶ Among the methine protons, the most shielded signals are assigned to H-5 and H-3, with H-5 slightly more shielded than H-3 except for **75**, where H-1 and H-8 are recorded in the lower frequency region with H-1 being more shielded. COSY and NOESY correlations are used to establish the assignments of the methylene protons H-7a (s) and H-11a (s). These geminal protons (H-7a (s) and H-11a (s)) exhibit an AB spin-spin splitting pattern and resonates as a pair of doublets with a coupling constant of approximately 10 Hz.⁵⁶ In the C-13 spectra, the most de-shielded signal was assigned to C-4 due to direct attachment to the electron-withdrawing carbonyl and amide nitrogen of the hydantoin ring.⁵⁶ C-3 and

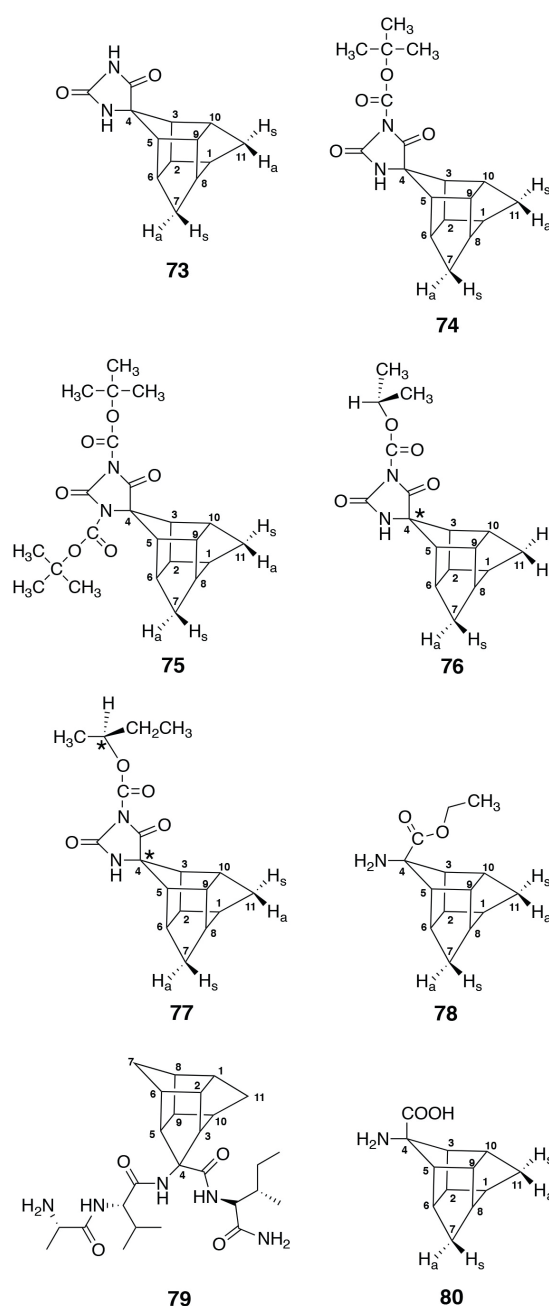


Figure 4 Structures of reported Trishomocubane derivatives **73–80**.^{56–57}

Table 6: ¹H NMR data for trishomocubane derivatives (chemical shift and coupling constant)

atom	73 ⁵⁶	74 ⁵⁶	75 ⁵⁶	76 ⁵⁷	77 ⁵⁷	78 ⁵⁷	79 ⁵⁶	80 ⁵⁷
1	2.1	2.18	2.09–2.13	2.17–2.18	2.17	2.07	2.09	2.07
2	2.18	2.27	2.38–2.40	2.27–2.30	2.28–2.31	2.16–2.18	2.08	2.11–2.15
3	1.97	2.09	2.52–2.53	2.08–2.10	2.09–2.11	1.94	2.58	1.94–1.95
4								
5	1.91	2.08	2.16–2.17	2.07–2.08	2.07–2.09	2.05	2.36	2.05
6	2.45	2.39	2.28	2.44	2.45	2.6	2.01	2.6
7a	1.36–1.39 (10.2 Hz)	1.46–1.49, 10.4 Hz	1.46–1.48, 8.6 Hz	1.45–1.48, 10.44 Hz	1.45–1.48, 10.6 Hz	1.39–1.42	1.35, 9.24 Hz	1.39–1.42, 11.7 Hz
7s	1.24–1.27 (10.2 Hz)	1.34–1.37; 10.4 Hz	1.30–1.33, 11.5 Hz	1.33–1.36	1.32–1.35	1.3	1.25, 9.84 Hz	1.30, 11.7 Hz
8	2.1	2.19	2.14–2.15	2.17–2.18	2.17	2.09	2.03	2.09
9	2.13	2.33	2.29	2.30–2.33	2.31–2.33	2.04	2.48	2.04
10	2.84	2.95	3.12	2.94	2.95	2.16–2.18	2.07	2.16–2.18
11a	1.36–1.39 (10.2 Hz)	1.46–1.49, 10.4 Hz	1.44–1.46, 8.6 Hz	1.45–1.48, 10.44 Hz	1.45–1.48, 10.6 Hz	1.39–1.39	1.31, 10.26 Hz	1.37–1.39, 11.7 Hz
11s	1.19–1.22 (10.2 Hz)	1.26–1.29, 10.4 Hz	1.27–1.30, 11.5 Hz	1.25–1.28, 10.44 Hz	1.26–1.28, 10.6 Hz	1.3	1.23, 10.38 Hz	1.30, 11.7 Hz

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