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Ranking the effect of [1A(ax), 1B(eq)] versus [1A(eq), 1B(ax)] cyclohexane ring substitution on the ^{1}H chemical shifts of γ-methylene cyclohexane ring protons using 2,2-disubstituted adamantanes as models

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Abstract—When two different substituents are placed in the nonbridgehead position of adamantane, the two [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] cyclohexane chair conformers are modeled and features of their NMR spectra can be studied from a single spectrum at 298 K. The effect of [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] cyclohexane ring substitution on the ^{1}H resonance separation within the γ-CH_2s of cyclohexane ring is compared for various substituent pairs; this aim is approached by measuring the ^{1}H chemical shift separation within the 4′,9′-H and 8′,10′-H methylenes from the ^{1}H NMR spectrum of the model 2A,2B-disubstituted adamantane at 298 K.

Cyclohexane derivatives are very popular model structures in organic chemistry and are particularly useful, both experimentally and theoretically for studying the shielding tensors contributing to proton chemical shifts, which are strongly linked with the position of the atoms or the stereochemistry in a molecule. Rather than analyzing the axial or equatorial proton interactions, the difference in chemical shift and one-bond spin–spin coupling constants between the axial and equatorial protons within one methylene in frozen cyclohexane is used as the experimental probes.[1] Nevertheless, the interpretation of the chemical shifts in cyclohexane[1a] or in any molecule,[2] in general, is still under research as is the analysis of the substituent effects on the axial–equatorial proton resonance separation, even when the case of the effect exerted by a substituent connected at the γ-axial cyclohexane ring position is considered, that is, the familiar γ-gauche effect.[3]

Undoubtedly, when compared with carbon NMR spectroscopy the experimental data concerning the effects exerted by substituents on the proton chemical shifts of model compounds is limited. Tracing the old[4] and current literature[1a,5] reveals that not much has been published on the effect of substituents on the chemical shift difference between axial and equatorial protons of cyclohexane rings. An explanation for the data deficiency is given below.

When an axial proton of a chair cyclohexane or any cyclohexane derivative is replaced by a substituent A, one of the expected major changes in the ^{1}H NMR spectrum of the axial substituted structure is a downfield shift of the resonance of the γ-*syn* axial protons and the compensate upfield shift of the corresponding equatorial protons. To observe this effect on the proton chemical shifts within a γ-CH_2, the ^{1}H NMR spectrum of the axial conformer of the desired cyclohexane derivative, being accessible only at low temperatures when ring inversion is a slow process,[6] requires analysis if spectral resolution permits. In addition, resonances due to the axial cyclohexane chair conformer should be observed at low temperatures only if the population is fair; for example, conformers having large axial *t*-Bu groups are often unpopulated.

An elegant way to investigate the features of the ^{1}H NMR spectrum of a substituted cyclohexane ring is

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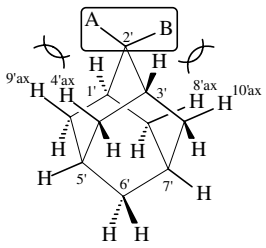
through studying the rigid cyclohexane ring sub-units included in a suitable tricyclo[3.3.1.1^{3,7}]decane or adamantane derivative.[7] In the 2,2-disubstituted adamantane shown in Scheme 1, each of the substituents A and B is axial in the different adamantane cyclohexane ring 1′–2′–3′–4′–5′–9′ and 1′–2′–3′–10′–7′–8′, respectively; consequently the C–A and C–B bonds have the orientation (ax, eq) in the adamantane cyclohexane ring 1′–2′–3′–4′–5′–9′ and (eq, ax) in ring 1′–2′–3′–10′–7′–8′. Thus, from a single NMR spectrum of a 2A,2B-disubstituted adamantane at ambient temperature, spectroscopic characteristics of the two conformers [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] of the 1A,1B-disubstituted cyclohexane, present in a '1:1 ratio' in the adamantane structure, can be investigated; often the ^{1}H signals of these conformers can barely be observed at low temperature because of a biased solution equilibrium and poor spectral resolution.

The most characteristic element in the ^{1}H NMR spectrum of a 2-substituted adamantane, is the appearance of a downfield and an upfield doublet ($J_{gem} = 11$–12 Hz), assigned to 4′ax,9′ax-H and 4′eq,9′eq-H, from the broad signal corresponding to the remaining adamantane protons.[8] In these molecules the equivalent axial protons of γ-*syn* carbons 4′ or 9′ interact with substituent A,[9] which is axial with respect to the 1′–2′–3′–4′–5′–9′ cyclohexane ring sub-unit, and their resonances are shifted downfield from the geminal 4′eq, 9′eq protons. In contrast, the separation of the signals due to the protons attached to the γ-*anti* carbons 8′ and 10′, that is the chemical shift difference between 8′ax,10′ax-H and 8′eq,10′eq-H, is small because of the equatorial position of substituent A in the 1′–2′–3′–10′–7′–8′ cyclohexane ring. When a second substituent B is attached at the 2-adamantane position, the resonances of 8′ax,10′ax-H and 8′eq,10′eq-H should be affected mainly by their interaction with B, which is axial in the 1′–2′–3′–10′–7′–8′ cyclohexane ring.

A comparison of the effects exerted from the two different orientations of the cyclohexane ring substituent pairs [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] on the proton signal separation within the cyclohexane ring γ-CH_2 group (Scheme 1) can be approached through measuring the proton resonance separation within 4′,9′-CH_2 and 8′,10′-CH_2 taken from the ^{1}H NMR spectrum of the corresponding 2A,2B-disubstituted adamantane recorded at 298 K.



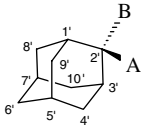
Scheme 1. In 2,2-disubstituted adamantanes each of the two substituents adopts an axial or equatorial orientation in a different cyclohexane ring sub-unit of adamantane.

Compounds **1**–**19**[10] are 2,2-disubstituted adamantanes bearing alkyl groups of various sizes (B = Me, Et, *n*-Pr, HC≡C, Ph, *t*-Bu) and some characteristic second row polar groups (A = NR_2, OH, F, $NHMe_2^+$, N_3, CN, OCOR, NHCOR) (Scheme 2). This piece of research originates from our on going efforts aimed at understanding how aminoadamantane drugs[11] and analogues interact with the M2TM influenza A receptor using ^{1}H NMR spectroscopy and suitable ^{19}F probes.[12]

4′,9′-H resonances are affected by Aax, Beq substitution, with A having an axial orientation in the 1′–2′–3′–4′–5′–9′ cyclohexane ring, and the 8′,10′-H resonances are affected by Bax, Aeq substitution, with substituent B being axial in the 1′–2′–3′–10′–7′–8′ cyclohexane ring (Scheme 1). In order to compare the proton chemical shift separation effect within the cyclohexane ring γ-CH_2 for the two fixed 1A,1B-cyclohexane conformational isomers included inside the adamantane framework the different doublets corresponding to the 4′,9′ and 8′,10′ protons must be assigned.[13]

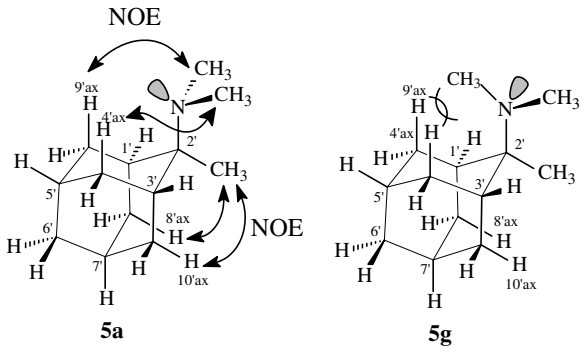
We will consider representatively the ^{1}H NMR spectrum, shown in Figure 1, of *N*,*N*-dimethyl-2-methyl-2-adamantanamine **5**, which is conformationally homogenous, that is, it exists in one conformation. Molecular mechanics calculations using MM3 or MMFF94 force fields[14] predict that conformer **5a**, having an *anti* arrangement with respect to the CH_3–C2′–N-lp dihedral angle, is the only populated conformer for **5** since the next different conformer **5g** has >10 kcal mol^{-1} higher energy (Scheme 3). Conformer **5g** results from **5a** either by rotation around the C2′–N bond or nitrogen inversion; in **5g** the *N*–Me group lies above the 1′–2′–3′–4′–5′–9′ cyclohexane ring where 1,5-steric interactions with the 4′ax and 9′ax methine groups are severe (Scheme 3).

The doublet resonance of protons 8′ax,10′ax ($J \sim 12$ Hz) was assigned at 1.85 ppm because of its dipolar NOE correlation with *C*–Me at 0.88 ppm, and



1: A = CN - B = CH_3
2: A = NH_2 - B = CH_3
3: A = NHMe - B = CH_3
4: A = NH_2 - B = C_2H_5
5: A = NMe_2 - B = CH_3
6: A = $NHMe_2^+$ - B = CH_3
7: A = NH - B = $(CH_2)_4$
8: A = NMe - B = $(CH_2)_4$
9: A = NH-$COCH_3$ - B = CH_3
10: A = NH-CO-*t*-C_4H_9 - B = CH_3
11: A = OH - B = CH_3
12: A = O-$COCH_3$ - B = CH_3
13: A = O-CO-*t*-C_4H_9 - B = CH_3
14: A = N_3 - B = CH_3
15: A = OH - B = C_2H
16: A = OH - B = *n*-C_3H_7
17: A = OH - B = C_6H_5
18: A = OH - B = *t*-C_4H_9
19: A = F - B = CH_3

Scheme 2. 2A,2B-disubstituted adamantanes, which were synthesized[10] to study the effect of [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] substitution on the ^{1}H resonance separation within cyclohexane ring γ-CH_2 protons.



Scheme 3. Left-hand part: NOE connectivities being consistent with the only populated conformer **5a** for compound **5**; right-hand part: 1,5-interactions strongly destabilize conformer **5g**.

differentiated from the 4′ax,9′ax-H doublet ($J \sim 12$ Hz) at 2.22 ppm, which showed an NOE correlation with *N*–Me at 2.08 ppm (Scheme 3, Fig. 1). Using the scalar connectivities in the ^{1}H–^{1}H COSY spectrum, the corresponding pairs of equatorial protons were identified at lower frequencies, the signal of 4′eq,9′eq-H appeared at 1.34 ppm and that of 8′eq,10′eq-H occurred at 1.64 ppm. A similar procedure was used for the signal assignment of the relevant proton resonances for the whole series **1**–**19**.[15] Protons 4′ax,9′ax are more deshielded than 8′ax,10′ax and the chemical shift difference is as large as 0.88 ppm for the 4′,9′-H pairs compared to 0.21 ppm for the 8′,10′-H pairs. This in turn implies that redistribution of electronic shielding over the γ-cyclohexane CH_2 group is affected more from its interaction with [NMe_2(ax), Me(eq)] rather than [Me(ax), NMe_2(eq)].

A stronger effect of [A(ax), B(eq)] compared to that of [B(ax), A(eq)] (Scheme 1) in the chemical shift separation within the γ-cyclohexane CH_2 was observed in the spectra of all compounds **1**–**19**, with a chemical shift difference, $\Delta\delta_{4',9'\text{-H}}$ of 0.5–0.9 ppm for the 4′,9′-H pairs and $\Delta\delta_{8',10'\text{-H}}$ of 0.1–0.5 ppm for the 8′,10′-H pairs (Table 1). This order was observed even in the case of compound **18** (A = OH, B = *t*-Bu) where 8′ax,10′ax-H are sterically compressed by the *syn* axial *t*-butyl group. Thus, the observed separation for the 8′,10′-H pairs was 0.49 ppm and the 8′ax,10′ax-H doublet resonance appeared at 2.17 ppm, whereas the values for the second γ-CH_2 indicated a more significant interaction; the electronic distribution within the 4′,9′ γ-CH_2 was affected to a greater effect by the substituent pair having the hydroxyl group in the axial position and the 4′ax,9′ax-H signal appeared more downfield at 2.26 ppm, that is, 0.79 ppm from the 4′eq,9′eq-H signal.

In the spectra of all the compounds examined, including **18**, the 8′ax,10′ax protons are more shielded than the 4′ax,9′ax protons. The most deshielded 4′ax,9′ax-H signal was that of compound **17**, in which the γ-*syn* axial protons interact with the [OH(ax), Ph(eq)] fragment; the resonance of these protons, which are not affected by significant steric crowding,[16] appeared at 2.45 ppm! In this compound the chemical shift difference between the 8′,10′-H pairs is infinitesimal suggesting a negligible interaction between the [Ph(ax), OH(eq)] fragment and the *syn* γ-CH_2 group. Molecular mechanics and HF/6-31G* calculations show that the phenyl ring is oriented perpendicular to the bisector plane of the cyclohexane chair[17] minimizing steric interactions between the axial cyclohexane C–H bonds and phenyl C–H moieties. While considerable deshielding of the 8′ax,10′ax protons was also observed in certain cases (see, e.g., in Table 1 compounds **15** and **18**), the relative effect of [A(ax), B(eq)] versus [B(ax), A(eq)] is demonstrated from the chemical shift separation within the relevant γ-*syn* methylene rather than the downfield resonance of the corresponding γ-*syn* axial proton.

On ranking the substituents effect, a more significant interaction was observed between the cyclohexane γ-*syn* CH_2 and groups bearing a lone pair (A = NR_2, OH, F) rather than the polar groups (A = N_3, NHCOR, OCOR, $NHMe_2^+$), see Scheme 2. In the same context, in all the cases studied, [NMe_2(ax), Me(eq)] exerted the strongest effect on the γ-*syn* methylene proton

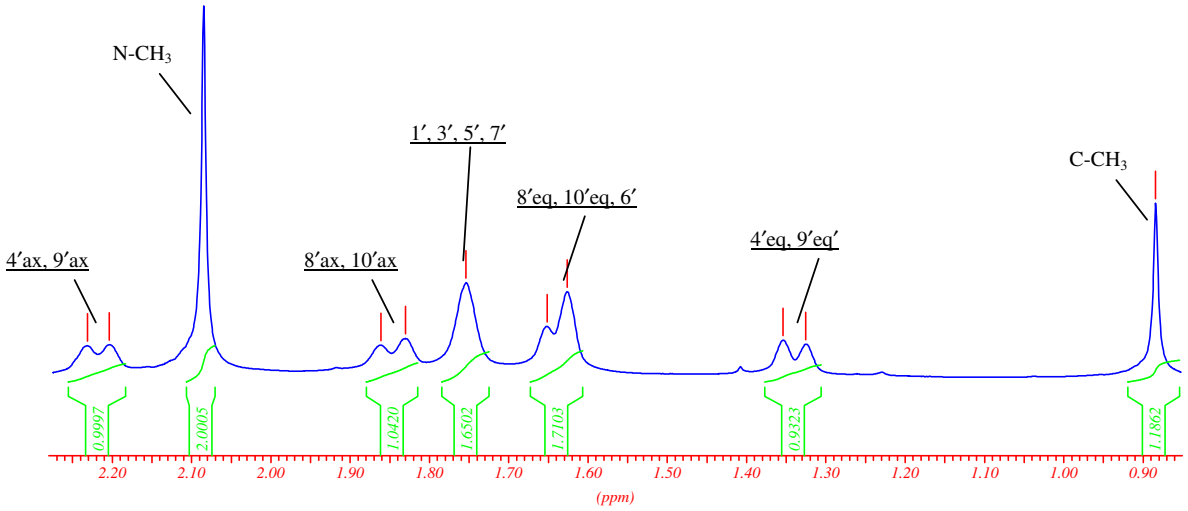


Figure 1. ^{1}H NMR spectrum of the *N*,*N*-dimethyl-2-methyl-2-adamantanamine **5** in $CDCl_3$ solution (400 MHz) at 298 K.

Table 1. ^{1}H chemical shifts (400 MHz, $CDCl_3$)[a] and signal separation of the γ-CH_2 pairs[b] of adamantane cyclohexane ring sub-units for 2,2-disubstituted adamantanes **1**–**19**

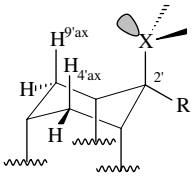
Compound	4′ax	9′ax	8′ax	10′ax	4′eq	9′eq	8′eq	10′eq	$\Delta\delta_{4',9'\text{-H}}$	$\Delta\delta_{8',10'\text{-H}}$
Adamantane[c]	1.75		1.75		1.75		1.75		0.0	0.0
1 (A = CN, B = Me)	2.27		1.94		1.64		1.73		0.63	0.21
2 (A = NH_2, B = Me)	2.0		1.93		1.39		1.59		0.61	0.34
3 (A = NHMe, B = Me)	2.01		1.91		1.49		1.59		0.52	0.32
4 (A = NH_2, B = Et)	1.98		1.91		1.47		1.59		0.51	0.32
5 (A = NMe_2, B = Me)	2.22		1.85		1.34		1.64		0.88	0.21
6 (A = $NHMe_2^+$, B = Me)	2.18		1.97		1.72		1.87		0.46	0.10
7 (A, B = $NH(CH_2)_4$)	1.93		1.87		1.45		1.53		0.48	0.34
8 (A, B = $NMe(CH_2)_4$)[d]	2.24	2.10	1.60	1.82	1.43	1.39	1.47	1.60	0.81; 0.71	0.13; 0.22
9 (A = NH–CO–Me, B = Me)	1.97		1.95		1.61		1.66		0.36	0.29
10 (A = NH–CO–*t*-Bu, B = Me)	1.94		1.86		1.62		1.57		0.32	0.29
11 (A = OH, B = Me)	2.15		1.83		1.52		1.70		0.63	0.13
12 (A = O–CO–Me, B = Me)	1.95		1.80		1.49		1.65		0.46	0.15
13 (A = O–CO–*t*-Bu, B = Me)	1.97		1.82		1.50		1.66		0.47	0.16
14 (A = N_3, B = Me)	2.11		1.87		1.56		1.68		0.55	0.19
15 (A = OH, B = C_2H)	2.14		2.11		1.52		1.75		0.62	0.36
16 (A = OH, B = *n*-Pr)	2.15		1.84		1.53		1.68		0.62	0.14
17 (A = OH, B = Ph)	2.45		1.76		1.77		1.74		0.68	0.02
18 (A = OH, B = *t*-Bu)	2.26		2.17		1.47		1.68		0.79	0.49
19 (A = F, B = Me)	2.17		1.80		1.56		1.77		0.61	0.03

[a] Signal of $CHCl_3$ residue was calibrated at 7.26 ppm; spectra were recorded at 298 K unless otherwise stated.
[b] Signals for the 4′,9′-H and 8′,10′-H pairs of compounds **1**–**19** are broad doublets with $J_{gem} \sim 12$ Hz.
[c] Data taken from the literature.[22]
[d] Spectra recorded at 273 K.[23]

resonances. The signal separation between the γ-*syn* axial and equatorial protons caused by this group was larger than that of the NH_2 and NHMe groups. In the former case, the nitrogen lone pair is oriented between the C-4ax′H and C-9ax′H bond axes, that is, above the 1′–2′–3′–4′–5′–9′ cyclohexane ring (Scheme 4), whereas in the latter cases, rapid averaging between two equally stable conformers can move the lone pair away from these hydrogens and thereby reducing their interactions.

The following two observations were also consistent with the presence of a lone pair effect (Scheme 3):

(a) When the amine or hydroxyl group lone pair of compounds **2** or **11**, respectively, was captured, through substitution with a small or a large acyl group (see derivatives **9**, **10**, **12** and **13**) changing the heteroatom stereochemistry from tetrahedral to planar, the chemical shift difference within the 4′,9′-H methylenes was reduced (Table 1) possibly because the interactions between the heteroatom lone pair and the γ-*syn* axial C–H bonds were no longer possible.



Scheme 4. Heteroatom lone pair oriented above the cyclohexane ring.

(b) When the NMe_2 group of compound **5** was protonated, upon addition of a drop of TFA inside the NMR tube resulting in **6**, $\Delta\delta_{4',9'\text{-H}}$ was reduced from 0.88 to 0.46 ppm. Here, it is interesting to note that the molecular mechanics or 6-31G(d) calculations showed that the N^+–H proton strongly repels the 4′ax proton since the distance between these protons was calculated to be ~1.99 Å. This can explain why protonation was so slow, the time required in order to obtain sharp signals in the ^{1}H NMR spectrum being several weeks!

Thus, the nature of the interaction between the cyclohexane ring γ-methylenes and [A(ax), B(eq)] or [B(ax), A(eq)] fragments (Scheme 1) in the studied compounds **1**–**19** merits attention. Since the effect of an equatorial substituent on the chemical shift difference between γ-axial and equatorial protons is small,[18] the prime interaction exerted by these fragments comes from the axial substituent in the fragment. In the case of the [B(ax), A(eq)] substitution, the steric crowding from the B = alkyl axial group results in the separation between the signals of the compressed γ-*syn* axial proton and the uncompressed equatorial proton.[16] A similar repulsion between the electron cloud on the A and C–H axial bonds is consistent with [A(ax), B(eq)] substitution where A is a polar group (A = CN, $NHMe_2^+$, NHCOR, OCOR, N_3; compounds **1**, **6**, **9**, **10**, **12**, **13** and **14**, see Scheme 2). However, when a second row heteroatom with lone pairs (A = F, NR_2, OR; compounds **2**–**5**, **7**, **8**, **11**, **15**–**19**, see Scheme 2) is in the axial position the interaction cannot be interpreted simply as steric repulsion between lone pairs and axial C–H bonds.[19] Although HF 6-31G(d) calculations predict shortening of the 4′,9′ axial C–H bonds and the maintenance of the 4′,9′ equatorial C–H bond lengths compared to the

adamantane bonds,[20] a different interaction may be present when A is axial and this is illustrated when the two extreme cases provided by compounds **18** and **19** are considered. The separation in the resonances of the γ-*syn* cyclohexane protons caused by *t*-Bu is $\Delta\delta_{8',10'\text{-H}} = 0.49$ ppm whereas the relevant value for fluorine, which is isosteric to hydrogen, is larger, that is, $\Delta\delta_{4',9'\text{-H}} = 0.61$ ppm. Analysis of this mechanism, being inherent in the redistribution of electronic shielding within the γ-methylene when A is a second row lone pair heteroatom, will be the subject of a different study.

In conclusion, through studying the NMR spectrum of a 2A,2B-disubstituted adamantane at 298 K, features of the NMR spectra of [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] cyclohexane chair conformers can be analyzed; the difficulties related with a biased equilibrium and poor spectral resolution often makes analysis of the latter spectra troublesome, which are accessible only at low temperatures. Thus, the effect of [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] cyclohexane ring substitution on the ^{1}H resonance separation within a cyclohexane ring γ-CH_2 was compared for some substituent pairs; this was achieved by measuring the chemical shift separation within the 4′,9′-H and 8′,10′-H methylenes from the ^{1}H NMR of suitable 2,2-disubstituted adamantanes (compounds **1**–**19**).[21] This signal separation is the result of the effect of [1A(ax), 1B(eq)] and [1A(eq), 1B(ax)] on the electronic shielding within the 4,9-CH_2 and 8,10-CH_2 groups of the cyclohexane ring sub-units 1′–2′–3′–4′–5′–9′ and 1′–2′–3′–10′–7′–8′, respectively, and reflects mainly the interaction between the relevant axial substituent and γ-*syn* methylene group.

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10. Compound **1** was synthesized through methylation of the carbanion of 2-cyanoadamantane, see Ref. 11b; the reaction of 2-adamantanone with CH_3MgBr resulted in alcohol **11**, which was treated with Ac_2O/Et_3N/rt to give acetate **12** (Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069); the bulky ester derivative **13** was afforded from the hindered alcohol **11** by means of pivalic anhydride/$MgBr_2/Et_3N$/rt (Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702); tertiary alcohols **15** and **17** were prepared through the reaction of 2-adamantanone with C_2HNa and PhMgBr, respectively, whereas the corresponding organolithium reagents were necessary for the preparation of **16** and **18** (Fry, J. L.; Engler, E. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 4628; Duddeck, H.; Rosenbaum, D. *J. Org. Chem.* **1991**, *56*, 1700); azide **14** was obtained through the reaction of alcohol **11** with $NaN_3/H_2SO_4/CHCl_3$/rt using a concentration of 78% w/w rather than the 57% w/w reported in the literature, which failed to afford **14** in our hands (Sasaki, T.; Egushi, S.; Toi, N. *J. Org. Chem.* **1979**, *44*, 3711); amine **2** was prepared by means of $LiAlH_4$/ether/rt reduction of **14**, and **4** was similarly prepared; derivatives **3** and **5** were afforded through conventional N-methylation procedures of amine **2**, and amides **9** and **10** by treatment of amine **2** with RCOCl/Et_3N/rt; the $CDCl_3$ solution of the TFA salt of **6** was obtained by treating the $CDCl_3$ solution of amine **5** (50 mg) with TFA (two drops) inside the NMR tube and the mixture was left to equilibrate for several weeks before recording the NMR spectra; compounds **7** and **8** were prepared according to Ref. 11a.
11. Between the numerous synthesized aminoadamantane derivatives, 2-alkyl-2-adamantanamines (e.g., compounds **2**–**5**, **7**, **8**) were the most potent in vitro. For some representative examples see: (a) Kolocouris, N.; Kolocouris, A.; Foscolos, G. B.; Fytas, G.; Neyts, J.; Padalko, E.; Balzarini, J.; Snoeck, R.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 3307; (b) Zoidis, G.; Kolocouris, N.; Fytas, G.; Foscolos, G. B.; Kolocouris, A.; Fytas, G.; Karayannis, P.; Padalko, E.; Neyts, J.; De Clercq, E. *Antiviral Chem. Chemother.* **2003**, *14*, 155; (c) Stylianakis, I.; Kolocouris, A.; Kolocouris, N.; Fytas, G.; Foscolos, G. B.; Padalko, E.; Neyts, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1699.
12. (a) Kolocouris, A.; Hansen, R.; Broadhurst, R. W. *J. Med. Chem.* **2004**, *47*, 4975; (b) Kolocouris, A.;

Broadhurst, R. W.; Zikos, C. *Bioorg. Med. Chem. Lett.*, submitted for publication.
13. Although the ^{13}C spectra of some 2,2-disubstituted adamantanes have been analyzed (Krishnamurthy, V.; Iyer, P. S.; Olah, G. A. *J. Org. Chem.* **1983**, *48*, 3373; Duddeck, H. *Top. Stereochem.* **1986**, *16*, 219) there is no information on their ^1H NMR spectra.
14. MM3 (*J. Am. Chem. Soc.* **1993**, *115*, 11918) and MMFF94 (*J. Comp. Chem*. **1996**, *17*, 587) force fields are implemented in PCMODEL (version 9.0), Serena Software.
15. For all ^1H–^1H correlation experiments a relaxation delay of 2 s was used; 2D NOE phase sensitive experiments were run using a mixing time of 1.5 s.
16. The interaction of groups that are close in space normally results in shielding of the carbon and deshielding of the protons involved. A remarkable demonstration of a steric compression effect is the δ- or ε-effect on the proton chemical shifts in some tetracyclic norbornyl systems, where the repulsion between groups separated by four or five bonds is so severe that the compressed proton appears uncommonly downfield by 3.1–3.5 ppm, but also, the uncompressed proton moves compensatingly upfield by 0.8–0.9 ppm (Winstein, S. P.; Carter, P.; Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005).
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18. For example, the chemical shift difference within the 4′,9′-H methylene in the case of 2-adamantanol or 2-*t*-Bu-adamantane is only ~0.10 ppm; in these cases axial –OH or –*t*-Bu groups adopt an equatorial position with respect to the 1′–2′–3′–4′–5′–9′ cyclohexane ring (see Scheme 1, A = H, B = OH or *t*-Bu).
19. Bushweller, C. H. Stereodynamics of Cyclohexane and Substituted Cyclohexanes. Substituent A Values. In *Conformational Behaviour of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995; p 25.
20. C–H bond shortening is often observed in cases where steric compression is present (Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001); in addition, calculations at the HF/6-31G* level show an excess positive charge on 4ax′-H and 9ax′-H compared to the charge on the equatorial protons and that of tricyclo[3.3.1.1^{3,7}]decane protons.
21. The signal dispersion in most of the ^1H NMR spectra of compounds **1**–**19** was striking; this high spectrum resolution is important for the liquid-state NMR measurements focusing on how suitable reporter adamantane derivatives contact with the transmembrane portion of the influenza A M2 protein receptor embedded in lipid bilayers (see, for example, Ref. 12a and also: Wang, J.; Schnell, J. R.; Chou, J. J. *Biochem. Biophys. Res. Commun.* **2004**, *324*, 212).
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