

Revisited conformational analysis of perhydro-3a,6a,9a-triazaphenalene based on Raman analysis[†]

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We have demonstrated experimentally by Raman analysis that **1a** exists as a mixture of ttt/cct conformers at 22 °C in liquid or CCl₄ solution, thus contrasting with the initial IR, NMR and X-ray analyses, which were strongly in favour of (ttt)-**1a**. The global stereoelectronic stabilization is *ca.* 4.0–4.2 kcal/mol for both parallel N lone pairs (lp) in (cct)-**1a**, based on a ΔH of 0.75 kcal/mol ($\pm 10\%$), as measured by Raman spectroscopy from 22 to 90 °C, as well as the roughly estimated MM2 MeNHET and MeNHCH₂NH₂ gauche interactions. DFT calculations using B3LYP/6-31G* yield a standard ΔH value of 1.04 kcal/mol, in good agreement with the experiment, and predict a ttt/cct ratio of *ca.* 77:23 at 25 °C. Broadening of the ¹³C-NMR signals was observed in either CCl₄ or CS₂ or even CDCl₃ solutions between –20 and –40 °C. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Initially discovered by Atkins at *du Pont de Nemours*,^[1–4] the synthesis and conformational analysis of perhydro-3a,6a,9a-triazaphenalene **1a** (Scheme 1) were published in 1980 in parallel with two other concurrent publications by Wuest *et al.* rationalizing the readily generation of H₂ under thermal acidic conditions^[5] and the non-central hydride transfer to Ph₃C⁺BF₄[–] at 25 °C,^[6] as well as a third paper by Weisman *et al.*^[7] All these authors, based on IR and NMR spectroscopic evidence, corroborated by calculations, concluded that orthoamide **1a** adopts essentially a C_{3v} symmetrical trans, trans, trans triple-chair conformation (ttt). This hypothesis was strengthened seven years later by an X-ray structure analysis of (ttt)-**1a**.^[8] These seminal papers were cited by more than 40 further publications, reporting either on more efficient syntheses of **1a**^[9–11] or on its 9b-substituted analogues, such as **1c,d**^[12–14] and **1e,f**,^[15] as well as X-ray structural analyses^[16,17] or chelation with diverse metals^[18–20] or as building blocks for more elaborated aza-macrocyclic ligands.^[21–27] Very recently, our attention was attracted by a publication of Alajarin *et al.*,^[28] which reiterated the preference for the ttt conformation of **1a** and encouraged us to revisit the subject. Here, we discuss the original arguments and present additional data.

RESULTS AND DISCUSSION

Firstly, we performed DFT calculations at the B3LYP/6-31G* level^[29] and found a very small difference of energy of 1.04 kcal/mol in favour of conformer (ttt)-**1a**, which contrasts with the 6.0 kcal/mol reported by Atkins to consolidate his conclusions.^[1]

We were indeed, particularly, astonished by this initial large energy difference, since a parent molecule like *cis*-perhydrophenalene (cct)-**2**,^[30] for example, is sterically disfavoured compared to its stereoisomer (ttt)-**2** by four gauche butane interactions ($4 \times 0.85\text{--}0.89 = ca. 3.40\text{--}3.56$ kcal/mol,^[31,32] $\Delta H^{298} = 4.54$ kcal/mol according to more detailed B3LYP/6-31G* calculations^[29]). Since conformer (cct)-**1a** benefits from two supplementary stereoelectronic stabilizations,^[33–36] in addition to the absence of a sterically demanding axial H atom in position 6a, the ΔH as well as ΔG , due to the non-negligible entropic factor, should be consequently even smaller for **1a**, since its C—N bond lengths are not very much shorter than the C—C bonds lengths in that specific case (*vide infra*, due to the anomeric effect, the C_{9b}—N_{6a} and N_{3a}—C_{9b} are elongated and shortened, respectively).^[8,16,17] Atkins mainly based his argument on Bohlmann trans (T) bands in the IR spectrum. These bands were expected to appear between 2690 and 2800 cm^{–1}, when a N lone pair (lp) is anti-periplanar (ap) to two C—H bonds.^[37,38] Furthermore, the signal at 2450 cm^{–1} was attributed to the

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central methine, with respect to its supplementary interaction with two other ap N lp.^[1] This attribution was based on comparison with the deuterated analogue (ttt)-**1b**, which exhibits a bathochromic displacement of this signal near 1800 cm⁻¹.^[6] In fact, Wiewiorowski *et al.* demonstrated in 1967 already, that these specific T bands may necessitate only a single C—H ap N lp interaction to be present between 2700 and 2800 cm⁻¹.^[39] Furthermore, he also showed that a C—H syn-periplanar (sp) to a N lp also exhibits T bands in the IR spectrum, although ca. 20% lower in intensity as compared to an ap disposition.^[40] We then prepared **1a** from commercially available and cheap 1,5,7-triazabicyclo[4.4.0]dec-5-ene, either by LiAlH₄ reduction of the isolated known stable tricyclic guanidinium⁺ BF₄⁻ intermediate salt,^[9] or preferentially by the reported one pot procedure using NaBH₄.^[10,11] We thus could record the IR analyses of **1a**, dried over CaH₂, either in the solid state,^[41] or in 3% CCl₄ solution, at 22 °C, as well as in the gas phase (ca. 150 °C). Unfortunately, with a resolution of ca. 3 cm⁻¹, we were initially unable to unambiguously and obviously distinguish the presence of a second conformer. Since our IR apparatus did not allow us to record the analysis at different temperatures, we turned our attention to Raman spectroscopy, which had earlier already allowed us to solve a similar problem.^[42] By performing the Raman analysis of the crystalline form, known to be in the (ttt)-conformation,^[8,43] and by comparison with the melted pure form, up to 90 °C, we were able to observe the presence of supplementary minor signals, also present in CCl₄ solution (such as at 786 cm⁻¹, as shown in Fig. 1). By plotting the natural logarithm of the ratio of two distinct signals intensities at 590 and 526 cm⁻¹, as a function of the inverse of the temperature, we calculated a slope corresponding to a ΔH of 0.75 kcal/mol ($\pm 10\%$) in favour of the crystalline (ttt)-**1a**, thus corroborating our theoretical calculations (Fig. 2). With $\Delta G = \Delta H - T\Delta S$, it is quite simple with an entropic factor of 2.18 cal/mol °K (resulting from the C_{3v} symmetry, leading to an identical cct-conformer on inversion of a six-membered heterocycle of (ttt)-**1a**,^[12,44] to estimate a ΔG of ca. 0.10 kcal/mol in favour of (ttt)-**1a** at 25 °C (0.736 kcal/mol according to more detailed B3LYP/6-31G* calculations,^[29] ca. a 70:30 mixture at 150 °C). We then calculated the theoretical Raman and IR spectra in terms of wavelengths, intensities and signal attributions (supplementary material).^[45–48] We found that the calculated spectrum of a 70:30 (ttt)-/(cct)-**1a** mixture was very similar and not incompatible, in terms of shifts and intensities, with the experimental spectrum, in the 700–1500 cm⁻¹ region. Furthermore, the simplicity of the simulated signals for the pure (ttt)-**1a** conformer, in the 2700–3000 cm⁻¹ window, is incompatible with

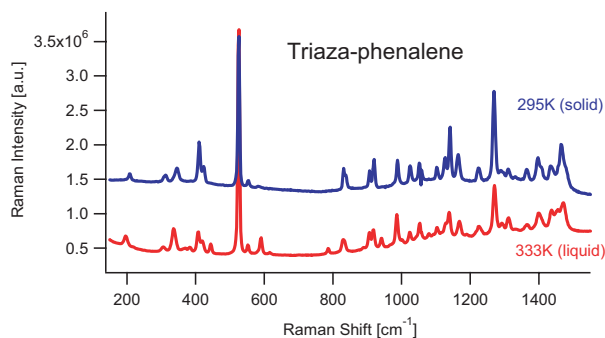


Figure 1. Raman analyses of crystalline and neat liquid **1a** at 22 and 60 °C

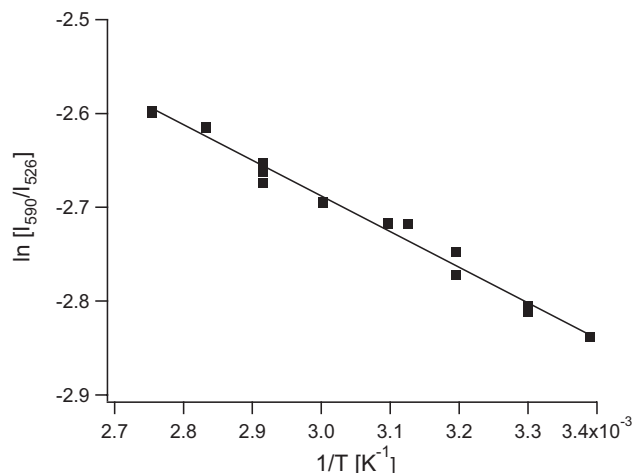


Figure 2. Inverse temperature dependence of the natural logarithmic signal intensities ratio at 590 and 526 cm⁻¹ for neat liquid **1a**

the more complicated experimental picture. Finally, the presence of a second conformer was confirmed by inspection of the IR analysis of **1b**. Indeed, the central methine stretching of (cct)-**1a**, initially hidden in the 2860 cm⁻¹ region, now clearly appears at 2040 cm⁻¹ for the (cct)-**1b** conformer, while the signal at 2442 cm⁻¹ was shifted at 1850 cm⁻¹ for (ttt)-**1a/1b**, respectively. The intensities of these latter absorptions are superior, due to the greater dipole moments of the elongated C—H/C—D bonds, when ap to all three N lp.

Both ¹H- and ¹³C-NMR analyses were earlier recorded from 25 to -100 °C, in either polar deuterio acetone or co-ordinating H-bond donor CDCl₃ solvents, without observing either coalescence or broadening of the signals.^[6,7] Furthermore, the simplicity of the pattern suggested a C_{3v} symmetry, which reinforced the conclusion in favour of the ttt-conformation.^[1,6,7] With this in mind, Wuest *et al.*^[6] suggested that the conformational equilibrium should be analogously slow, by comparison with simple 1,3-disubstituted-perhydropyrimidine.^[49] As a consequence, such motions should be detectable on the NMR time scale.^[50–55] We initially thought that **1a** is a quite different and specific substructure, eventually allowing a much faster interconversion.^[56,57] We indeed envisaged an eventually fast and hypothetical momentary fragmentation of one central bond^[58–60] in order to generate a 10-membered ring, incorporating both a N atom and a formamidinium ion, thus allowing a conformational change below the NMR analytical detection level. To test this hypothesis and to influence the formation and stabilization of a transient possible ionic species, we recorded the ¹H- and ¹³C-NMR spectra of **1a** at 25 °C in eleven different solvents of increasing E_T(30) polarity.^[61–67] First of all, apart from CD₃OD and D₂O, which in the latter case gives a very broad signal at 2.74 ppm, we observed an upfield displacement, from apolar CCl₄ (2.33 ppm) to polar CD₃NO₂ (2.21 ppm), for the central methine ¹H-signal, consistent with a greater stabilization of the dipole moment of the (ttt)- versus (cct)-**1a** conformers (1.24 vs. 1.15 Debye according to B3LYP/6-31G** calculations, respectively). The methine ¹H-signal appears at 5.03 ppm for the fully sp 1,4,7-triazatricyclo[5.2.1.0]^[4,10]decane^[1,7,8] and at 3.81 ppm for a cct conformer of **1a** analogue^[8]. More conclusively, 100.6 MHz ¹³C dynamic NMR spectroscopy revealed considerable line broadening of the signals of **1a** at 23.4 (3t), 53.3 (6t) and 98.7

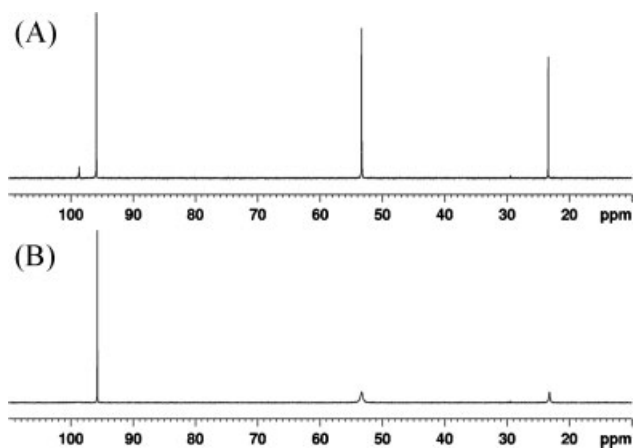


Figure 3. ^{13}C -NMR analysis of **1a** at (A) 25 °C and (B) –20 °C in CCl_4

(d) ppm in an apolar CCl_4 solution at –20 °C (Fig. 3). The narrow signal of the solvent at 96.1 ppm confirms that this broadening does not result from the increased viscosity of the solution but is rather due to a slower interconversion rate between different conformers. This is in contrast to the experiments carried out by both Wuest *et al.* and Weisman *et al.* who did not observe any dynamic line broadening. However, their ^{13}C -NMR experiments have obviously been recorded at lower magnetic field strength.^[68] As a consequence, the resulting lower ΔV of the slow exchange limit signals leads to a decrease of the coalescence temperature which apparently could not be reached at their field strengths.

The relatively high melting point of CCl_4 did not allow a further decrease of the temperature and therefore we repeated the experiments in apolar CS_2 in the range between +25 and –100 °C (Fig. 4). Similarly, at –26 and –40 °C all the signals of **1a** (24.3 (3t), 53.9 (6t) and 99.3 (d) ppm) experience considerable line

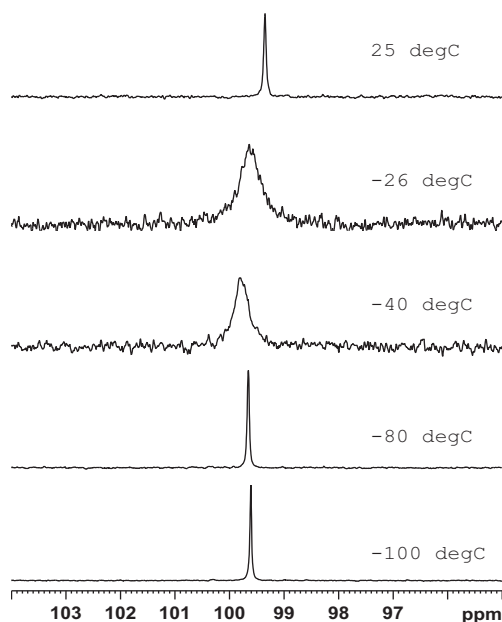


Figure 4. ^{13}C -DNMR C(9b) methine signal of **1a** from 25 (top) to –100 °C (bottom)

broadening. Again, this is consistent with a slowing of the dynamic conformational equilibrium between significant populations of both ttt and cct conformers. Interestingly, a further decrease in temperature (–80, –100 °C) leads to a resharping of the signals showing that the slow exchange regime could be reached at these temperatures. The presence of only one set of three peaks in these spectra indicates an equilibrium between ttt and cct conformers, that is, shifted towards the ttt conformer. The signals of the minor cct conformer are not detectable, which might either be because of its low concentration in a strongly biased equilibrium, or due to the fact that the slow exchange limit is not reached yet and the signals of the minor isomer are broadened beyond detection. In any case, the absence of distinct slow exchange limit signals for the cct conformer did not allow the measurement of the kinetics of the conformational exchange. It appears that even for higher homologues such as **1c**^[12] and **1e,f**,^[15] the NMR analyses in solution were also unable to distinguish the presence of a second conformer by additional attributable signals at low temperatures, even though a different symmetry was exhibited in the solid state, and broadening was observed in the case of **1c**. This was earlier rationalized by a rapid interconversion.^[15] It is noteworthy that for **1d**, a preferred cct conformation was assigned on the basis of a dynamic ^{13}C -NMR analysis.^[12]

We also recorded the ^{13}C -NMR of the homogeneous solid at 25 °C and observed the appearance of a broad major signal for the central methine at 100.6 ppm, while, curiously, the other signals were apparently unaffected. Minor signals at 99.6 and 29.0 ppm, essentially imperceptible in solution, also appeared. Additionally, at –5 °C, all the signals were, particularly, broadened (Fig. 5).

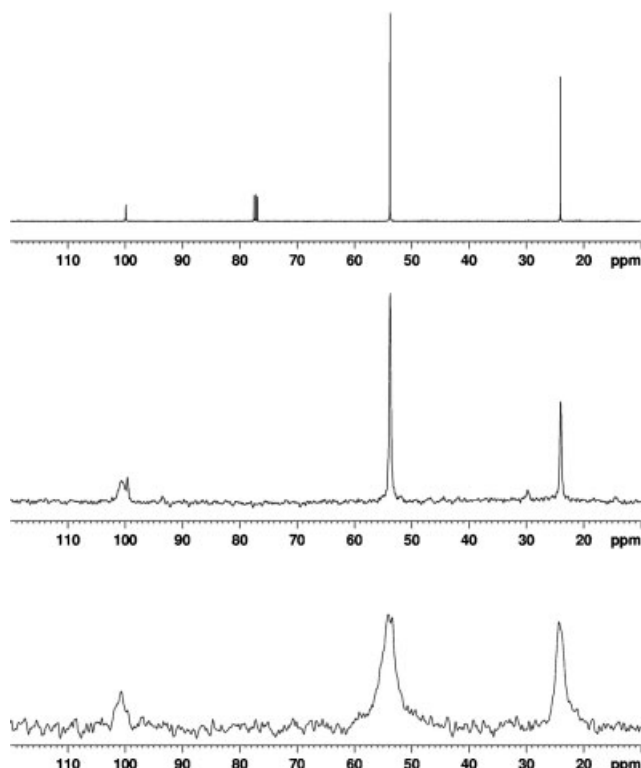
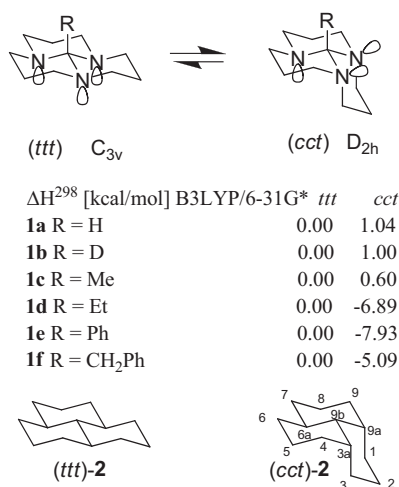


Figure 5. ^{13}C -NMR analyses of **1a** in CDCl_3 solution (top), homogeneous solid **1a** at 25 °C (centre) and homogeneous solid **1a** at –5 °C (bottom)

Our solid state NMR equipment did not allow us to perform these analyses at lower temperatures to confirm a possible coalescence process. In order to ensure that the minor signals did not result from local fusion, due to the high rotational speed (4000 Hz), we also performed the ^{13}C -NMR analysis of the melted neat liquid with a HRMAS probe head. At 50°C , the spectrum is as expected, while at 35 and 25°C , the peak at 29 ppm represents 6 and 13% of that at 24 ppm, respectively. In all cases, for the neat liquid in the HRMAS spectrum, the broad peak at 100 ppm disappeared, leaving a narrower signal at 99 ppm, with respect to increasing temperature. Whereas both CPMAS and HRMAS (high resolution magic angle spinning) make use of magic angle spinning for signal narrowing, they distinguish between different properties of the sample. With cross polarization technique in CPMAS the solid as a whole gives rise to signals in the NMR spectrum. On the other hand, HRMAS is based on liquid-state NMR technology, and only the more mobile segments of a molecule or of the sample are visible in the spectrum.

This brings us to the solid-state structural argument. Earlier we also demonstrated that, in case of a very small difference of conformational energy, crystallization may displace the equilibrium by means of additional packing forces.^[42] It should nevertheless be mentioned that Joule *et al.* performed their X-ray structure analysis of (ttt)-**1a** at -100°C from a sublimed rather than crystallized material.^[8] We thus do not exclude a possible displacement of the thermodynamic equilibrium by a selective more rapid solidification of the conformer (ttt)-**1a**.^[69]

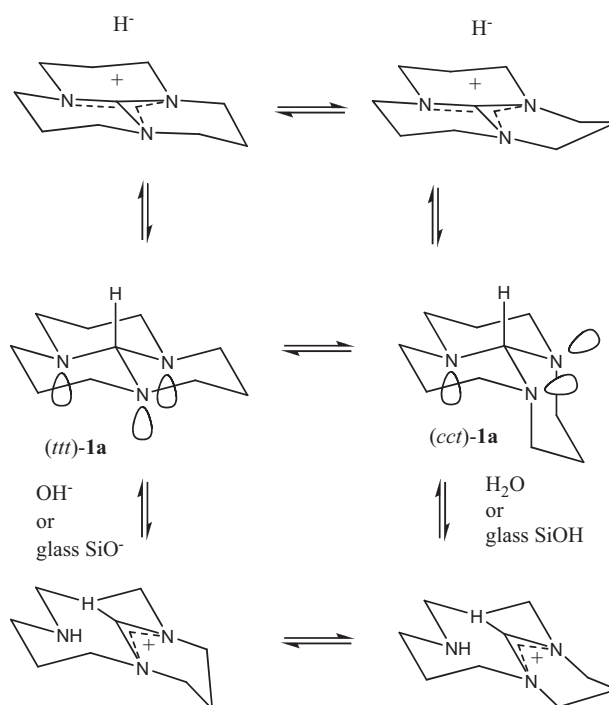
Conformational change from (ttt)- to (cct)-**1a** involves only two basic processes, ring and N inversions.^[70] Both guanidinium and formamidinium ions, by rendering both entities more planar, should notably decrease the inversion barrier. A trigonal co-planar guanidinium geometry may easily conformationally invert one of the six-membered heterocyclic rings to regenerate the conformationally interchanged orthoamide **1a**. Alternatively, the central hydride may also attack intermolecularly from the opposite side, with inversion of two rings. Both these hypotheses are completely incompatible with either the absence of **1b**/CaH₂ D scrambling,^[71] or the GC/IR analysis at high dilution in the gas phase, also suggesting a mixture of conformers. The guanidinium pathway may thus be excluded (Scheme 2).



Scheme 1. Conformational stability of 9b-substituted **1a-f**

We also calculated that scission of the C_{9b}—H bond is much more energetically demanding than breaking one of the central C—N bonds via a formamidinium moiety. This suggests that a low transition state could eventually be reached via inversion of a more flexible and entropically driven pseudo-planar 10- rather than 6-membered ring.^[72-76] In such a case, the glassware acidity could eventually replace the strict absence of H₂O, in order to catalytically protonate **1a**. The fact is that the broadening at -20°C in either CCl₄ or even CDCl₃ ^{13}C -NMR analyses of **1a**, is still observable, either in a silanized NMR tube, or in the presence of 1.5 mol-equivalent of 1,5-diazabicyclo[4.3.0]non-5-ene.^[77] This suggests that the formamidinium pathway should also be abandoned, to the profit of simple conformational dynamic motions.^[57]

Having nevertheless experimentally proven the presence of a second conformer by means of both Raman spectroscopy in the liquid state and careful comparison/interpretation of the theoretical/experimental IR analyses, we then decided to quantify the anomeric effect. The measured ΔH may be separated into both steric and stereoelectronic factors. Conformer (cct)-**1a** is destabilized by two CH₃—NH—CH₂—CH₃ and two CH₃—NH—CH₂—NH₂ gauche interactions. For comparison with butane, the main conformers of these subunits were calculated at both the B3LYP/6-31G** and MM2 levels and are reported in Table 1. Indeed, we intentionally chose a primitive method, which does not include stereoelectronic parameters, in order to evaluate the sole steric factors. In the case of the (cct)-**1a** conformer, one N_{3a}—C₃ axial substituent is $-syn-clinal$ ($-sc$) with the C₄—C₅ bond, while $+sc$ with the C_{9b}—N_{6a} bond. The N_{3a}—C_{9b} bond being $+sc$ with the N_{6a}-lp. The situation is exactly inverted for the second axial substituent. Since the C—N bond is shorter than the C—C bond (*ca.* 1.454–1.457 vs. 1.499–1.502 Å in (ttt)-**1a**,^[8] the steric gauche interaction of methyl ethyl amine is slightly superior to that of butane (1.12 kcal/mol on



Scheme 2. Hypothetic mechanism for the 6- or 10-membered ring inversion

Table 1. Gauches interactions for C—N—C—C, C—N—C—N and C—C—C—N sequences

| (H kcal/mol) | Method | sp | +sc | +ac | ap | −ac | −sc |
|---|------------------|------|-------------------------|-------------------|------|-------------------|-------------------------|
| Torsion angle | | 0° | 60° | 120° | 180° | 240° | 300° |
| CH ₃ —CH ₂ —CH ₂ —CH ₃ | DFT | 5.65 | 0.88 | 3.39 | 0.00 | 3.39 | 0.88 |
| | MM2 | 4.73 | 0.89 | 3.35 | 0.00 | 3.35 | 0.89 |
| CH ₃ —NH—CH ₂ —CH ₃ | DFT | 6.63 | 1.16^a | 3.40 ^b | 0.00 | 3.02 ^c | 1.52^d |
| | MM2 | 5.10 | 1.16^a | 3.77 ^b | 0.00 | 3.94 ^c | 1.08^d |
| CH ₃ —NH—CH ₂ —NH ₂ ^e | DFT | 6.16 | 0.00^f | 4.09 ^g | 0.24 | 2.22 ^h | 0.89ⁱ |
| | MM2 | 5.50 | 2.06^f | 4.38 ^g | 0.97 | 2.80 ^h | 0.99ⁱ |
| CH ₃ —NH—CH ₂ —NH ₂ ^j | DFT | 8.59 | 1.28^k | 4.33 ^l | 5.14 | 5.34 ^m | 1.79ⁿ |
| | MM2 | 4.62 | 0.59^k | 3.13 ^l | 1.98 | 4.22 ^m | 1.36ⁿ |
| CH ₃ —NH—CH ₂ —NH ₂ ^o | DFT | 7.59 | 1.39 | 5.33 | 0.82 | 5.16 | 5.49 |
| | MM2 | 5.77 | 1.39 | 2.91 | 0.00 | 3.68 | 2.43 |
| CH ₃ —NH—CH ₂ —NH ₂ ^p | DFT | 8.57 | 1.75 | 5.30 | 3.73 | 8.04 | 4.08 |
| | MM2 | 6.65 | 1.80 | 3.86 | 2.38 | 6.15 | 3.57 |
| CH ₃ —CH ₂ —CH ₂ —NH ₂ ^q | DFT | 5.00 | 0.34 | 3.76 | 0.00 | 3.76 | 0.34 |
| | MM2 | 4.81 | 1.01 | 3.74 | 0.12 | 3.74 | 1.01 |
| CH ₃ —CH ₂ —CH ₂ —NH ₂ ^r | DFT | 5.85 | 0.99 | 4.12 | 0.53 | 3.96 | 0.61 |
| | MM2 | 4.42 | 0.91 | 3.61 | 0.00 | 3.64 | 0.69 |
| CH ₃ —CH ₂ —CH ₂ —NH ₂ ^s | DFT ^t | 7.32 | 2.23 | 6.10 | 2.37 | 6.10 | 2.23 |
| | MM2 | 6.50 | 2.60 | 5.60 | 1.83 | 5.60 | 2.60 |

^a N lp ap C—CH₃; ^b N lp sp C—H; ^c N lp sp C—CH₃; ^d N lp ap C—H; ^e N lp ap C—NMe; ^f N lp ap C—NH₂ (stereoelectronically doubly stabilized); ^g N lp sp C—H; ^h N lp sp C—NH₂; ⁱ N lp ap C—H; ^j N lp +sc C—NMe; ^k N lp ap C—H; ^l N lp sp C—NH₂; ^m N lp sp C—H; ⁿ N lp ap C—NH₂; ^o N lp ap C—C; ^p N lp sp C—NMe; ^q N lp −sc C—NMe; ^r H—N ap C—C; ^s N lp sp C—C. Gauche interactions in bold, values discussed in this report for the specific conformation of (cct)-**1a** in italic. ^t No ZPE corrections for all these B3LYP/6-31G** calculations.

average, since +sc and −sc conformations are considered). Alternatively, the CH₃—NH—CH₂—NH₂, although less crowded at the terminal NH₂ position, also suffers from the shorter C—N bond lengths and its gauche interaction amounts to ca. 1.37 kcal/mol on average. This allows us to roughly estimate the single anomeric influence of a N lp in conformer (cct)-**1a** as ca. 1.9–2.1 kcal/mol.^[78] This rough estimation is slightly superior to the usual 1.4–1.5 kcal/mol stabilisation either calculated or measured for acetals, sugars or amins.^[79–81] This value is also close to that reported by Crumbie *et al.* for 5-hydroxyhexahydropyrimidine,^[54] but should certainly be minimized, since our calculations do not correspond to stabilizing solvated conditions. Finally, there is little difference between the gauche-butane and the gauche-*n*-propylamine interactions,^[82] the latter being slightly higher in energy, with respect to the smaller steric demand of the NH₂ as compared to CH₃ moiety,^[83] associated with the shorter C—N versus C—C bond lengths for conformations of low energy. The 6-31G** basis set corrects very well the conformational analysis of CH₃—NH—CH₂—NH₂, as shown by the global minimum corresponding to a double anomeric stabilization.

CONCLUSIONS

More than 30 years after its discovery, we experimentally demonstrated by Raman and IR analyses that **1a** exists as a mixture of ttt/cct conformers at 22 °C in liquid or CCl₄ solution, thus contrasting with the initial IR, NMR and X-ray evidence in favour of (ttt)-**1a**. The stereoelectronic stabilization amounts to ca. 2.0 kcal/mol (± 0.1) for each of the anomeric N lp ap to the polarized C—N bond, based on a ΔH of 0.75 kcal/mol (± 10%), as measured by Raman spectroscopy from 22 to 90 °C.^[84] Despite

the signals broadening in the CDCl₃, CCl₄ and CS₂ ¹³C-DNMR analyses, the absence of distinct slow exchange-limit signals for cct-**1a** did not allow us to measure the kinetics of the ttt/cct conformation interchange. The T Bohlmann band observed and confirmed by calculations at ca. 2442 cm^{−1} in the IR analysis of (ttt)-**1a**, belongs to one of the weakest values for a C—H stretching vibration, and thus underlines the peculiar nature of this bond. The presence of C(9b)-D stretchings at 2040 and 1850 cm^{−1} in the IR analysis of **1b** confirms a mixture of (cct)/ (ttt)-conformers. These observations shall certainly stimulate new studies in the field of metal free enzyme-like reductions,^[85,86] as well as pH dependent H₂ material storage,^[87–90] a source of energy that promises to be of increasing interest in the future. Reactions of **1a,b** as well as their 2-substituted analogues, with CH₂Cl₂ and CD₂Cl₂ are currently under study and will be reported in due time.

SUPPORTING INFORMATION

IR analyses of **1a** in the solid, 3% CCl₄ solution and gaseous states. Comparative simulated/experimental IR analyses and attributions of pure/mixed **1a** conformers. ¹³C- and ¹H-NMR displacements of **1a** in different solvents. ¹³C-NMR analyses of neat **1a** at 50 °C, 35 °C and 25 °C. Detailed DFT calculations for **1** and **2** with ZPE corrections.

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- [78] 0.75 to 1.04 kcal/mol = 1.36 kcal/mol + 1.39 kcal/mol + 1.16 kcal/mol + 1.08 kcal/mol – $2 \times$ anom. effects. The single steric factor, ca. 4.99 kcal/mol, is also below the global 6.0 kcal/mol calculated by Pensak¹.
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