Conformation of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene: an experimental and theoretical NMR study

María Luisa Jimeno,[a] Ibon Alkorta,[a] José Elguero,*,[a] J. Edgar Anderson,[b] Rosa María Claramunt[c] and José Luis Lavandera[c]

[a] *Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain*
[b] *Chemistry Department, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, UK WC1H 0AJ*
[c] *Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey, s/n, E-28040 Madrid, Spain*

Hybrid *ab initio* calculations (GIAO/B3LYP/6-31G*) together with new DNMR experiments (^{1}H and ^{13}C) have been used to clarify the problem of the conformation of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene. The carbon-13 chemical shifts have been assigned unambiguously to the chair **C** and twist-boat **TB** conformations. Lineshape analysis of the ^{1}H NMR spectra has been carried out at several temperatures using an estimated set of Karplus-type vicinal coupling constants.

The exploration of the conformational space of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene, **1**, by ^{1}H DNMR (dynamic NMR) and molecular mechanics calculations represents a classical example of the complementarity of the two techniques. Studied in solution by Ollis[1,2] and St-Jacques[3,4] and their coworkers at about the same time and calculated by Ollis[1,2] and Allinger,[5] and their coworkers, its X-ray structure, a chair **C**, was determined more recently by some of us.[6] It might appear that the problem had been definitely solved, both in solution and in the solid state, and that nothing remained to be studied; however, several interesting aspects were still unknown, so we set out: (*i*) to investigate the compound by low temperature ^{13}C NMR spectroscopy and identify the signals obtained for the two different conformations, matching calculated and experimental chemical shifts, (*ii*) to determine the [1]H–[1]H coupling constants of the aliphatic AA′BB′ systems (CH$_2$—CH$_2$) and verify if the vicinal ones followed a Karplus relationship (which is not the case for the bispyrazolium analog)[6] and (*iii*) to study, by methods other than molecular mechanics, the three minima of the conformational space: the chair **C**, the twist-boat **TB** and the twist **T**.

C, **TB** and **T** are the conformational descriptors used by Allinger and Sprague.[5] Earlier workers[1–4] have given these conformational descriptors to slightly different structures. The twist-boat **TB** conformation is *chiral* and has C_2 symmetry, that is the *ca.* 40° C$_{4a}$—C$_5$—C$_6$—C$_{6a}$ and C$_{10a}$—C$_{11}$—C$_{12}$—C$_{12a}$ torsion angles are *internally homotopic*. The signs of these *synclinal* (*gauche*) torsion angles may be used as descriptors for the two enantiomeric **TB** conformations [(+)-**TB** and (−)-**TB**]. *Interconversion* of (+)-**TB** and (−)-**TB** can take place by a *torque* about the C$_5$—C$_6$ and

C$_{11}$—C$_{12}$ bonds in which the two *synclinal* torsion angles decrease to *synperiplanar* (0°) values in the achiral boat **B** C_{2v} transition state and then once again increase in magnitude to *synclinal* values of opposite sign. When we mention **TB** we mean the very fast, on the NMR timescale, (+)-**TB** ⇌ [**B**]‡ ⇌ (−)-**TB** equilibrium mixture. The two hydrogens on any saturated carbon in an isolated **TB** or **C** conformation can be distinguished, because one points outwards (*exo*) and the other points inwards (*endo*).

There exist ring-inverted chair and twist-boat conformations, **C′** and **TB′**, in which *endo*-H has become *exo*-H and *vice versa*. Various interconversions of conformation are possible (see Scheme 1), and all the earlier reports[1–5] paid much attention to this because of a contemporary awareness of cyclohexane conformations, rather than to the direct **C** ⇌ **B** interconversion. All agreed that this is of very high energy, so we will not consider it further. A more extensive set of rotations takes molecules *from either a C or a TB* conformation to the twist (+)-**T** or (−)-**T** conformations with a φ about ±75°. **T** is a relatively high energy conformation but as Scheme 1 shows, it is the pivotal intermediate not only for intercon-

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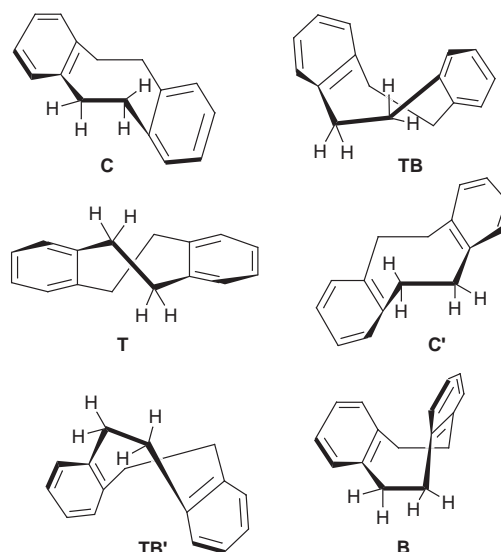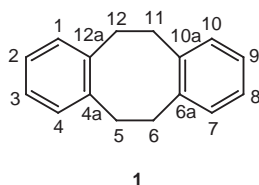
* E-mail: IQMBE17@fresno.csic.es
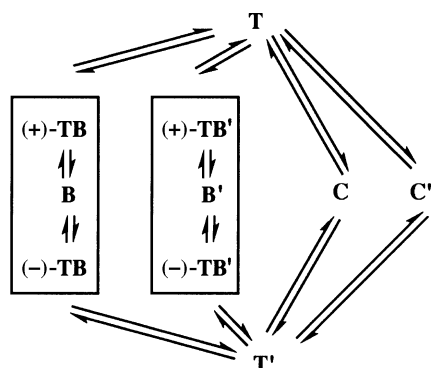
Scheme 1 Pathways for interconversions *within* the twist-boat set of conformations, and *within* the chair set of conformations, as well as *between* the two sets, all of which involve the twist conformation, although it is of too high energy to be significantly populated. Some high-energy interconversions such as $\mathbf{C} \rightleftharpoons \mathbf{B}$, are not shown

version of the chair **C** and twist-boat **TB** sets, but also for ring inversion within the sets $\mathbf{C} \rightleftharpoons \mathbf{C}'$ and $\mathbf{TB} \rightleftharpoons \mathbf{TB}'$.

Previous proton NMR results[1–4] confirm this scheme and can be summarized as follows. At $-86\,^{\circ}\text{C}$ in CDCl_3–CS_2, there is a near 50 : 50 ratio of the two sets of signals: a singlet for **TB** and an AA'BB' spectrum for **C**. Passage over the four $\mathbf{C} \rightleftharpoons \mathbf{T}$ pathways is slow on the NMR timescale, with a barrier $\Delta G\ddagger$ of 10.0 kcal mol^{-1}, so that both interconversion of the chair and twist-boat sets of conformations, and of **C** with **C'**, are slow, but $\mathbf{TB} \rightleftharpoons \mathbf{TB}'$ is still fast on the NMR timescale. At lower temperatures in a different solvent, the **C** and **TB** populations are rather different and the **TB** signal splits into two, indicating that passage over the four $\mathbf{TB} \rightleftharpoons \mathbf{T}$ pathways, and thus the $\mathbf{TB} \rightleftharpoons \mathbf{TB}'$ interconversion, has become slow. The barrier $\Delta G\ddagger$ is 7.8 kcal mol^{-1}.[3,4]

Results and Discussion

Ab initio calculations of the chair, twist-boat and twist conformations

To interpret the ^{1}H and ^{13}C NMR results, we decided to use the hybrid GIAO-DFT approach, which has yielded good results in three previous studies.[7–9] First, we optimized the structures of **C**, **TB** and **T** at the B3LYP/6-31G** level and then verified (first derivatives) that all of them are minima. The optimized geometry of the chair is very similar to that determined by X-ray crystallography[6] (superposition of heavy atoms, RMS = 0.021 Å), which is not a surprise owing to the extreme rigidity of this conformation. The energies and dipole

moments are reported in Table 1.

The relative energies show that, for isolated molecules, only the **C** and **TB** conformations should be present in appreciable amounts. We calculated, as did Ollis and his coworkers[1,2] before us, that the chair conformation is more stable than the twist-boat. Allinger and Sprague[5] calculated the reverse, as is observed by experiment, but clearly the equilibrium is solvent-dependent.

^{13}C NMR experiments

Two ^{13}C NMR spectra of compound **1** at 100 MHz in CD_2Cl_2, one at room temperature (RT) and the other at $-80\,^{\circ}\text{C}$, were recorded. The RT spectrum shows four narrow average signals while the spectrum at $-80\,^{\circ}\text{C}$ shows eight signals: four for the chair (12%) and four for the twist-boat (88%), as expected (see experimental *vs.* calculated chemical shifts in Fig. 1). The relative abundance identifies both conformations (see ^{1}H NMR discussion). Some signals are quite sensitive to conformation, such as C_{4a} ($\Delta\delta = 3.9$) and the CH_2 ($\Delta\delta = 2.2$).

GIAO-DFT calculations: ^{13}C NMR

The GIAO results (^{1}H and ^{13}C) are reported in Table 1. There are two enantiomeric twist-boats, $(+)$-**TB** and $(-)$-**TB**, separated by a very low barrier (estimated, using molecular mechanic calculations, to be 1–2 kcal mol^{-1}).[1,2,5] There are eight different carbon positions in any **TB**, but $(+)$-$\mathbf{TB} \rightleftharpoons (-)$-**TB** interconversion averages these to four, so computed values have been averaged appropriately. The relative values have been obtained using the shieldings calculated for TMS at the same level.

The differences $(\delta_{\mathbf{TB}_{av}} - \delta_{\mathbf{T}})$ between calculated values for C_{4a}, C_{12a} *ipso* and for C_5, C_{12} *benzylic* nuclei in $\mathbf{TB}_{av}$ *vs.* those for the corresponding nuclei in **T** are -1.46 and 2.57 ppm,
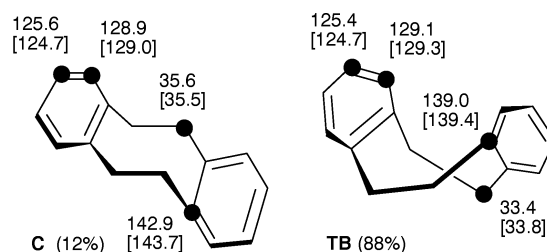
Fig. 1 Comparison between experimental NMR shifts and fitted values (in brackets) for **1** using eqn. (1)

Table 1 Total energies, relative energies, dipole moments, absolute shieldings and chemical shifts relative to TMS[a]

	Chair **C**			Twist-boat **TB**			Twist **T**	
Energy/hartree	−619.348 747			−619.347 396			−619.343 038	
Relative energy[a]/kcal mol^{-1}	0.00[a]			0.85			3.58	
Dipole moment/Debye	0.00			0.54			0.00	
	C (abs)	**C** (rel)[b]	$(+)$-**TB** (abs)	$(-)$-**TB** (abs)	$\mathbf{TB}_{av}$ (abs)	$\mathbf{TB}_{av}$ (rel)[b]	**T** (abs)	**T** (rel)[b]
^{13}C NMR								
C-1 (*ortho*)	66.29	123.40	65.32	66.87	66.095	123.60	65.50	124.19
C-2 (*meta*)	70.24	119.45	70.09	70.40	70.245	119.44	70.19	119.50
C-4a (*ipso*)	53.06	136.63	53.93	56.99	56.96	132.73	55.50	134.19
C-5 (CH$_2$)	150.97	38.72	153.93	151.04	152.485	37.20	155.06	34.63
^{1}H NMR								
H-1	25.16	7.02	25.49	25.39	25.44	6.74	25.26	6.92
H-2	25.17	7.01	25.29	25.39	25.34	6.84	25.19	6.99
H-inside	29.46	2.72	28.94	28.88	28.91	3.27	28.80	3.38
H-outside	29.37	2.81	29.47	29.49	29.48	2.70	29.32	2.86

[a] Molecular mechanic calculations yield the following relative strain energies: **C** 0.00, **TB** 0.04 and **T** 1.01 kcal mol^{-1}.[2] [b] TMS (GIAO/B3LYP/6-31G*): ^{13}C 189.69, ^{1}H 32.18 ppm.
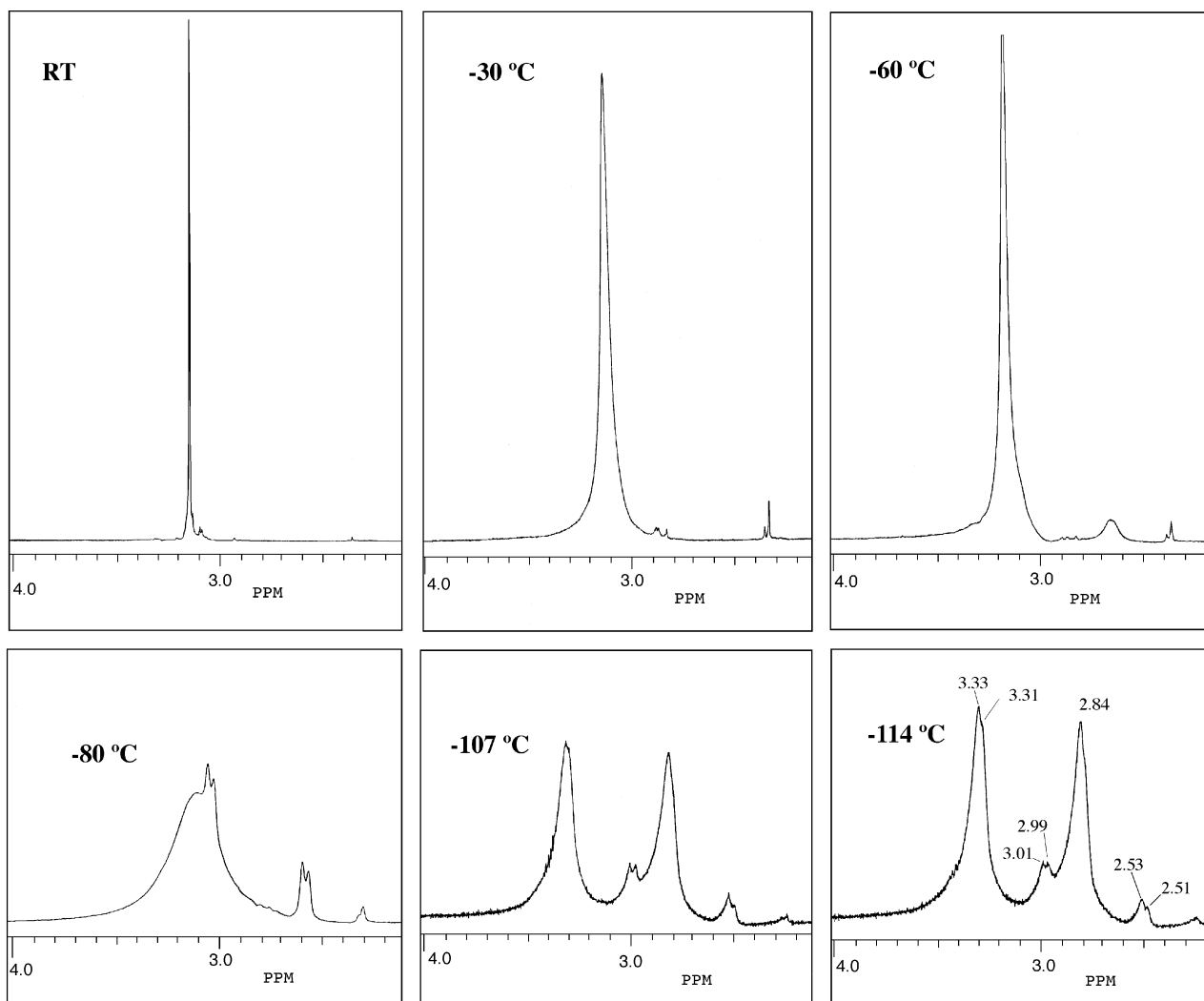
Fig. 2 Proton magnetic resonance spectra (400 MHz) of the aliphatic (CH$_2$) protons of **1** in CD$_2$Cl$_2$ at several temperatures

respectively. These differences are not that much different from those between **C** and **TB$_{av}$** : (δ_C–$\delta_{TB_{av}}$) is 3.90 and 1.52 ppm, respectively. Nevertheless, the RMS residuals are always lower using the calculated values of **TB$_{av}$** than using those of **T**. For example, for the eight carbon atoms, RMS(**TB$_{av}$**) = 0.62, RMS(**T**) = 1.08 ppm, and for the most sensitive carbons (C$_{4a}$ and CH$_2$), RMS(**TB$_{av}$**) = 0.33, RMS(**T**) = 1.27 ppm.

The comparison between calculated and experimental chemical shift values together with the corresponding ^{1}H

Fig. 3 ^{1}H chemical shifts (ppm) and ^{1}H–^{1}H coupling constants (Hz) used in the simulations

NMR results (see below) allows us to assign **TB** and **C** conformational descriptors to the major and minor species, respectively. There is an excellent correlation, eqn. (1), between both sets (the fact that the slope is not exactly 1 is usual for this level of calculation).[7–9]

$$\delta^{13}C(C + TB_{av})_{exp} = -7.3 \pm 0.6 + 1.105 \pm 0.006 \, \delta^{13}C$$
$$\times (C + TB_{av})_{rel}, \, n = 8, r^2 = 1.000 \quad (1)$$

The calculated values agree well with the differences of chemical shifts in the case of the most sensitive carbon atoms, C$_{4a}$ ($\Delta\delta$ = 4.3) and CH$_2$ ($\Delta\delta$ = 1.7), differences that otherwise would have been difficult to explain.

^{1}H DNMR experiments

The spectra of **1** in CD$_2$Cl$_2$ between RT and $-114\,°$C (see Fig. 2 for the CH$_2$CH$_2$ part of the spectrum) were recorded at 400 MHz. The values measured in the lowest temperature spectrum are consistent [see eqn. (2)] with those reported by Sauriol-Lord St-Jacques[4] for the tetradeuterated derivative in propene–CD$_2$Cl$_2$ (2 : 1) at $-136\,°$C (CH$_2$CH$_2$) and in CDCl$_3$–CS$_2$ (2 : 3) at $-90\,°$C (aromatic protons).

$$\delta^1H \, (\text{ref. 3}) = 0.098 \pm 0.026 + 0.995 \pm 0.005 \, \delta^1H \, (\text{this work}),$$
$$n = 8, r^2 = 1.000 \quad (2)$$

These authors determined the barriers for the two dynamic processes using the coalescence temperature approximation; in this way they calculated $\Delta G\ddagger(C/TB)_c$ = 10.0 kcal mol^{-1} for

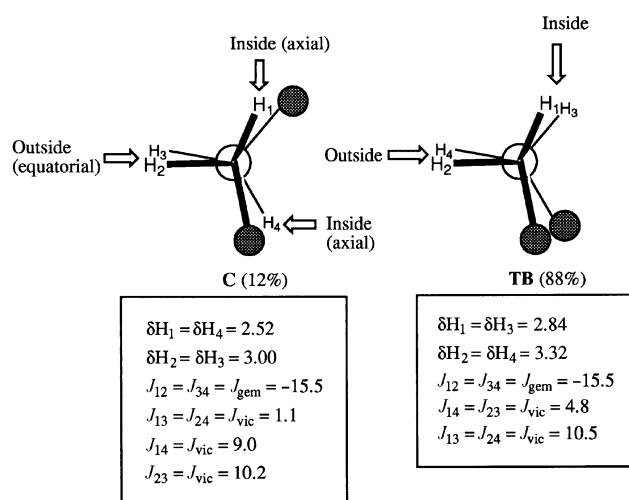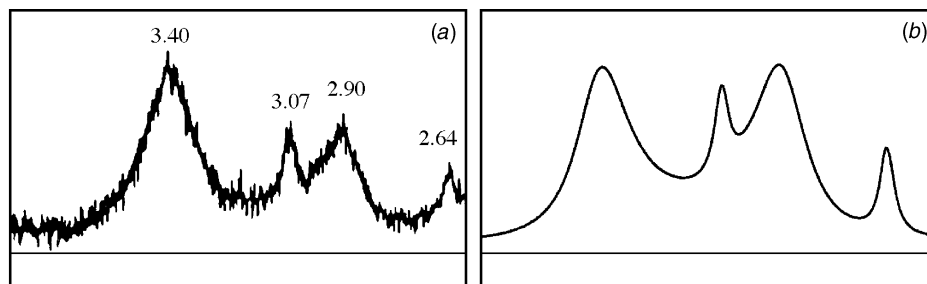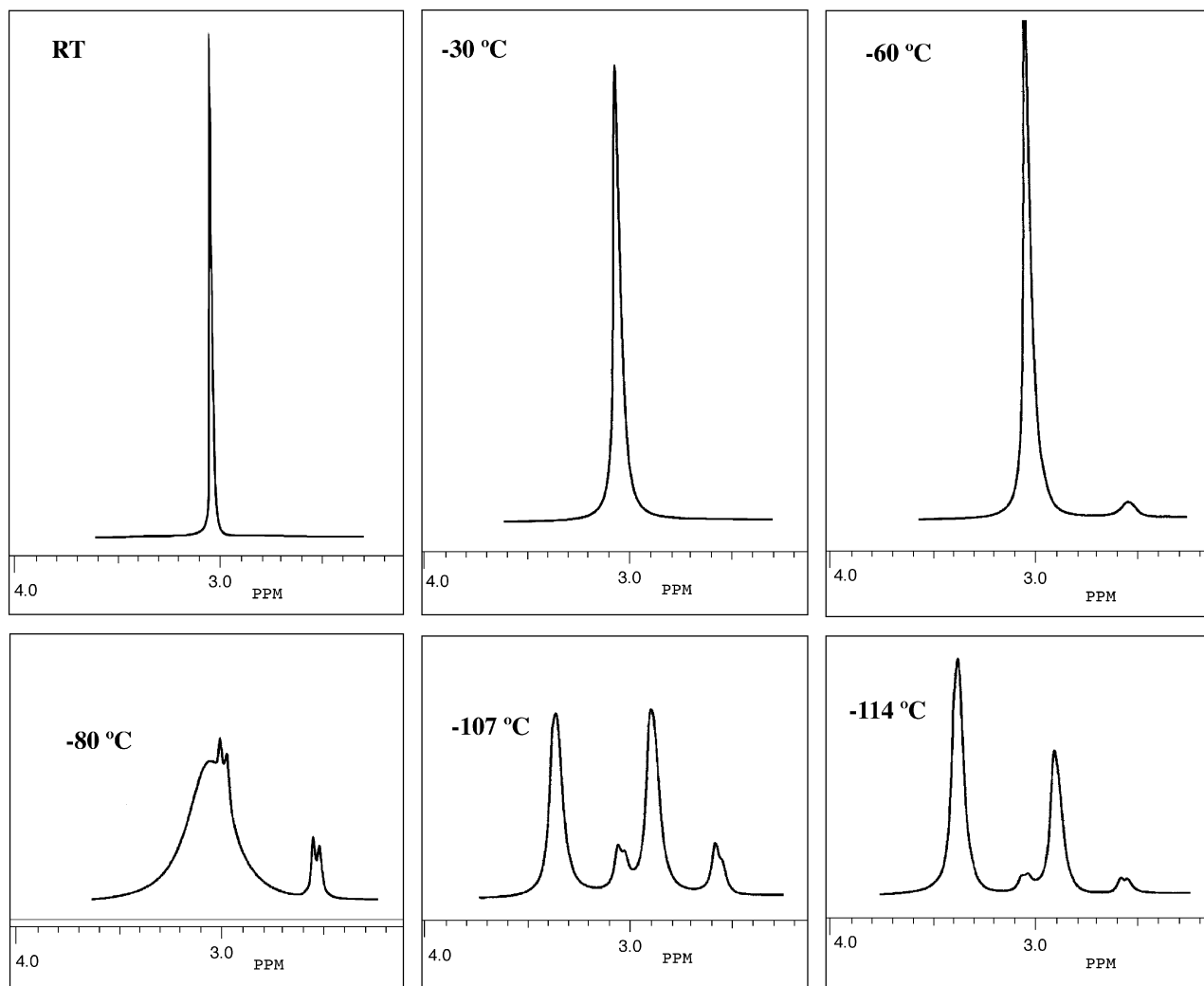**Fig. 4** Proton magnetic resonance spectra (100 MHz) of the aliphatic (CHD) protons of **1**-d_4 in CD_2Cl_2–C_3H_6 (2 : 1) at −121 °C. (*a*) Experimental.[4] (*b*) Simulated (this work)

Fig. 5 Simulation corresponding to the experimental spectra of Fig. 2

Table 2 Activation barriers for the **C/TB** and **TB/TB′** interconversion pathways

Species	Solvent	T_c/°C	$\Delta G\ddagger$(**C/TB**)/ kcal mol^{-1}	T_c/°C	$\Delta G\ddagger$(**TB/TB′**)/ kcal mol^{-1}	Ref.
CH_2CH_2	$CDCl_3$–CS_2 (1 : 1)	−66	10.2^a	—	—	1
CH_2CH_2	CD_2Cl_2–propene (2 :)	−72	10.2 ± 1^a	−115	7.5 ± 1^b	3
CHDCHD	$CDCl_3$–CS_2 (2 : 3)	−72	10.0 ± 0.5^a	—	—	4
		−70	9.9 ± 0.5^b	—	—	
CHDCHD	CD_2Cl_2–propene (2 : 1)	−72	10.0 ± 0.5^a	−115	7.8 ± 0.3^b	4
CH_2CH_2	CD_2Cl_2	—	10.5^b	—	8.4^b	This work

^{a} Using aromatic protons. ^{b} Using aliphatic protons.

$T_c = -72 \,^{\circ}C$ and $\Delta G\ddagger(\text{TB/TB}')_c = 7.8$ kcal mol^{-1} for $T_c = -115 \,^{\circ}C$.[3,4] To apply the lineshape method on the CH$_2$CH$_2$ signals, we needed: (*i*) the populations p_C and p_{TB} (we used those determined by ^{13}C NMR, $p_C = 0.12$ and $p_{TB} = 0.88$, identical to those reported previously); (*ii*) the two barriers $\Delta G\ddagger(\text{C/TB})_c$ and $\Delta G\ddagger(\text{TB/TB}')_c$; (*iii*) the chemical shifts of the four CH$_2$ protons [we used those determined at $-114 \,^{\circ}C$, Fig. 2: 2.52 and 3.00 (**C**), and 2.84 and 3.32 ppm (**TB**)] and (*iv*) a set of coupling constants. Although we used a 400 MHz spectrometer, the resolution at low temperatures is not good enough for the analysis of the two AA′BB′ systems; the same was true in the experiments of Sauriol-Lord and St-Jacques [AB systems (CHD—CHD), 100 MHz but lower temperatures].

The vicinal coupling constants reported in Fig. 3 are those calculated using the Karplus equation[10] and the dihedral angles of the minimized conformations. The geminal coupling constant is that measured for a cyclic structure possessing a Ph—CH$_2$—CH$_2$—Ph moiety.[11]

First we simulated the evolution of the two AB systems reported by Sauriol-Lord and St-Jacques (**1**-d$_4$) using their chemical shifts, activation barriers and our calculated [1]H–[1]H coupling constants for the remaining two protons: **C**, $J_{13} = 1.1$ Hz; **TB**, $J_{13} = 10.5$ Hz (deuteration in **1**–d$_4$ occurred in the *cis* positions). Since the simulated and experimental spectra are similar (see one example in Fig. 4), we are confident that the NMR parameters of Fig. 3 are realistic.

The simulation with the experimental results obtained by us in CD$_2$Cl$_2$ for the non-deuterated compound (two AA′BB′ systems, Fig. 2) was then tried. Finding that the fit was not entirely satisfactory, we decided to adjust the experimental spectra to the best barriers using the Eyring equation. The best fit (Fig. 5) was obtained for $\Delta G\ddagger(\text{C/TB}) = 10.5$ kcal mol^{-1} (instead of 10.0 ± 0.5 kcal mol^{-1})[4] and $\Delta G\ddagger(\text{TB/TB}') = 8.4$ kcal mol^{-1} (instead of 7.8 ± 0.3 kcal mol^{-1}).[4] We have gathered in Table 2 the different barriers reported in the literature together with those determined in the present work.

GIAO-DFT calculations: ^{1}H NMR

The assignment of the in (*endo*) and out (*exo*) protons of the **C** and **TB** conformations is independent of the analysis of the AA′BB′ pattern. Since the broadening prevents the use of zig-zag couplings with aromatic protons,[11] we resorted to the calculated values of Table 1. Only the inside proton (2.52 ppm) of the **C** conformation is not well-reproduced with the calculations. For the seven other protons (four aromatic and three aliphatic), eqn. (3) holds:

$$\delta[1]\text{H}(\textbf{C} + \textbf{TB}_{av})_{exp} = 0.17 \pm 0.05 + 0.988 \pm 0.009 \, \delta[1]\text{H}$$
$$\times (\textbf{C} + \textbf{TB}_{av})_{rel}, \quad n = 7, \, r^2 = 1.000 \quad (3)$$

In any case, the definitive assignment of the four aliphatic protons is: 2.52 (**C**, inside), 3.00 (**C**, outside), 2.84 (**TB$_{av}$**, outside) and 3.32 ppm (**TB$_{av}$**, inside).

Conclusions

The combination of high-level calculations with DNMR experiments has enabled us to clarify the conformational behaviour of 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene **1**. The two most stable conformations, **C** and **TB**, have similar energies and interconvert through processes having activation energies slightly higher than previously reported. To these two conformations correspond a set of coupling constants (the vicinal ones following the Karplus relationship) that can be used to reproduce the lineshapes at different temperatures.

Experimental

5,6,11,12-Tetrahydrodibenzo[*a,e*]cyclooctene, **1**, has been reported several times; we used the sample we had prepared

previously.[6] The spectra were recorded in a Varian VXR 400 spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) (for experimental conditions see ref. 11). The variable temperature was computer-controlled and the internal temperature calibrated by employing the methanol thermometer method. Calculations for complete lineshape analyses were carried out using the DNMR4 program.[12] Theoretical spectra were calculated to obtain the best fit with the observed spectra by varying the rate constants for each temperature. The activation parameters were obtained from the Eyring equation, plotting $\log(k/T)$ as a function of $1/T$ and performing a regression analysis of these data. The results, $\Delta G\ddagger(\text{C/TB}) = 10.53 \pm 0.03$ kcal mol^{-1} and $\Delta G\ddagger(\text{TB/TB}') = 8.36 \pm 0.02$ kcal mol^{-1} are of very good quality ($r^2 = 0.99998$); however, since the coupling constants used (see Fig. 3) have not been measured but estimated, the errors on the barriers are probably much larger. For this reason, we have not given the corresponding errors in Table 2.

The *ab initio* calculations have been performed with the Gaussian-94 program.[13] The hybrid HF-DFT, Becke3LYP level of calculation[14] and the 6-31G* basis set have been used.[15] The structures have been fully optimized maintaining their symmetry characteristics. The absolute NMR shieldings of the three conformers have been calculated using the GIAO perturbation method[16] as implemented in the Gaussian-94 program. The relative chemical shifts have been obtained by subtracting the absolute shieldings for TMS optimized at the same computational level.

Acknowledgements

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