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TETRAHEDRON

Conformational analysis of heterocyclic analogues of 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene: 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*][1,5]diazocine and 6,7,13,14-tetrahydrobispyrido[1,2-*a*:1',2'-*e*]diazocinediium dibromide

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(Dedicated to Professor Alan R. Katritzky on the occasion of his 70th birthday)

Abstract.— The ^{1}H and ^{13}C NMR spectra of the title compounds have been recorded. While the spectrum of 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*][1,5]diazocine **3** does not show any dependence with the temperature in the studied range (-65 to +75 °C), that of 6,7,13,14-tetrahydrobispyrido[1,2-*a*:1',2'-*e*] diazocinediium dibromide **4** shows a clear variation, narrow lines appearing only at + 85 °C. The differences in the dynamic behaviour of these compounds has been analyzed using different semi-empirical calculations (MNDO, AM1, PM3) of the ground and transition states. For comparison purposes, two other compounds belonging to the 6,8,6 series of ring derivatives have also been calculated, 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclooctene **1** and 5,6,12.13-tetrahydrobispyrazolo[1,2-*a*:1',2'-*e*][1,2,5,6]tetrazocinediium cation **2**.

INTRODUCTION

In previous papers we have studied the conformational behaviour of 5,6,11,12-tetrahydrodibenzo [*a,e*]cyclooctene **1** and several 5,6,12,13-tetrahydrobispyrazolo[1,2-*a*:1',2'-*e*][1,2,5,6]tetrazocinediium dihalides **2** (the so-called 6,8,6 and 5,8,5 ring systems). The carbocycle, 5,6,11,12-tetrahydrodibenzo [*a,e*]cyclooctene **1**, exists in the solid state in the chair conformation, whereas both the chair **C** and the boat **B** forms are present in solution: 60% **B** - 40% **C** in $CDCl_3$-CS_2 2:3 at 183 K (**1B** $\rightleftharpoons$ **1C**, $\Delta G^{\ddagger}$ = 10.0 kcal·mol^{-1} and **1B** $\rightleftharpoons$ **1B**, $\Delta G^{\ddagger}$ = 7.8 kcal·mol^{-1}).[1] In the case of **2a** ($R_3 = R_5$ = H) and its 1,3,8,10-tetramethyl derivative **2b** ($R_3 = R_5$ = Me), which present the tetrazocine central ring in a chair conformation in solid state, the rotational barriers for the chair-chair interconversion were estimated to be of 13.5 kcal mol^{-1} (T_c 288 K in ethyleneglycol-d_6-D_2O 2:1) and 12.8 kcal mol^{-1} (T_c 276 K in DMF-d_7-CD_3OD 10:1), respectively.[2]

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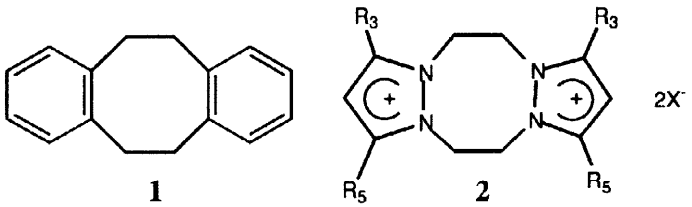
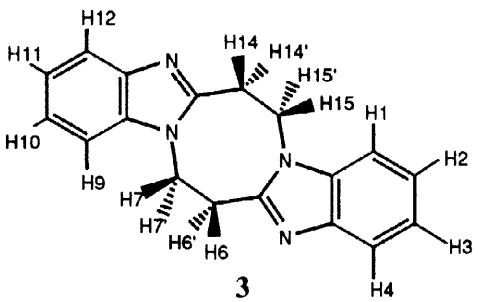


1 2

Now we have studied two new 5(6),8,5(6) systems: the 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*][1,5]diazocine **3**, first described by Katritzky *et al.*[3] and the 6,7,13,14-tetrahydrobispyrido[1,2-*a*:1',2'-*e*] diazocinediium dibromide **4**, in which two different kinds of nitrogen atoms have been introduced in the cyclooctene ring making these compounds intermediate situations between **1** (no nitrogen atoms) and **2** (two nitrogen atoms).



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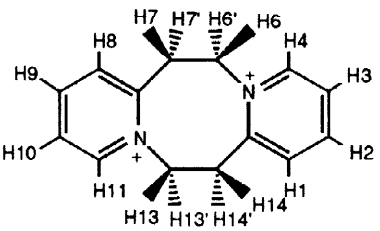

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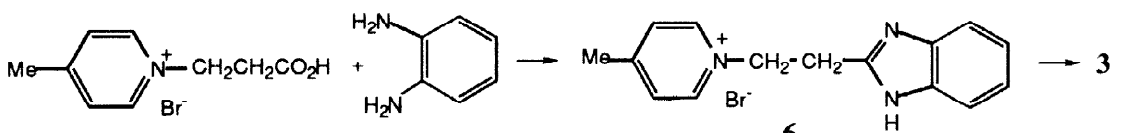
RESULTS AND DISCUSSION

Chemistry. We prepared 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*][1,5]diazocine **3** according to Katritzky's procedure,[3] by dimerization of 2-[2-(4-methylpyridinium)ethyl]benzimidazole bromide **6**, which in turn is obtained, by means of the Phillips synthesis, from 3-(4-methylpyridinium)propionic acid bromide **5** and *o*-phenylenediamine (Scheme 1). This reaction has been explored systematically by Alcalde *et al.*[4]



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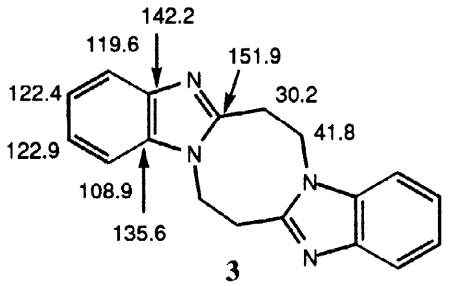
Scheme 1

We have already described the synthesis of 6,7,13,14-tetrahydrobispyrido[1,2-*a*:1',2'-*e*]diazocinediium dibromide **4** starting from 2-(β-bromoethyl)pyridine.[1]

NMR analysis and variable temperature experiments.

1.- Static aspects. We recorded the ^{13}C NMR spectra of compounds **3** and **4**, that of compound **3** in $CDCl_3$ and that of compound **4** in DMSO-d_6. The purpose of these spectra is to assign the directly linked protons through 2D (^1H-^{13}C) experiments.



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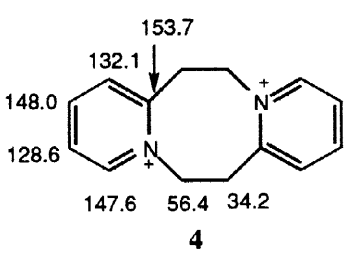

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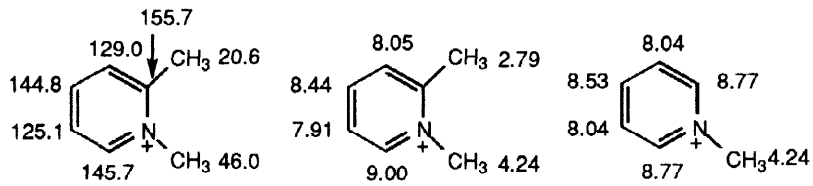
The corresponding ^{1}H-NMR spectra are gathered in Tables 1 (compound **3**) and 2 (compound **4**). 1,2-Dimethylpyridinium iodide **7** has been used as a model compound for compound **4**. The chemical shifts, ^{1}H and ^{13}C, in DMSO-d_6 for a concentration of 160 mg in 0.5 mL are reported below; the data for the 1-methyl-pyridinium salt **8** have been reported in reference 5 (solvent D_2O).



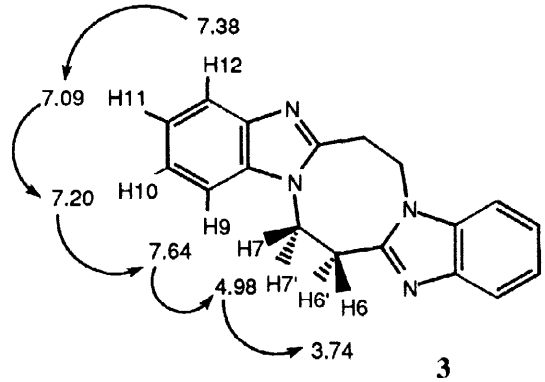
7 **7** **8**

Table 1. ^{1}H NMR data (δ in ppm, J in Hz) for compound **3** at 298 K (200 MHz)

Solvent	H-1 H-9	H-2 H-10	H-3 H-11	H-4 H-12	C-CH_2	N-CH_2
DMSO-d_6	7.65 (d) J_{76} = 8.3	7.19 (t) J_{65} = 7.5	7.07 (t) J_{54} = 7.5	7.33 (d)	3.62 (t) J = 6.8	4.92 (t)
CD_3OD	7.66 J_{76} = 8.1 J_{75} = 1.2 J_{74} = 0.8	7.32 J_{65} = 7.3 J_{64} = 1.3	7.20 J_{54} = 7.9	7.39	3.77 (t) J = 6.8	5.04 (t)
$CDCl_3$	7.66	----------7.38-7.20----------			3.69 (m)	4.64 (m)
DMF-d_7[a]	7.64 J_{76} = 8.4 J_{75} = 1.1	7.20 J_{65} = 7.6 J_{64} = 1.1	7.09 J_{54} = 7.6	7.38	3.74 (t) J = 6.9	4.98 (t)
CF_3CO_2H	-------7.62-7.70-------		-------7.50-7.65-------		4.22 (t)	5.24 (t)

[a]Spectrum recorded at 300 MHz.

The assignment of the ^{1}H-NMR spectrum of **3** has been carried out through "Relay-H" and "Noesy-Tocsy" experiments (frequency: 299.94 MHz, solvent: DMF-d_7, temperature 75 °C):



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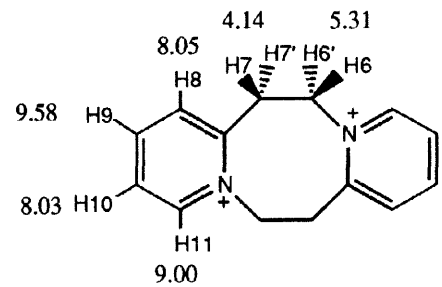

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The spectrum has two parts, the aromatic ABCD system and the aliphatic AA'XX' system. The ABCD system has been analyzed yielding the following chemical shifts (in ppm) and coupling constants (in Hz): 7.385 (H-4), 7.090 (H-3), 7.199 (H-2), 7.635 (H-1), 7.59 (J_{34}), 1.14 (J_{24}), 0.76 (J_{14}), 7.59 (J_{23}), 1.14 (J_{13}) and 8.35 (J_{12}). The second one is too degenerate to be analyzed and only an apparent ^3J coupling can be measured: 4.981 (H7), 3.739 (H6), 6.90 (J_{67}). In other solvents, like $CDCl_3$, the chemical shifts of the CH_2CH_2 are closer (4.64 and 3.70 ppm) and the system becomes AA'BB'.

Table 2. ^1H NMR data (δ in ppm, J in Hz) for compound **4** in different conditions.

Solvent	Temp (°C)	H-1 H-8	H-2 H-9	H-3 H-10	H-4 H-11	C-CH_2	N-CH_2
D_2O/EG[a] (1:2)	85	8.05	8.51	8.03	9.00	4.14	5.31
DMSO-d_6	55	8.07*	8.52	8.05*	9.14	4.07 (t) J = 6.4	5.24 (t)
DMSO-d_6/D_2O	80	7.93	8.38	7.93	8.92	4.00 (t) J= 6.4	5.17 (t)

[a] Ethyleneglycol-d_6.

The average ^1H NMR spectrum of compound **4** [at 85 °C in D_2O-EG (1:2) to have narrow lines] has been assigned through ^1H-^{13}C COSY experiments.

2.- Dynamic aspects. The ^1H-NMR spectra of compound **3** have been recorded at different temperatures and different solvents: between -65 °C and +75 °C and in $CDCl_3$, DMF-d_7, acetone-d_6 and in mixtures of these solvents: the spectra, save changes in the chemical shifts, remains identical; in particular the CH_2CH_2 multiplets are always formed by narrow lines. At temperatures lower than -65 °C compound **3** precipitates.

Compound **4** being a double quaternary salt is much less soluble in common NMR solvents, especially in those used for low temperature studies. At room temperature (25 °C) in DMSO-d_6, the spectrum is very broad pointing to a dynamic process within the range of phenomena that can be studied by DNMR. We have recorded its spectrum in acetone/D_2O (2:1) at -30 °C (Fig. 1a); it has two components, one that is still broad and another that it is well resolved, although in some parts they overlap. To demonstrate that the well-resolved spectrum corresponds to the chair **C** (Scheme 2), we have simulated the spectrum (Fig. 1b) corresponding to the CH_2CH_2 system using as starting vicinal coupling constants those derived from a Karplus relationship and the dihedral angles corresponding to the AM1 minimized structure (see next section). The Karplus equation we used was $^3J_{HH} = 8.25 \cos^2\phi - 0.28$ ($0 < \phi < 90°$) and $^3J_{HH} = 9.25 \cos^2\phi - 0.28$ ($90 < \phi < 180°$).[6] The ABCD system has the following parameters (in Hz at 300 MHz): δ_A = 1592.4, δ_B = 1547.5, δ_C = 1260.7, δ_D = 1180.9, J_{AB} = 15.00, J_{AC} = 8.9, J_{AD} = 0.50, J_{BC} = 0.44, J_{BD} = 4.80 and J_{CD} = 17.70, the vicinal ones being close of those deduced by application of the Karplus relationship to conformation **C**: J_{AC} = 8.96, J_{AD} = 0.52, J_{BC} = 0.28 and J_{BD} = 5.23 Hz. The average vicinal coupling constants J_{AB} and J_{CD} are very different and even a slight modification changes considerably the simulated spectrum. In conclusion, the conformation which is blocked at -30 °C is the chair and that which remains above the coalescence is the family of interconverting **TB**s.

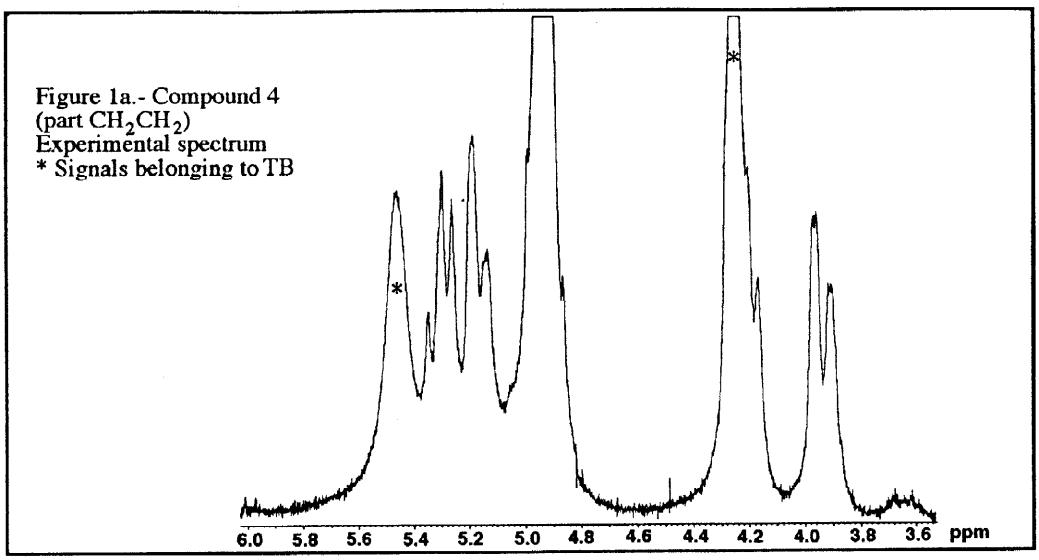


Figure 1a.- Compound 4 (part CH_2CH_2) Experimental spectrum * Signals belonging to TB

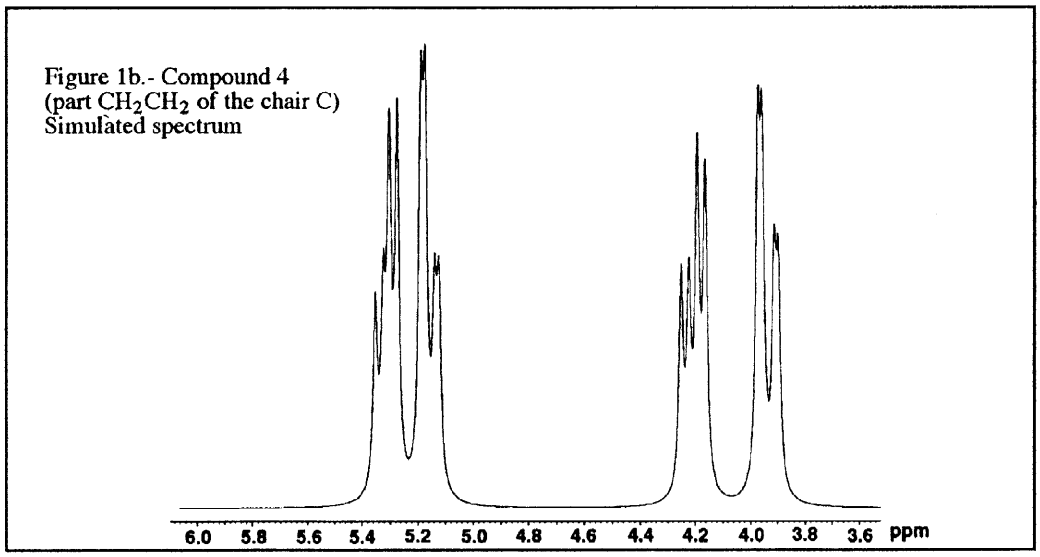
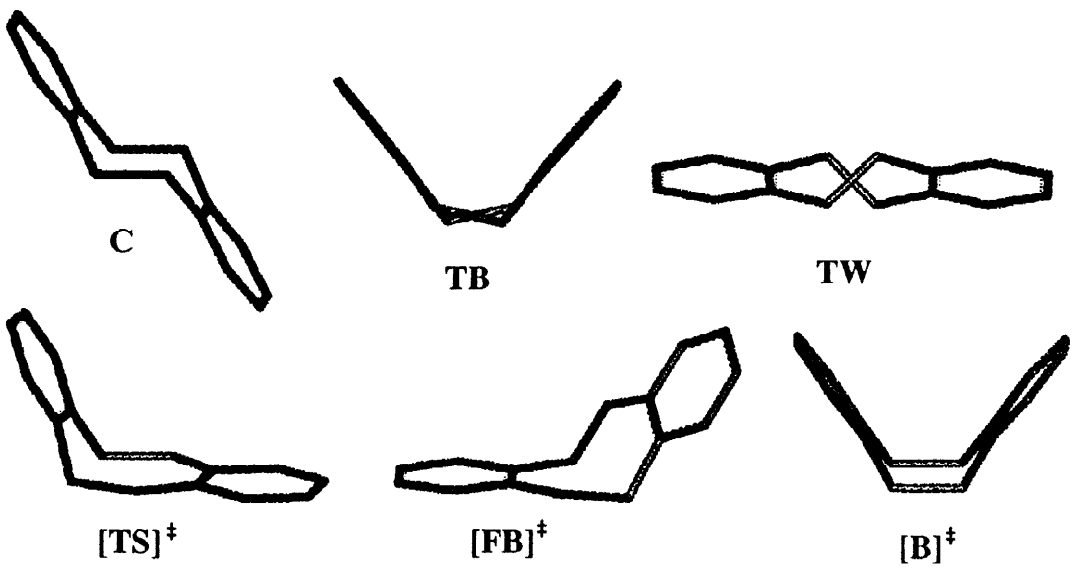


Figure 1b.- Compound 4 (part CH_2CH_2 of the chair C) Simulated spectrum



Scheme 2

The aromatic protons (necessary to assign the aromatic carbons, *vide infra*) appear at -30 °C at: **TB** 7.92 (H-1), 8.33 (H-2), 7.92 (H-3), 9.06 ppm (H-4); **C** 8.14 (H-1), 8.51 (H-2), 8.00 (H-3) and 9.06 ppm (H4). A two dimensional relay ^{1}H-^{1}H spectrum has been used to verify the assignments.

In ^{13}C NMR, acetone/D_2O (2:1) as solvent, the same phenomenon can be observed. At room temperature (+ 30 °C) the seven lines corresponding to an average conformation are present in the spectrum. At -30 °C, two conformers are observed in a 55/45 ratio (Table 3). A ^{1}H-^{13}C bidimensional spectrum connects the ^{13}C lines of the less abundant conformer to the **TB** (^{1}H broad) and the most abundant to the **C** (^{1}H well-resolved), therefore, the ratio is 55% **C**/45% **TB**, which corresponds to a ΔG of less than 0.1 kcal mol^{-1} at 243 K.

Table 3. ^{13}C NMR data (δ in ppm, Δν in Hz) for compound **4** at 303 and 243 K in acetone/D_2O (1:1).

Temp (°C)	C-1 C-8	C-2 C-9	C-3 C-10	C-4 C-11	C-1a C-7a	C-6	C-7
+30	131.85	147.60	128.18	147.24	153.9 br	56.42	33.89
TB	131.36	146.59	127.60	146.76	154.99	54.42	33.38
C	130.56	146.59	126.82	146.20	151.51	56.43	32.44
-30							
Δν (Hz)[a]	60.0	0.0	59.1	42.2	262.8	-152.0	70.5
Δν (Hz)[b]	100.1	0.0	98.4	70.3	438.0	-253.3	117.5
T_c (K)[c]	~280	---	~280	---	---	~295	~285

[a] Splitting of the signals in Hz at 75.42 MHz; [b] Splitting of the signals in Hz at 125.71 MHz; [c] Coalescence temperature in K for the 125.71 MHz spectra.

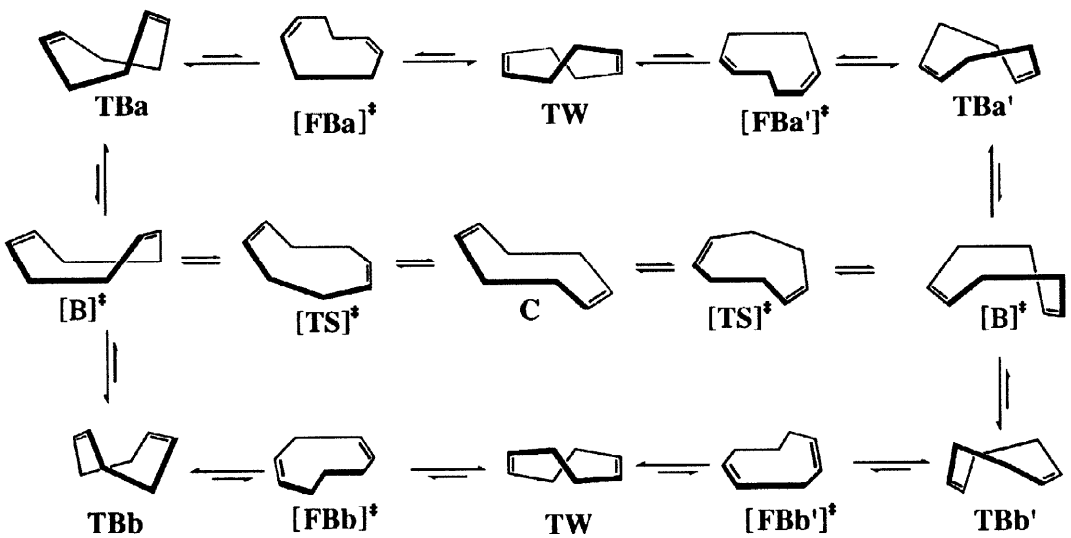
Since the values at +30° C are an average of those at -30 °C plus a certain shift due to the temperature change and assuming that this shift is the same for all signals, it results that δ(+30 °C) ppm = [1.01±0.12 + 0.448 δ(-30 °C) **TB** + 0.552 δ(-30 °C) **C**] ppm, n = 7, r^2 = 1.00000. This allows the assignment to **TB** and **C** of the quaternary carbon C-7a signals and yields a more precise, although essentially identical, value for the equilibrium constant (0.552/0.448 instead of 0.55/0.45).

We have recorded at 125.71 MHz nine ^{13}C NMR spectra between these two temperatures (-30, -5, 0, 5, 10, 15, 18, 27 and 30 °C) and simulated these spectra assuming that the populations of the **C** (p_C = 0.55) and the **TB** (p_{TB} = 0.44) do not change with the temperature. We selected the signals of the two sp^3 carbons, C6 and C7, and obtain a good visual fitting (see Fig. 2 in the Experimental Section) for the following rates: -30, 20 s^{-1}; -5, 114 s^{-1}; 0, 155 s^{-1}; 5, 209 s^{-1}; 10, 279 s^{-1}; 15, 429 s^{-1}; 18, 474 s^{-1}; 27, 848 s^{-1}, and 30 °C, 928 s^{-1}. With these values we have calculated, applying the Wynne-Jones-Eyring equation (9 points, r^2 = 0.997), $\Delta S^{\ddagger}$ = -15.5±0.6 cal deg^{-1} mol^{-1} and $\Delta H^{\ddagger}$ = 8.93±0.17 kcal mol^{-1}. Therefore, at 298 K, the activation barrier corresponding to [**TS**]‡ is $\Delta G^{\ddagger}$ = 13.2±0.2 kcal mol^{-1}, this being the value we have reported in Table 4.

MNDO, AM1 and PM3 semiempirical calculations

The conformation of 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene **1** and related 5(6),8,5(6) systems has been thoroughly examined by several authors and although their analyses are not exactly identical, for the purposes of the present work their main conclusions coincide.[7-10] i) There are three minima in the potential

hypersurface: the chair **C** which is a rigid almost perfect "chair", the twist-boat **TB** which is a mixture of deformed "boat" conformations with a quite flat potential hypersurface and the twist **TW**; ii) there are three transition states connecting these conformations (and their enantiomers), between the twist-boat **TB** and the chair **C**, [**TS**]‡, between twist-boats (**TBa** and its enantiomer **TBa'** through **TW**), [**FB**]‡, and between both twist-boats **TBa** and **TBb** (pseudorotation), [**B**]‡; iii) experimental (NMR) and molecular mechanic calculations coincide that, for compound **1**, the chair is slightly more stable than the twist-boat and that the three transition states range in the order [**TS**]‡ (~ 10 kcal mol^{-1}) > [**FB**]‡ (~ 7 kcal mol^{-1}) > [**B**]‡ (2 kcal mol^{-1}) (the last one being not measurable by NMR is a computed value). We have adopted Allinger's representation (Scheme 3)[10] omitting aromatic rings (benzene **1**, pyrazolium **2**, benzimidazole **3**, pyridinium **4**) for the sake of clarity. We have calculated, for the four systems, the six stationary points **C**, **TB**, **TW**, [**TS**]‡, [**FB**]‡, and [**B**]‡ using different approximations (see Table 5). We have verified, using the option FORCE, that **C**, **TB** and **TW** are ground states.



Scheme 3

The results of Table 4 deserve some comments. i) The relative energies of the stationary states (the chair **C** is used as reference) are loosely related, **TB**, [**TS**]‡ and [**B**]‡ on one hand and **TW** and [**FB**]‡ on the other, which seems logical since they are close in the reaction pathway (see Scheme 3); ii) the results obtained by the three methods are linearly related ($r^2 \approx 0.96$), the MNDO and PM3 being slightly larger (1.08±0.04, n = 24, 1.02±0.05, n = 23, respectively) than the AM1; iii) the experimental values are rather scarce but for the three molecules (no data for **3**) the comparison with the calculations gives the following results: **1** (AM1 $r^2 = 0.96$, MNDO $r^2 = 0.98$, PM3 $r^2 = 0.90$), **2** (AM1 $r^2 = 1.000$, MNDO $r^2 = 0.994$, PM3 $r^2 = 0.95$), **4** (AM1 $r^2 = 0.95$, MNDO $r^2 = 0.94$, PM3 $r^2 = 0.94$) and the three together:

Exp. = 0.92±0.06 AM1, n = 10, $r^2 = 0.96$
Exp. = 0.86±0.06 MNDO, n = 10, $r^2 = 0.96$
Exp. = 0.91±0.09 PM3, n = 10, $r^2 = 0.92$

It can be concluded that the three methods yield acceptable values, the AM1 should be preferred taking into account the correlation coefficient and that the slope is closer to unity.

Table 4. Summary of the conformational analysis of 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene and related compounds (all values in kcal mol^{-1})

	Theoretical Calculations (MNDO)						Theoretical Calculations (AM1)					
Compound	C	TB	TW	[TS]‡	[FB]‡	[B]‡	C	TB	TW	[TS]‡	[FB]‡	[B]‡
1 [6,8,6]-CC	0.0	1.8	4.9	10.3	7.7	2.1	0.0	2.8	2.6	10.9	8.0	4.3
2 [5,8,5]-NN+	0.0	2.9	4.2	13.9	8.1	3.6	0.0	1.8	2.6	12.1	7.6	3.4
3 [5,8,5]-CN	0.0	2.1	4.2	10.7	6.0	2.5	0.0	2.4	2.7	10.2	5.4	4.1
4 [6,8,6]-CN+	0.0	4.3	6.0	16.2	10.9	5.4	0.0	3.6	3.2	14.9	8.5	4.8

	Theoretical Calculations (PM3)						Experimental Results (Solution)[a]					
Compound	C	TB	TW	[TS]‡	[FB]‡	[B]‡	C	TB	TW	[TS]‡	[FB]‡	[B]‡
1 [6,8,6]-CC	0.0	2.8	3.1	13.1	5.6	4.7	0.4±0.2[b]	0.0	---	10.0	7.8	[c]
2 [5,8,5]-NN+	0.0	4.2	5.0	11.3	N.c.[d]	6.0	0.0	1.8[e]	---	12.8[f]	---	---
3 [5,8,5]-CN	0.0	2.1	2.9	12.5	3.5	5.2	---	---	---	---	---	---
4 [6,8,6]-CN+	0.0	3.6	3.5	13.9	6.6	7.0	0.0	0.1	---	13.2	---	---

[a] In the solid state the four compounds crystallize as chairs **C**: **1**,[1] **2**,[11] **3**,[3] and **4**.[1] [b] Depending on the solvent. [c] The **CC** interconversion takes place through **[B]**‡, then the barrier is 10.0 + 0.4 kcal mol^{-1}. [d] No convergence was achieved. [e] Assuming a ratio ≈ 95/5 (**C**/**TB**).[2] [f] Depending on the substituents on the pyrazole ring, between 12.8 (**2a**) and 13.5 (**2b**) kcal mol^{-1}.[1]

CONCLUSIONS

To simplify the discussion we will consider only the AM1 calculations and the experimental results. Concerning the ground states, the calculation overestimates the stability of the chair when compared with the experimental data in solution, a fact that may be related to the dipole moments of the **C** and **TB** conformers (for instance, in the case of compound **3** the AM1 values are **C** μ = 0.00 D, **TB** μ = 2.91 D and **TW** μ = 1.17 D); if the chair is always well defined, the other ground states, **TB** and **TW**, having similar stabilities, their structure has to be determined experimentally. Concerning the transition states, the [**TS**]‡ one divide into two classes, low values (about 10 kcal mol^{-1}) for **1** and **3** (this suggest that the coalescence for compound **3** should be well below -65 °C) and high values (about 13-14 kcal mol^{-1}) for **2** and **4**. Henceforth it is not the ring size [5,8,5 (**2**, **3**) *vs* 6,8,6 (**1**, **4**)] but the charge [neutral compounds (**1**, **3**) *vs* dications (**2**, **4**)] that determines the barrier between chair and boat. For the other barriers ([**FB**]‡ and [**B**]‡), the experimental data are almost inexistent (see Table 4, only [**FB**]‡ for compound **1**) but the calculated ones seem to depend on both the ring size and the charge.

EXPERIMENTAL SECTION

General. Melting points were determined on a hot-stage microscope and are uncorrected. The ^1H and ^{13}C NMR spectra in solution were recorded on Varian and Bruker instruments working at 200, 300, 400 and 500 MHz for ^1H. The ^{13}C CPMAS NMR spectrum of compound **3** (see below) was recorded in the same instrument and using the conditions described in reference 12.

3-(4-Methylpyridinium)propionic acid bromide **5**. Prepared following the experimental procedure of reference 3 in comparable yield and with same melting point (164 °C). ^1H-NMR (CF_3CO_2H) δ 2.60 (s, 3H, CH_3), 3.24 (t, 2H, CH_2-2, J = 6.1 Hz), 4.80 (t, 1H, CH_2-3, J = 6.1 Hz), 7.76 (d, 2H, H-3 and H-5, J = 6.5 Hz), 8.65 (d, 2H, H-2 and H-6, J = 6.5 Hz); (DMSO-d_6) δ 2.59 (s, 3H, CH_3), 3.05 (t, 2H, CH_2-2, J = 6.7 Hz), 4.72 (t, 1H, CH_2-3, J = 6.7 Hz), 7.97 (d, 2H, H-3 and H-5, J = 6.6 Hz), 8.96 (d, 2H, H-2 and H-6, J = 6.6 Hz), 12.7 (bs, 1H, CO_2H).

2-[2-(4-Methylpyridinium)ethyl]benzimidazole bromide **6**. Prepared according to reference 3, with a slight lower yield (19% instead of 22%) and the same melting point (105 °C). ^1H-NMR (DMSO-d_6) δ 2.56 (s, 3H, CH_3), 3.56 (t, 2H, CH_2-2, J = 7.0 Hz), 5.05 (t, 1H, CH_2-3, J = 7.0 Hz), 7.12-7.17 (m, 2H, benzimidazole), 7.46-7.94 (m, 2H, benzimidazole), 7.95 (d, 2H, H-3 and H-5, J = 6.6 Hz), 8.96 (d, 2H, H-2 and H-6, J = 6.6 Hz), 12.4 (br s, 1H, NH).

6,7,14,15-Tetrahydrobisbenzimidazo[1,2-a:1',2'-e][1,5]diazocine **3**. Both procedures described in reference 3 (with pyridine or acetonitrile as solvents) were used. The yields were lower in both cases to those reported (pyridine 38% instead of 42%; acetonitrile 17% instead of 51%). The compound melts at 270-280 °C (lit, mp 297-300 °C). MS (EI) m/z 288 (M, 100), 273 (24), 260 (14), 170 (14), 169 (30), 157 (31), 156 (13), 145 (19), 144 (40), 143 (32), 132 (24), 131 (10), 129 (11). ^{13}C NMR (DMSO-d_6, 160 mg in 0.5 mL) δ 151.3 (C-5a), 137.9 (C-4a), 116.8 (C-4, ^1J=164.2, ^3J=7.9), 122.9 (C-3, ^1J=160.6, ^3J= 6.9), 122.7 (C-2, ^1J=161.7,

^3J= 8.0), 110.2 (C-1, ^1J=164.2, ^3J= 8.2), 133.9 (C-8a), 42.0 (C-6), 29.1 (C-7); ^{13}C NMR CPMAS δ 152.4, 140.6, 133.2, 123.4, 113.5, 40.8 and 25.9.

6,7,13,14-Tetrahydrobispyrido[1,2-a:1',2'-e]diazocinediium dibromide **4**. This compound is described in reference 1 and their FAB mass spectrometry behaviour in reference 13.

1,3-Dimethylpyridinium iodide **7**. Prepared from picoline and methyl iodide in acetone at room temperature following the procedure described in reference 14 (mp 231-232 °C). ^{1}H-NMR ($CDCl_3$, saturated) δ 7.91 (d, H-3, J_{34} = 7.5 Hz), 8.38 (q, H-4, J_{45} = 7.8 Hz), 7.93 (q, H-5, J_{56} = 6.3 Hz), 9.64 (d, H-6), 4.55 (s, 1-CH_3), 2.97 (s, 2-CH_3); (DMSO-d_6, 9.7 mg in 0.5 mL) δ 8.03 (d, H-3, J_{34} = 7.8 Hz), 8.46 (q, H-4, J_{45} = 7.8 Hz), 7.93 (q, H-5, J_{56} = 6.4 Hz), 8.96 (q, H-6, J_{46} = 1.5 Hz), 4.21 (s. 1-CH_3), 2.77 (s, 2-CH_3); (DMSO-d_6, 160 mg in 0.5 mL) δ 8.05 (H-3), 8.44 (H-4), 7.91 (H-5), 9.00 (H-6), 4.24 (1-CH_3), 2.79 (2-CH_3); ^{13}C NMR (DMSO-d_6, 160 mg in 0.5 mL) δ 155.7 (C-2), 129.0 (C-3, ^1J = 174.7, ^3J = 7.9, $^3J_{Me}$ = 4.0 Hz), 144.8 (C-4, ^1J = 171.1, ^3J = 6.7 Hz), 125.1 (C-5, ^1J = 174.4 Hz), 145.7 (C-6, ^1J = 191.5 Hz), 46.0 (1-CH_3, ^1J = 144.5, ^3J = 3.8 Hz), 20.6 (2-CH_3, ^1J = 130.8, ^3J = 3.0 Hz).

Dynamic ^{13}C NMR experiments on compound **4**. The variable temperature was computer controlled and the internal temperature calibrated with the methanol thermometer. Calculations for complete lineshape analysis were carried out using the GNMR vs. 4 program.[15] Theoretical spectra were calculated to obtain a good visual fitting with the observed by varying the rate constants for the corresponding temperatures (see, Fig. 2). The data were analysed using the equation of Wynne-Jones and Eyring.[16]

Theoretical Calculations.- The starting geometry of each compound was build with Insight[17] and optimized with the Molecular Mechanic cff95 force field, implemented within Insight. The resulting 3D structure was then subjected to energy minimization with the Semiempirical Quantum Methods AM1, MNDO and PM3 within the MOPAC v. 6.0 package[18] with PULAY and the option PRECISE.

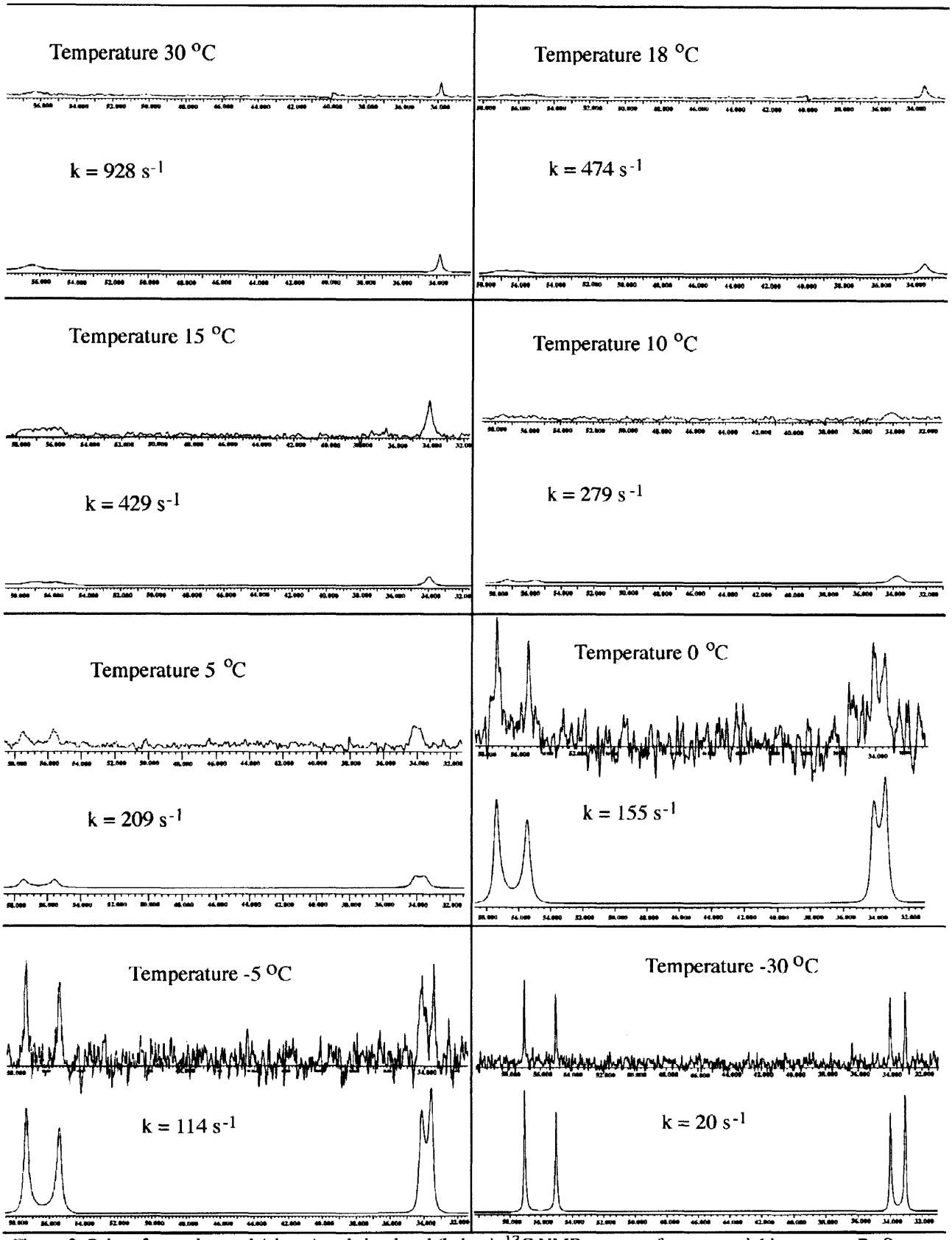


Figure 2. Pairs of experimental (above) and simulated (below) ^{13}C NMR spectra of compound **4** in acetone-D_2O at different temperatures (the spectrum corresponding to +27 °C is not shown).

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