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Side-chain Rotational Processes in Pentaethylated Benzenes

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Abstract: The barriers for conformational exchange processes in pentaethylbenzenes C_6Et_5R (R = H, Br, $COCH_3$, $OCOCH_3$ and OCOPh) were determined by NMR lineshape analysis; for the latter three substances these processes include both the stepwise rotation of the ethyl groups and the 180° reorientation of the side-chain R. The experimental barriers were compared to those calculated by molecular mechanics (MM3). These results have implications in the long-standing argument about the barrier of ethyl group rotation in hexaethylbenzene (R = Et) and some of its metal complexes.

Keywords: Benzenes; Conformation; NMR; Molecular mechanics.

Introduction

In a paper published a few years ago, Iverson *et al.* discussed the structure of hexaethylbenzene (**1**) [1]. Using X-ray crystallography, these authors showed that this compound has the six benzylic carbons in the plane of the aromatic ring, while the methyl groups alternate in an up/down fashion. The high symmetry of the molecule, however, does not allow an experimental observation of the expected rotation of the ethyl groups around the CH_2-Ar bonds. Instead, information was obtained by molecular mechanics calculations. Thus, the authors concluded that the said process occurs in a stepwise rather than a concerted process, and that the energy of activation thereof is 11.8 kcal mol^{-1}. This result was supported by an analysis of the low-temperature NMR lineshapes of the tricarbonylchromium and tricarbonylmolybdenum complexes of **1**. Since the metal atom is located on one side of the arene ring, the symmetry is broken, and barriers for the site-exchange processes in these complexes are found to be 11.5 and

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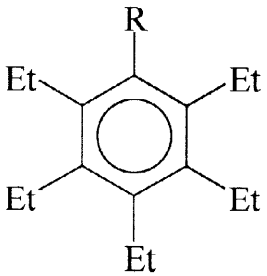
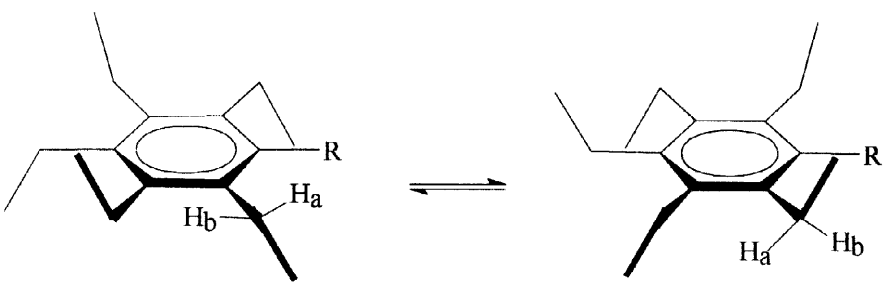
11.6 kcal mol^{-1}, respectively, in excellent agreement with the calculation. The attribution of the dynamic process in the complexes with ethyl group rotation is, however, far from unambiguous, and several papers followed in which these conclusions were vigorously debated [2-5].



1 R = Et
2 R = H
3 R = Br
4 R = $COCH_3$
5 R = $OCOCH_3$
6 R = OCOPh
7 R = C_6Et_5

In order to avoid these complicating issues, we decided to study the rotation of the ethyl groups by preparing pentaethylated benzenes **2-6**. In the absence of rotational processes, the methylene hydrogens on both the ortho and meta ethyl groups of these molecules (*e.g.* H_a and H_b in Scheme 1) are diastereotopic and will give rise to an AB quartet (further split into quartets by the three methyl hydrogens). If ethyl rotation is fast on the NMR timescale, these hydrogens are enantiotopic and they will appear as a simple quartet. Inbetween, the lineshape will provide the rate constant for topomerisation.



Scheme 1

Results and Discussion

NMR studies

The NMR data for compounds **2-6** is presented in Table 1. For the simpler **2** and **3**, the methylene hydrogens of the *ortho-* and *meta-* ethyl groups were found to be diastereotopic in the low temperature regime but equivalent at room temperature, and line fitting was performed using

a programme derived from the lineshape equations developed by Alexander [6] for the AB→A_2 dynamic process (as an example, Fig. 1 shows the experimental and calculated spectra of pentaethylbromobenzene (**3**) as a function of temperature). The rate constants and free energies of activation for the these and other NMR-derived conformational processes (*vide infra*) are shown in Table 2.

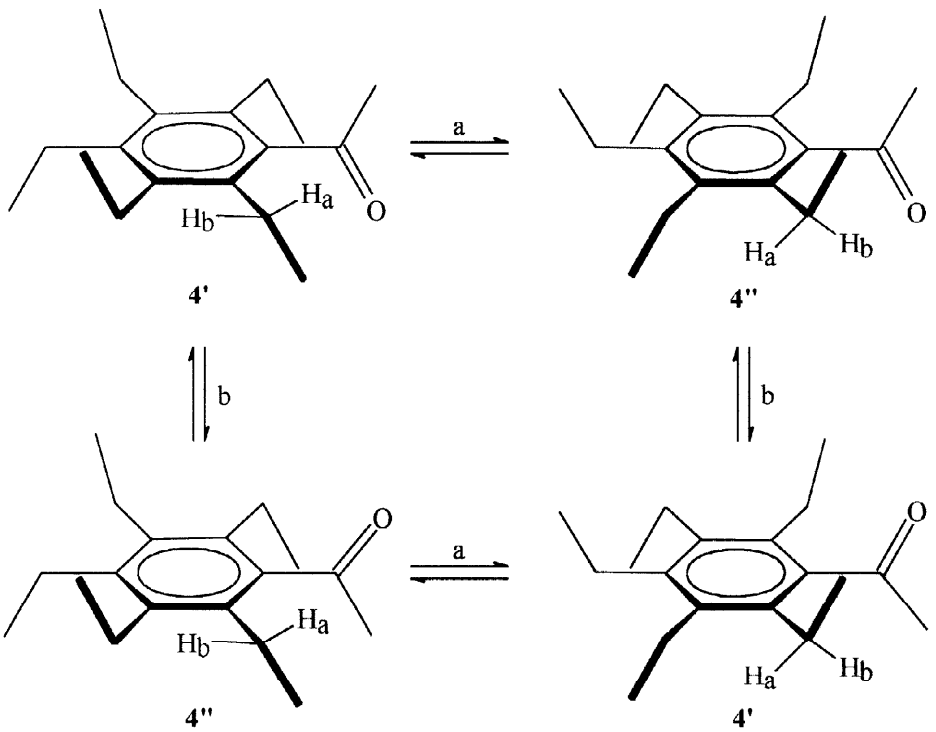
Ketone **4** and esters **5** and **6** give ^{1}H NMR spectra which are qualitatively similar, but the processes that lead to isochronicity of the methylene protons have a much higher free energy of

Table 1
NMR Data for **1** - **6**[a]

	1	**2**[b]	**3**	**4**[c]	**5**[d]	**6**[e]
			^{13}C[f]			
ipso-C	137.82	126.55	126.73	141.60	146.46	146.57
ortho-C	137.82	139.45	139.37	133.81	131.62	131.84
meta-C	137.82	137.55	139.37	138.63	138.93	138.98
para-C	137.82	139.76	137.83	140.91	138.04	138.08
o-CH_2	22.19	25.74	27.11	23.63	20.73	20.77
m-CH_2	22.19	21.77	23.13	21.58	22.18	22.20
p-CH_2	22.19	22.09	22.19	22.06	22.22	22.24
o-CH_3	15.76	15.64	14.17	16.34	14.61	14.92
m-CH_3	15.76	15.64	15.72	15.81	15.78	15.82
p-CH_3	15.76	15.97	15.72	15.81	15.83	15.89
			^{1}H[g]			
o-CH_2	2.63	2.59	2.85	2.46	2.42	2.46
m-CH_2	2.63	2.63	2.65	2.65	2.64	2.60
p-CH_2	2.63	2.66	2.63	2.67	2.64	2.61
o-CH_3	1.19	1.20	1.16	1.15	1.13	1.13
m-CH_3	1.19	1.13	1.15	1.19	1.16	1.06
p-CH_3	1.19	1.15	1.15	1.19	1.17	1.08

a. At 297±2K. b. Ring ^{1}H: 6.84 ppm. c. Side-chain ^{13}C: 209.46(CO), 33.39(CH_3); ^{1}H: 2.53 ppm. *Ortho*-methylene protons give rise to a very broad, featurless signal at RT. d. Side-chain ^{13}C: 169.92(CO), 20.83(CH_3); ^{1}H: 2.33 ppm. *Ortho*-methylene protons give rise to two broad signals at RT, centred at 2.42 ppm. e. Side-chain ^{13}C: 165.38(CO), 129.23(*i*), 130.0(*o*), 128.59(*m*), 133.33(*p*); ^{1}H: 8.25(*o*), 7.51(*m*), 7.63(*p*). *Ortho*-methylene protons appear at RT as an ABq of q, with J_{gem} = 14 Hz, $\Delta\delta$ = 0.14 ppm, centred at 2.46 ppm. f. In $CDCl_3$. g. **2** and **3** in CD_2Cl_2, others in $CDCl_3$; $^3J_{HH}$ = 7.5 Hz for all ethyl groups.

activation; for **6**, for example, the methylene protons are diastereotopic with almost no kinetic-induced broadening even at room temperature! As we will confirm by molecular mechanics calculations (*vide infra*), it is unlikely that ethyl group rotation is responsible for these higher-energy processes. Closer inspection of these molecules reveals that for each, the ethyl side-chains force the plane of the carbonyl into an orientation virtually perpendicular to the aromatic ring, as illustrated in Scheme 2 for **4**. It is then no longer sufficient to rotate the ethyl groups to obtain full topomerisation ("a" in Scheme 2); it is ***also*** necessary to flip the CH_3CO (**4**) or R'COO (**5**, **6**) moieties by 180° ("b"). Probably, "b" is the rate-determining step, corresponding to a higher energy of activation.



Scheme 2

This being the case, these molecules may adopt two energetically distinct conformations (*e.g.* **4'** and **4"** in Scheme 2), with different relative orientations of R and the ethyl side-chains. Since these conformers can interconvert by rotation of ***either*** the ethyl groups **or** the carbonyl moieties, we may expect to detect, at low temperature, two sets of NMR lines, not necessarily of the same intensity, which coalesce at the rate of the lower-barrier ethyl rotation ("b" in Scheme 2). Indeed, the low-temperature ^{13}C NMR spectra of **5** and **6** (the ^{1}H NMR spectra were too complex), showed splitting of all the carbon signals. Lineshape analyses [7] yielded $\Delta G^{\dagger}$ values which are similar to those observed for **2** and **3** (*ca.* 9 kcal mol^{-1}, see Table 2). Unfortunately, no line

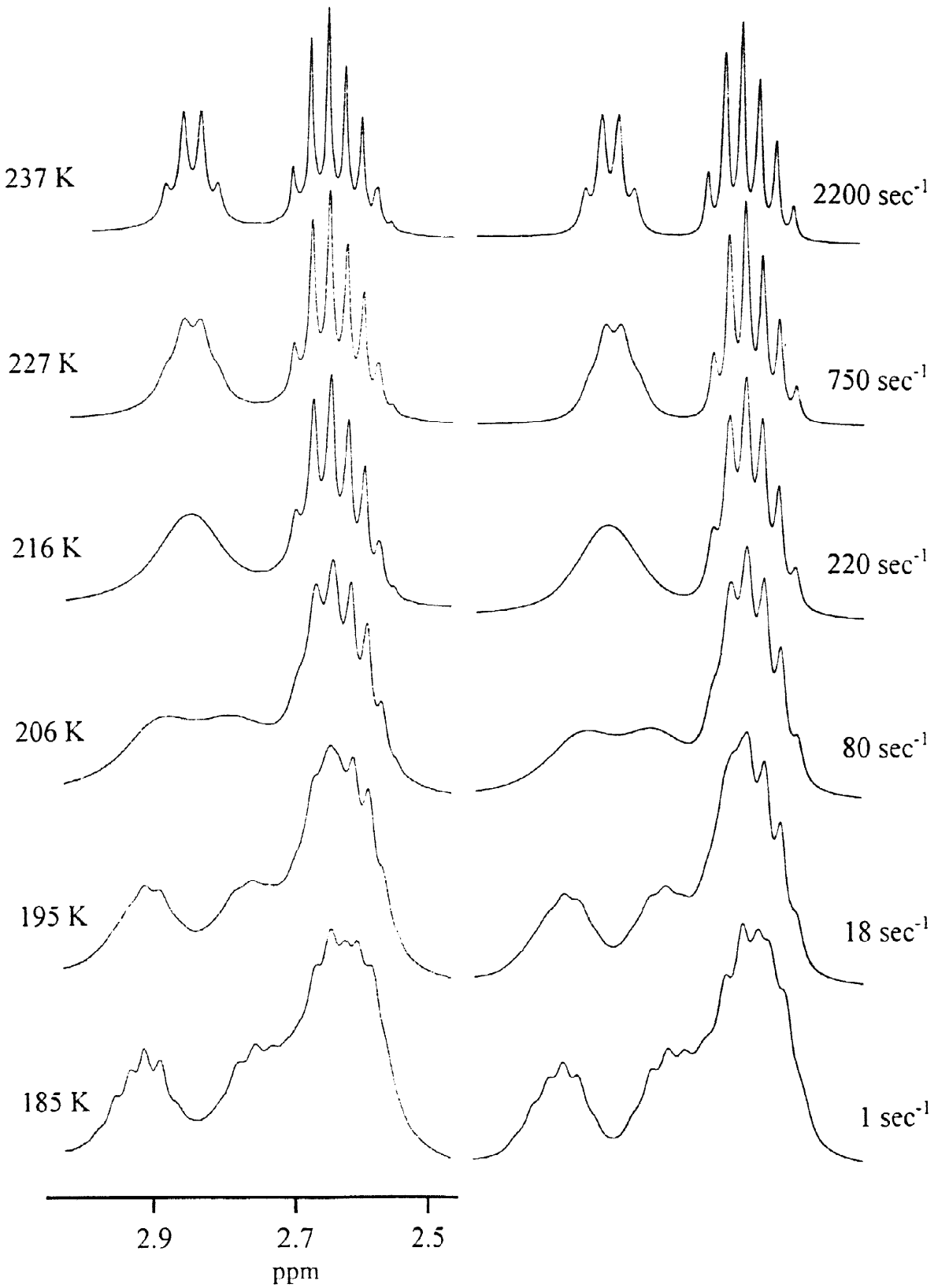


Fig. 1. Experimental (left) and calculated (right) ^{1}H NMR spectra for the CH_2 protons of pentaethylbromobenzene (**3**), as a function of temperature. The rate constants indicated gave the best fit to the experimental traces.

splitting was observed for **4**; probably, conformer **4''** is not significantly populated at *ca.* 190 K (*vide infra*), and the ethyl rotation rate could not be determined for this derivative.

We also prepared perethylated biphenyl **7**, but this compound is more complex because of interactions among the alkyl substituents in the two rings. The analysis of its static and dynamic stereochemistry has been published elsewhere [9].

Table 2
Dynamic NMR-derived rates of conformational processes for **2 - 6** (see text)

T/K[a]	k/sec^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
	2[b, e]	
167.0	1.0	9.6±0.5
177.0	8.0	9.4±0.2
187.0	75	9.2±0.1
196.5	230	9.2±0.1
206.0	700	9.2±0.1
215.8	2000	9.2±0.1
	3[b, e]	
185.0	1.0	10.6±0.4
195.2	18	10.2±0.1
205.5	80	10.1±0.1
216.2	220	10.2±0.1
227.0	750	10.2±0.1
237.0	2200	10.1±0.1
	4[c, e]	
234.8	1.0	13.6±0.5
248.6	3.0	13.9±0.2
263.0	25	13.7±0.1
283.2	175	13.6±0.1
290.8	260	13.8±0.2
296.1	450	13.7±0.2
306.0	750	13.9±0.2
316.0	1500	13.9±0.2
324.8	2500	14.0±0.2
330.1	3280	14.1±0.2

Molecular mechanics calculations

Ethyl group rotation

In order to gain a more quantitative understanding of the conformational processes described in the previous section, we decided to use molecular mechanics calculations to estimate their activation barriers. The calculations were performed using the MM3 force field (1994 version) [10], in which the dihedral angle driver option was extensively employed to determine the

Table 2 (cont.)

T/K[a]	k/sec^{-1}	$\Delta G^{\dagger}$/kcal mol^{-1}	K
	5 (high temperature process)[c, e]		
256.4	2.1	14.6±0.2	
270.5	8.5	14.6±0.1	
284.0	35	14.6±0.1	
298.2	120	14.6±0.1	
312.2	360	14.7±0.1	
324.9	950	14.7±0.1	
	5 (low temperature process)[b, f]		
182.9	15	9.5±0.1	2.7
192.9	140	9.3±0.1	2.0
202.9	300	9.4±0.1	1.5[g]
	6 (high temperature process)[d, e]		
294.9	1.5	17.0±0.3	
318.0	27	16.6±0.2	
341.6	150	16.7±0.1	
360.0	550	16.7±0.1	
381.0	2000	16.7±0.2	
400.4	8000	16.5±0.3	
	6 (low temperature process)[b, f]		
182.9	50	9.1±0.1	2.7
187.9	70	9.2±0.1	2.4
192.9	160	9.3±0.1	2.2[g]

a. Temperatures believed to be accurate to ±0.5K. b. In CD_2Cl_2. c. In $CDCl_3$. d. In C_6D_5Br. e. Coalescence of AB quartets in the ^1H spectrum (see text). f. Coalescence of ^{13}C NMR lines of unequal intensity (see text). g. Extrapolated through the calculation of values for the two lowest temperatures.

energies of transition states. Unfortunately, we could only consider derivatives **2-4**, since our version of the programme is not parametrised for aryl esters.

A full computation of the ethyl rotation process would require, as a start, the calculation of the 10 energetically distinct conformers of a pentaethylbenzene derivative. The possible pathways which would lead to the full topomerisation shown in Scheme 1 have to involve five individual rotation steps, in which each of the ethyl substituents flips by 180°; a clockwise or a counterclockwise flip give the same result but are not necessarily isoenergetic. Since dozens of different pathways would have to be considered for each molecule, we decided to focus on the most likely low-energy route: the consecutive rotation of neighbouring ethyl groups, starting from the 2-Et, followed by the 3-Et, etc. This pathway leads to intermediates which have only **one** *syn* interaction between adjacent ethyl groups per molecule (some alternative pathways we examined confirmed that conformers with more *syn* interactions lead to higher-energy transition states). The results are shown in Table 3.

Table 3
Calculated and experimental ethyl rotation barriers in kcal mol^{-1}

		Calculated energy barriers							Experimental
		2-Et		3-Et		4-Et		overall	
	R	tow. 1	tow. 3	tow. 2	tow. 4	tow. 3	tow. 5		
2	H	2.74	8.39	9.05	9.99	10.21	10.21	10.21	9.2±0.1
3	Br	9.35	9.88	10.46	10.94	10.86	10.86	10.86	10.2±0.1
4	$COCH_3$	7.22	9.11	10.40	10.61	10.77	10.94	10.77	
5	$OCOCH_3$								9.4±0.1
6	OCOPh								9.2±0.1

Let us consider initially **2** and **3**, for which rotation of the R substituent is irrelevant. For the first two steps, the molecule will follow the lowest-energy of the clockwise and anticlockwise rotations; the two directions are isoenergetic for the 4-Et. The rate-determining step will then be the one with the highest of the three individual barriers. There is no need to calculate the last two steps, since they are equivalent to the first two by symmetry. For ketone **4** (and esters **5** and **6**) the degeneracy of the two directions for the 4-Et is lost, as is the one between the 2- and 6-, or 3- and 5-Et rotations. We do not show in Table 3 the barriers for the 5- and 6-Et rotations for **4**.

The results in Table 3 indicate that in every case examined, the rotation of the 4-Et is the rate-determining step, and that, excluding the rotation of the 2-Et towards the R substituent, the energy barriers involved are quite similar, as might be expected if one ignores minor buttressing effects. It is also clear that the calculations overestimate the ethyl rotation barrier by 0.7-1.0 kcal mol^{-1}. This may be due to inaccuracies in the parametrisation of transition states, but could also result from a small positive entropy of activation.

Side-chain rotation

We can also simulate the rotation of the acetyl group in **4**, starting from conformation **4'** (Scheme 2). The calculated barrier (15.5 kcal mol^{-1}) is again higher than the experimentally determined value (*ca.* 13.8 kcal mol^{-1}, see Table 3). In the transition state, the energy gained in reaching conjugation between the ketone carbonyl and the aromatic ring is clearly more than offset by the two close contacts between the acetyl methyl and oxygen moieties and the adjacent C-Et positions. The MM3 force field predicts **4''** to be 0.53 kcal/mol less stable than **4'**; since we do not see peaks due to the former in the low-temperature ^{13}C NMR spectrum of **4**, we estimate the experimental energy difference to be at least 0.8 kcal mol^{-1}. We know that **4''** is not the dominant conformer, since in a NOESY experiment, performed at 275 K, we do not see a strong interaction between the methyl groups of the acetyl and the *ortho*-Et moieties. It may be worth adding that that in the X-ray determined structure of **4.Cr(CO)$_3$**, as reported by Downtown *et al.* [4], the organic ligand takes conformation **4'**.

While we cannot calculate the barriers for the rotation of the R group in esters **5** and **6** (*vide supra*), we know experimentally that they are even higher than for ketone **4**. Inspection of the structures obtained by rotation of the substituent around the C(1)-O bond suggests that in the transition state the ester function is forced out of planarity in order to avoid steric clashes. The resulting loss of resonance stabilization may account for the high $\Delta G^{\dagger}$ values for these derivatives.

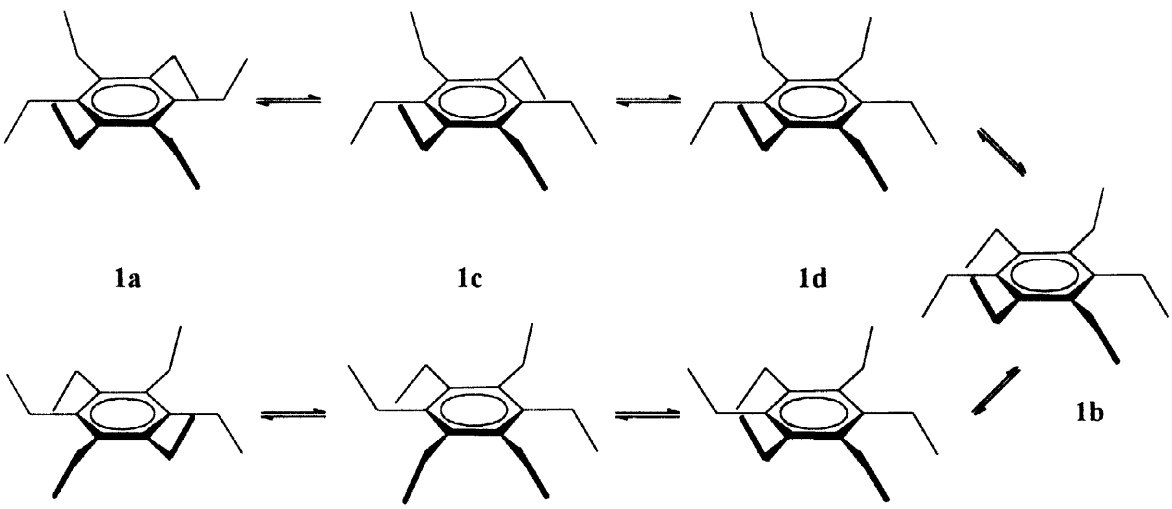
Hexaethylbenzene

Finally, we calculated the barriers for the rotation processes of the ethyl groups in hexaethylbenzene (**1**), as had been done by Iverson *et al.* [1], but using the MM3 force field. We confirmed the overall pathway these authors derived, **1a**→**1c**→**1d**→**1b** and back to **1a** (Scheme 3; the nomenclature for these conformers is the same as in the original paper), but the barriers we obtain (9.99, 12.01 and 12.49 kcal mol^{-1}, respectively), indicate that the third of these steps (and not the first) is rate-determining, similarly to the other compounds examined in the present work. It is interesting to note that this pathway also involves the consecutive rotation of neighbouring ethyl groups (*vide supra*).

The possibility that the ethyl group rotation is a correlated, rather than a stepwise process, was ruled out by considering the following two results:

• The calculated barrier (using a double dihedral angle driver) for the simultaneous rotation of two adjacent ethyl groups, starting from conformer **1a**, is 18.5 kcal mol^{-1}. The energy investment is thus approximately double that of the rotation of one ethyl group, and no synergism is observed.

• The energy of a structure in which all six CH_3-CH_2-C-C dihedral angles were kept fixed at 0° is 57.1 kcal mol^{-1} above that of the ground state. While this is only a rough approximation of the transition state for the fully correlated process, it is clear that the latter is highly unfavourable.



Scheme 3

In summary, our calculations support the original conclusion [1] that the overall barrier for ethyl group rotation in hexaethylbenzene is very close in energy to that of the process measured in the NMR study of its metal complexes.

Experimental

NMR spectra were run on Bruker AM-300 and DMX-600 spectrometers, at 300.1 and 600.1 (^1H) and 75.5 and 150.9 MHz (^{13}C), respectively. Chemical shifts are reported in ppm downfield from internal TMS and coupling constants in Hz. Probe temperatures were measured with a calibrated Eurotherm 840/T digital thermometer and are believed to be accurate to 0.5 K. Unless

otherwise indicated, $CDCl_3$ was used as a solvent. Mass spectra were obtained with a Varian MAT 731 high resolution instrument in the EI mode.

Pentaethylbenzene 2 was prepared by the method of Ogimachi *et al.* [11]; vacuum distillation afforded a mixture containing *ca.* 80% pentaethylbenzene (main impurity: tetraethylbenzenes), which was purified to an analytical sample by preparative GLC (SE30, 200 °C).

Pentaethylbromobenzene 3 - 760 mg of the mixture (containing *ca.* 2.8 mmol of pentaethylbenzene, see previous paragraph), 15 ml water and 0.2 ml Br_2 (3.9 mmol) were dissolved in 100 ml acetic acid. The reaction mixture was stirred overnight at RT, then diluted with 500 ml CH_2Cl_2, and washed once with a solution of 66 g NaOH in 500 ml water and several times with 200 ml portions of sat. $NaHCO_3$ until the aqueous layer was no longer acidic. Drying (Na_2SO_4) and removal of the solvent gave 928 mg of a crude product which was submitted to column chromatography (50 g neutral alumina, elution with hexane) to give 610 mg (73% yield based on pentaethylbenzene) of white crystalline **3**. mp 43-44 °C. HRMS: m/z (%) 298.1119 (M^+, 298.1119 for $C_{16}H_{25}{}^{81}Br$, 100); 296.1148 (M^+, 296.1140 for $C_{16}H_{25}{}^{79}Br$, 94); 283.0885 (283.0884 for $C_{15}H_{22}{}^{81}Br$, 70); 281.0901 (281.0905 for $C_{15}H_{22}{}^{79}Br$, 71); 217.1955 (217.1956 for $C_{16}H_{25}$, 14).

Pentaethylacetophenone 4 was prepared by the method of Downtown *et al.* [4].

Pentaethylphenol was prepared by the method of Koptyug and Krysin [12], but we were unable to obtain it in pure form. The crude material was used to prepare the two following esters.

Pentaethylphenyl acetate 5 - 1.0 g of crude pentaethylphenol was dissolved in a mixture of 1.3 ml dry pyridine and 1.3 ml acetic anhydride, and left for 3 days at RT, under N_2. The reaction mixture was then diluted with 10 ml CH_2Cl_2, washed with 20 ml dil. HCl and 20 ml sat. $NaHCO_3$, and the residue was purified by column chromatography (alumina, elution with CH_2Cl_2) to give 245 mg of **5** (yield: 21%) as a colourless oil. An analytical sample was obtained by preparative TLC (silica plate, elution with benzene) as a white crystalline material, mp 41-43 °C. HRMS: m/z (%) 276.2072 (M^+, 276.2089 for $C_{18}H_{28}O_2$, 14), 235.2020 (235.2061 for $C_{16}H_{27}O$, 16), 234.1985 (234.1983 for $C_{16}H_{26}O$, 100), 233.1914 (233.1904 for $C_{16}H_{25}O$, 8), 219.1713 (219.1748 for $C_{15}H_{23}O$, 74).

Pentaethylphenyl benzoate 6 - The same procedure was followed as for acetate **5**, with 1.0 g pentaethylphenol and 1.5 ml benzoyl chloride. The crude product was purified by column chromatography (alumina, elution with hexane/CH_2Cl_2 1:1) to give 230 mg of a white solid (yield: 15%). An analytical sample was obtained by recrystallisation from hexane, mp 146-147 °C. El. analysis: Found: C, 81.35; H, 9.17. Calc. for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93%. HRMS: m/z (%) 338.2295 (M^+, 338.2246 for $C_{23}H_{30}O_2$, 50), 234.1936 (234.1982 for $C_{16}H_{26}O$, 16), 233.1896 (233.1904 for $C_{16}H_{25}O$, 81), 217.1931 (217.1956 for $C_{16}H_{25}$, 20), 216.1880 (216.1878 for $C_{16}H_{24}$, 79), 77.0370 (77.0391 for C_6H_5, 100).

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