DETERMINATION OF THE VERY HIGH BARRIERS TO CONFORMATIONAL PROCESSES BY THE NEAT RACEMIZATION TECHNIQUE. PART 1: BARRIERS TO RING INVERSION IN DIBENZO [a,c] DINAPHTHO [2,3-e; 2,3-g] CYCLOOCTATETRAENE AND HINDERED ROTATION IN 2,2′ - DIMETHYL BINAPHTHYL

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(Received: Oct. 9th 1995 , Accepted: Jan. 14th 1996)

ABSTRACT: *A method is described by which it is possible to determine the high barriers to ring inversion and hindered rotation by neat racemization of optically active compounds when the racemization is caused by ring inversion or hindered rotation. The method is based on preparation of sufficiently pure enantiomers, mainly by chromatography on swollen microcrystalline triacetylcellulose (TAC). By this technique the barrier to ring inversion in dibenzo [a,c] dinaphtho [2,3-e; 2,3-g] cyclooctatetraene, a tetrabenzocyclooctatetraene analogue, was determined to be 67.2±0.8 kcal/mol, a record as the highest conformational barrier ever reported. The barrier to hindered rotation in 2,2'- dimethyl binaphthyl was determined by this method to be 49.5±0.5 kcal/mol.*

KEY WORDS: *Racemization, High Barrier, Ring Inversion, Hindered Rotation, Chiral Chromatography, Eight Membered Rings.*

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1021/9981/96/1/18 5 / $ / 2.50

INTRODUCTION

The determination of barrier to conformational processes have been the subject of extensive work for decades. A number of methods have been developed by which the barriers could be determined accurately. However determination of the very high barriers have been a problem so far. In search for determination of barrier to ring inversion in tetrabenzocyclooctatetraene we developed the neat racemization technique and have used it to determine the barrier to hindered rotation in 2,2'- dimethyl binaphthyl. The method and results are discussed here.

EXPERIMENTAL

Materials

Synthesis of dibenzo [a,c] dinaphto [2,3-e; 2,3- g] cyclooctatetraene is already described [1]. 2,2'- Dimethyl binaphthyl were used as received [2] without furthur purification.

Spectra

CD spectra were recorded on a JASCO Model J-500A spectropolarimeter, and UV spectra with a *Cary* Model 2290 spectrophotometer. NMR spectra were recorded on *Varian* XL-300 spectrometer using the solvent line as reference.

Chromatographic and racemization procedure

The chromatographic separations using ethanol as the mobile phase (1 mL/min) were performed with two connected TAC columns by the equipment described earlier [3,4]. Both a UV (225 nm) and a polarimeter (365 nm) were used as detector.

1 mg of dibenzodinaphto compound *(2)* was dissolved in 1 mL ethanol and injected on two succesive triacetylcellulose columns. This was repeated several times; in each run six different fractions were collected. The first or the last fractions of each run were combined together. The solvent was evaporated and the partially resolved material was reinjected on the columns. This was repeated six times until a very pure fraction of enantiomers were obtained. The solvent was evaporated and the residue dissolved in minimum amount of methylene chloride and divided into small ampules, each one about 0.2 mL, and allowed the solvent to evaporate gradually. The ampules were sealed under high vaccum and placed in an accurate oven at an elevated temperature. The (+) enantiomer was chosen for the racemization experiments since very small amount of (-) enantiomer can be observed with greater certainty due to shape of chromatogram. Temperatures between 300-600°C were checked before final runs. The ampules were cooled immediately after heating times and opened carefully. Noncarbonized material was extracted by chloroform which then was evaporated. The residue was dissolved in ethanol and injected on the TAC columns. The UV and polarimeter traces showed 2-3% of (-)-2 at 550° (17 min), and 7-10% of (-)-2 at 600°C (5 min), (Fig. 1).

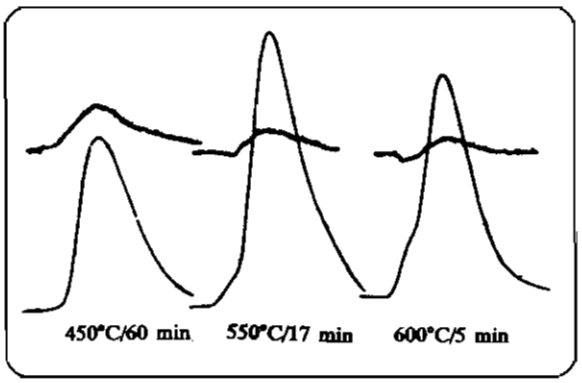


Fig. 1: The polarimetric trace (——) at 365nm and UV trace(—) at 225nm for three different racemization experiments.

Separation of 2,2'- dimethyl binaphtyl was almost the same as dibenzodinaphto compound unless the number of runs were less. The temperature used for racemization were between 300 to 450°C.

Calculations

The molecular mechanics calculations were

performed with the MMP2-87 force field [5] using the MOLBUILD program [6] for construction of the input structure.

RESULTS AND DISCUSSION

It has long been known that cyclooctatetraene undergoes two distinct dynamic processes, ring inversion and bond shifts. The transition state for both processes is assumed to be planar, giving rise to an antiaromatic effect which disfavors the transition state [7]. Annelation of one or two non-adjacent benzene rings to cyclooctatetraene makes the bond shift impossible but not the ring inversion; also the antiaromaticity of the transition state is diminished, resulting in a lower barrier to ring inversion [8]. However introduction of adjacent benzene rings increases the inversion barrier through interaction between the ortho hydrogen atoms in the transition state. In spite of this fact, there was a report of a barrier of 5.71 kcal/mol for ring inversion in the tetrabenzocyclooctatetraene [9] but subsequent works established lower limits of 26-45 kcal/mol [10,11] for the ring inversion in monosubstituted tetrabenzocyclooctatetraenes. As a suitable chiral analogue to tetrabenzocyclooctatetraene *(1)* which can stand the high temperatures, the dibenzo [a,c] dinaphtho [2,3-e; 2,3-g] cyclooctatetraene *(2)* was chosen (Fig.2). The pure enantiomers of *(2)* was heated at elevated temperature to determine the barrier to racemization which occurs by ring inversion. The compound (+)- *2* gave only partial decomposition and racemization at 550° and 600°C when kept for 17 and 5 minutes respectively and complete decomposition at 650°C after 5 minutes.

The expressions used and the calculated values are given in the following equations. Here *p* is the fraction in percent of the other enantiomer observed after racemization, k and h are the *Boltzman* and *Planck* constants respectively.

$k_{inv} = (t)^{-1}\ln[100/(100-p)]$

$\Delta G^{\#}_{inv} = -RT(\ln k_{inv} - \ln \varkappa T/h)$

$\Delta G^{\#}_{inv}$ = 66.9–67.5 kcal/mol (at 550°C)

$\Delta G^{\#}_{inv}$ = 66.8–67.4 kcal/mol (at 600°C)

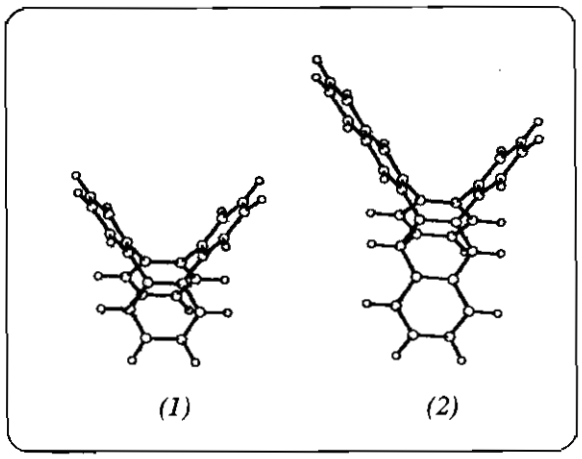


Fig. 2: The structure of tetrabenzo cyclooctatetraene (1) and dibenzo [a,c] dinaphto [2,3-e; 2,3-g] cyclooctatetraene (2), calculated by MMP2-87.

The average value of 67.2 kcal/mol and taking into account 0.8 kcal/mol due to uncertainty in temperature and heating time, will give the free energy barrier to inversion, 67.2±0.8 kcal/mol. The inversion barrier in *(1)* must have a rather similar value.

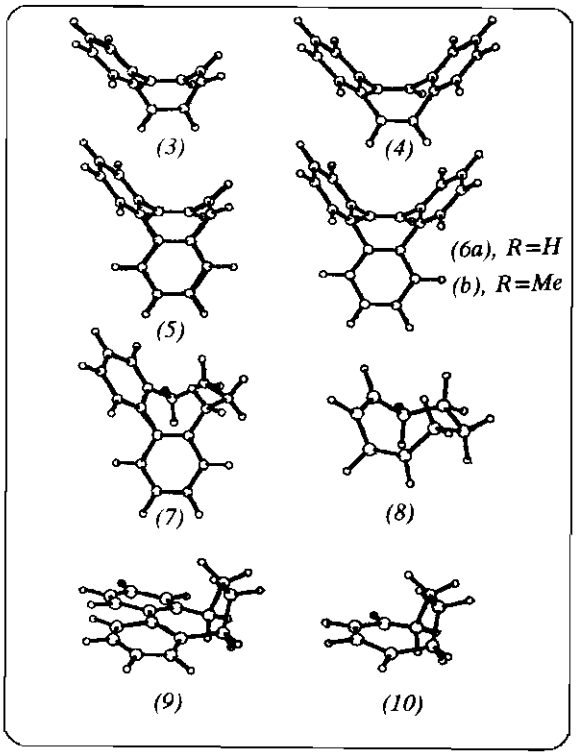
This barrier corresponds to a true ring inversion process and cannot be related to a ring opening-ring closure mechanism involving free radicals. In this latter case other products from hydrogen abstraction, dimerization and trimerization had to be formed. However, a 300 MHz ^{1}H NMR spectrum of a sample kept for 5 min at 580°C showed no trace of impurities but only strong resonances of *(2)*.

Another piece of support for the assignment of this barrier to ring inversion comes from the comparison of cyclooctatetraene, mono, [a,e]-di, [a,c]-di and [a,c,e]-tri-benzo- cyclooctatetraene *(3, 4, 5, 6a)* barriers to ring inversion. All of them adopt a boat conformation as determined experimentally [12] or by molecular mechanics calculations (Scheme 1 and Table 1).

Cyclooctatetraene has a barrier to ring inversion of 14.8 kcal/mol [7] and its monobenzo derivative one of 13.4 kcal/mol [8]. The barrier to ring inversion in [a,e] and [a,c]-dibenzo-

cyclooctatetraene are found to be 12.37 [13] and 30.0 kcal/mol [14], respectively. The chiral derivative of [a,c,e]-tri-benzo-cyclooctatetraene, namely 6-methyl-[a,c,e]- tribenzo-cyclooctatetraen *(6b)* has a barrier of 41.7 kcal/mol to ring inversion [15]. The transition state for ring inversion in cyclooctatetraene is assumed to be planar with D_{8h} symmetry, and the differences between corresponding values for cyclooctatetraene, benzocyclooctatetraene *(3)* and [a,e]-dibenzo-cyclooctatetraene *(4)* are related to the decrease of antiaromatic character of transition state due to annelation of benzene rings and also the small difference in bond length between a double bond and an aromatic double bond. It seems that annelation of a benzene ring onto cyclooctatetraene or its benzo derivative causes about 1.2 kcal/mol diminishment of the barrier to ring inversion. As a rough estimate, annelation of four benzene rings to cyclooctatetraene should decrease the antiaromatic destablization of the transition state by about 4.8 kcal/mol, leaving 10 kcal/mol for a hypothetical transition state without any antiaromatic character, neglecting the interaction between ortho hydrogens.

The differences between the barriers to ring inversion in [a,e] and [a,c]- dibenzo- cyclooctatetraene should mainly be due to different contributions from repulsion between the ortho hydrogens. In *(5)* there is one ortho hydrogen interaction, therefore a value of about 17.7 kcal/mol for one ortho-ortho hydrogen repulsion in a planar transition state could be estimated. In *(6a)* there are two ortho-ortho hydrogen repulsions in the transition state. Correcting the experimental value of the ring inversion for the decrease in antiaromaticity of the transition state by 3×1.2 kcal/mol, will give a value of 15.25 kcal/mol for each ortho-ortho hydrogen repulsion contribution to the transition state.



Scheme 1: The structure of some benzo derivatives of cyclooctatetraene, dibenzo [a,c] cyclooctadiene (7), cycloocta 1,3- diene (8) and the transition state structures for ring inversion in (7) and (8).

Table 1: The steric energy of cyclooctatetraene and its aromatic analogues, calculated by MMP2-87.

Compound	Steric energy (kcal/mol)
Cyclooctatetraene	10.006
Monobenzo *(3)*	6.002
Dibenzo [a,e]*(4)*	0.877
Dibenzo [a,c]*(5)*	0.9135
Tribenzo *(6)*	-4.96
Tetrabenzo *(1)*	-11.489
Dibenzo dinaphto *(2)*	-25.969

A comparison of the barrier to ring inversion for 1,2,3,4-dibenzo-1,3-cyclooctadiene *(7)*, 23.2 kcal/mol [14] with that of 1,3-cyclooctadiene *(8)* value, 8.6 kcal/mol [16] (a calculated value for the *Cs* transition state *(10)* which is likely to be similar to the transition state *(9)* for inversion of *(7)*) gives 14.6 kcal/mol for the ortho hydrogen interactions. Comparison of these values give an average value of 15.8 kcal/mol for ortho-ortho hydrogen repulsion in the transition state. In tetrabenzocyclooctatetraene, there are four ortho-ortho hydrogen repulsion interactions, which contribute ca. 63 kcal/mol to the

transition state. Addition of the 10 kcal/mol for the hypothetical transition state of the cyclooctatetraene ring will give a value of 73 kcal/mol for the total activation energy to ring inversion in tetrabenzocyclooctatetraene, close enough to the experimental value 67.2±0.8 kcal/mol. Thus, a nearly planar transition state seems to be a realistic model. Therefore, the experimental value should be the true free energy to ring inversion, rather than a new lower limit.

This technique was also used to determine the barrier to hindered rotation in 2,2'-dimethyl binaphthyl, the global conformation of which is estimated to be a bisected form (Fig. 3). The barrier to hindered rotation was determined to be 49.5±0.5 kcal/mol. In this case the $\Delta H^{\#}$ and $\Delta S^{\#}$ values were also determined which will be reported together with barrier to hindered rotation in 2-methyl binaphthyl elsewhere.

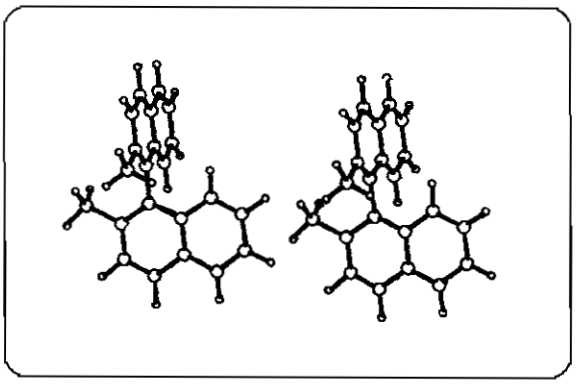


Fig. 3: The stereoview of 2,2'- dimethyl binaphthyle, calculated by MMP2-87.

In conclusion, the neat racemization technique has proved to be the method of choice when the conformational process cause racemization. The compound should be chiral, resolvable into enantiomers and should stand under high temperature.

ACKNOWLEDGMENT

The author is grateful to the Research Council of Tehran University for financial support. The Swedish Natural Science Research Council and the Knut and Alice Wallenberg Foundation are highly acknowledged for financial support through grants to J. Sandström.

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