Conformational analysis of some 5-substituted 5*H*-dibenzo[*a*,*d*]-cycloheptenes

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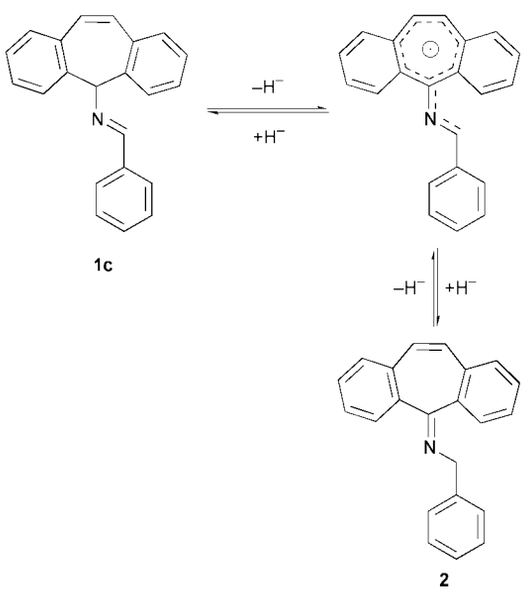
Conformations and inversion barriers of 5*H*-dibenzo[*a*,*d*]cycloheptene (**1a**), 5-amino-5*H*-dibenzo[*a*,*d*]cycloheptene (**1b**), 5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1e**), 5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (**1d**), 5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (**1f**), *N*-benzyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (**2**) and *N*-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)benzylideneamine (**1c**) have been studied by means of dynamic nuclear magnetic resonance spectroscopy (DNMR) techniques, and comparison of the experimentally derived thermodynamic parameters was made with MM3, PM3 and *ab initio* calculated results. Attempts to determine the inversion barrier of 3-isopropyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**3**) failed.

Introduction

The tricyclic framework of the 5*H*-dibenzo[*a*,*d*]cycloheptene system constitutes an important feature of many tricyclic pharmacologically interesting substances; amitriptyline,[1] protriptyline[2] and cyproheptadine,[3] and has thus been of great interest in pharmaceutical as well as stereochemical contexts. Since the introduction of amitriptyline as an amine uptake inhibitor in the treatment of depression,[4] the dibenzocycloheptene theme has been varied almost infinitely in the search for improved biological activity.[1] The pharmacological properties are linked to the stereochemistry of the organic molecule in question by the topology of the receptor for the drug.[5] Usually only one stereoisomer is found to have the desired effect while the opposite enantiomer may be inactive or display other biological effects.[6] Knowledge of the factors governing the conformation of organic molecules is thus of great importance. In an on-going project aimed at accomplishing transamination *via hydride transfer*, we have synthesised some closely related dibenzocycloheptene imines.[7] The concept of this project is to establish whether it is possible to achieve transamination[8] *via hydride transfer*, instead of proton transfer. Some earlier reports concerning transamination *via hydride transfer* have been made, using transition metal catalysts.[9] [1,3]-Hydride transfer would require a hydride donor–acceptor system. In search of a suitable substrate we thus resorted to the dibenzocycloheptene system due to its ability to effectively stabilise the incipient carbocation in the reaction (Scheme 1).

As a part of this study our interest turned to the conformation of this type of substrate. In this investigation the aim was to put forward the thermodynamic parameters involved in the inversion process of 5-substituted 5*H*-dibenzo[*a*,*d*]cycloheptene. The studied compounds are shown in Scheme 2.



Scheme 1

Results and discussion

Conformational analysis

It has long been known that cycloheptatriene is not planar[10] but saddle shaped and experiences a butterfly movement as far as molecular dynamics is concerned (Scheme 3). Several studies on the non-planarity of 5*H*-dibenzo[*a*,*d*]cycloheptene have been made as well as determination of the relevant thermodynamic parameters.[11]

With proper choice of substitution of the dibenzocycloheptene core a conformational restriction can be obtained to the point of induction of two distinct isomers (*i.e.* isolable at room temperature). The inversion of the dibenzocycloheptene system is presumed to involve a (near) planar transition state.[11a] The main argument for the preferred non-planar conformation is the steric interactions of substituents in the 4-, 5-, 9- and 10-positions respectively, which would be severe in a planar conformation (Scheme 4, with the depicted interactions of A, B, C and H). This can also be seen from the analogous case of methylene dihydroanthracene.[12] Depending on the degree of steric interaction between substituents in the above mentioned positions, the barrier height of inversion will vary. Another factor influencing the barrier height is the substituent in the 5-position, which can also be seen in other derivatives of cycloheptatriene.[13] An elongation of the conjugation in the 5-position such as a carbonyl group, imine or alkene would contribute to a higher degree of conjugation of the presumed planar transition state and would hence partly contribute to a stabilisation of the transition state. In contrast, the lack of such

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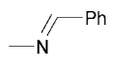
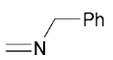
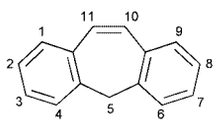
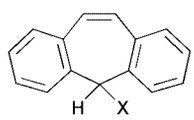
Table 1 Experimentally derived thermodynamic parameters for the inversion of 5-substituted dibenzocycloheptenes

Substituent	Solvent	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}	T/K
-H	CD_2Cl_2	11.83	8.1	9.9	232
-CH_3	$C_6D_5CD_3$	17.24	0.0	17.2	302
-NH_2	$CDCl_3$	15.52	3.4	14.5	284
-NH_2	$C_6D_5CD_3$	11.53	−6.6	13.2	257
-OH	$CDCl_3$	8.27	−13.7	11.8	257
-Cl	$C_6D_5CD_3$	11.95	−8.3	14.1	257
	$CDCl_3$	9.40	−12.9	12.7	257
	$C_6D_5CD_3$	19.87	3.0	18.9	318





1a: X= -H

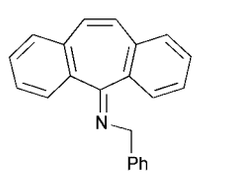
1b: X= -NH_2

1c: X= 

1d: X= -OH

1e: X= -Cl

1f: X= -CH_3



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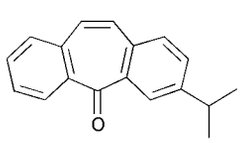

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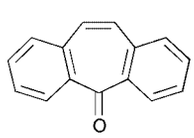

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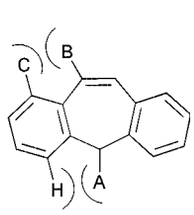
Scheme 2

a **e**

Scheme 3



Scheme 4

a conjugative subsituent would result in a destabilisation of the transition state and increase the barrier to inversion. Indeed this can be seen in the example of tribenzocycloheptenes.[11a]

As pointed out above, the dibenzocycloheptene system interconverts between two main conformations *via* a planar transition state. In the case of **1a** (as with other equally 5,5-disubstituted dibenzocycloheptenes) the two conformers are unrecognisable and hence we have a degenerate case (*homomers*). If one of the H-atoms in the 5-position is exchanged for another atom or group, two different diastereomers result from the inversion; one in which the substituent is in a pseudo-axial position and one in which the substituent is in the pseudo-equatorial position. Under this condition we have a non-degenerate case and the distinction between the two conformers is clear. It has been pointed out in several investigations that the general preference of the non-hydrogen substituent in the 5-position mainly resides in a pseudo-axial position.[14] The reason for this is the steric interaction of the substituent itself and the hydrogens in the 4- or 6-position. A third case in this series can be seen from dibenzocycloheptenes bearing a substituent in any other position than the 5-position. Inversion of the ring system in this case leads to energetically degenerate conformations which both result in two *enantiomers*.

5*H*-Dibenzo[*a*,*d*]cycloheptene (1a)

Studies concerning the inversion barrier of this compound have been made previously. According to Sutherland *et al.*, the inversion barrier for **1a** was estimated to be about 9.1 kcal mol^{-1} in CS_2.[11a] Our result was in good agreement with this (see Table 1). The room temperature spectrum showed only one sharp peak for the methylene group due to the rather low inversion barrier. A complete distinction of the two invertomers could only be made below −65 °C, giving rise to an AB-quartet.

3-Isopropyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (3)

Earlier attempts have been made to determine the inversion barrier of dibenzosuberenone,[11a] by substitution of the 7-membered ring at the 10-position with a 1′-hydroxy-1′-methylethyl group. This will however affect the inversion barrier by the steric interaction of the substituent and the 9-H proton on the benzo ring, and the inversion barrier for this compound cannot be regarded as an entirely true representative for dibenzosuberenone. A detailed study of the effect of Eu-shift reagent concentration on the ^{1}H-shifts for dibenzosuberenone has been reported,[15] though no attempts were made to determine the height of the barrier to inversion. Our attempt to elucidate the inversion barrier of dibenzosuberenone consisted of substituting the ring system in the 3-position with an isopropyl group as a prochiral probe. Upon cooling the sample (in toluene-d_8) to −85 °C no broadening of the proton signals could be observed. Adding europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate [Eu(fod)$_3$] in varying concentration did not result in any appreciable broadening of the signals, even upon cooling to −55 °C. Calculations by the PM3 method yielded a barrier of 10.4 kcal mol^{-1} (see Table 2), which is lower than the calculated barriers for the other compounds studied in this work. *Ab initio* calculations indicate a markedly lower inversion barrier (see Table 3). Using the 3-21G basis set yields 0.4 kcal mol^{-1}, and extending the basis set to 6-31G* results in a barrier to inversion of 1.5 kcal mol^{-1}. The discrepancy between the PM3 and *ab initio* results is not clear. Judging from these theoretically derived results and what has been experimentally observed it is plausible to assume a low inversion barrier (<8.2 kcal mol^{-1}) for dibenzosuberenone. Furthermore, the double bonded oxygen can be conjugated with the ring system in the transition state, and thus has a stabilising effect, resulting in a lower barrier to inversion compared

Table 2 PM3 semi empirical conformational heat of formation (kcal mol^{-1}) of 5-substituted dibenzocycloheptenes in the gas phase, going from conformation *a* to *e* according to Scheme 3

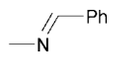
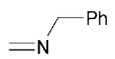
Substituent (-X)	Transition state	Pseudo-axial	Pseudo-equatorial	$\Delta E^{\ddagger}$	ΔE^{0}
-H	70.95	60.84		10.11	0.00
-Cl	68.82	58.84	58.66	9.98	−0.18
-OH	34.25	21.75	24.76	12.50	3.01
-NH_2	81.72	64.79	69.57	16.93	4.78
-CH_3	72.06	58.53	58.87	13.53	0.34
	129.24	115.07	116.35	14.17	1.28
	132.14	111.11		21.03	0.00

Table 3 *Ab initio* calculations for 5-substituted dibenzocycloheptenes in the gas phase, going from conformation *a* to *e* according to Scheme 3

Substituent (–X)	$\Delta E^{\ddagger}$/kcal mol^{-1}	ΔE^{0}/kcal mol^{-1}
	3-21G	
-H	13.03	0.00
-NH_2	13.21	−2.31
=O	0.42	0.00
	6-31G*	
-H	10.55	0.00
-NH_2	13.15	0.14
=O	1.59	0.00

to dibenzocycloheptene. However, investigation of the different geometries in the ground state as well as in the transition state, showed a small change in dihedral angle. The stabilising contribution of extended conjugation in the transition state *contra* ground state should not be considerable.

5-Amino-5*H*-dibenzo[*a*,*d*]cycloheptene (1b)

Two broad resonances could be seen for the 5-methine proton at 298 K, indicating exchange between two non-equivalent sites and slow enough to be observed on the NMR time scale. The ratio of the populations of the two conformers was 0.55 : 0.45, with the larger population in the more down-field absorption in $CDCl_3$ (Fig. 1). Calculations using the PM3 parameterisation resulted in an energy difference of 4.8 kcal mol^{-1} between the two conformations, with a pseudo-axial amino group being lowest in energy. Using information about the populations resulted in an energy difference of 0.07 kcal mol^{-1} at 223 K. On the basis of ring current effects in the dibenzocycloheptene system, one can assume that the pseudo-equatorial 5-methine proton should be shifted to lower-field due to the deshielding effect of the ring currents of the benzo moieties. This assignment was also confirmed in the NOESY-spectrum at −50 °C, where the up-field shifted absorption showed no cross coupling, and hence no relative proximity to the 4- and 6-protons in the adjoining benzene rings. The down-field shifted proton however displayed a clear cross coupling and was thus assigned as the pseudo-equatorial proton in the 5-position. In toluene-d_8, however, this situation was most markedly reversed. In this solvent the population seemed to be shifted towards the strongly preferred pseudo-equatorial position of the amino group. The only detectable absorption at room temperature was seen at 4.37 ppm. On cooling the NMR-sample, a small absorption (population of 20%) could be seen down-field of the first observed absorption. This should be a sign that the preferred conformation has the amino group in the pseudo-equatorial position. Indeed this was what the NOESY-spectrum taken at −65 °C showed. The larger absorption did not indicate any cross coupling, which was in accordance with the above stated argument.

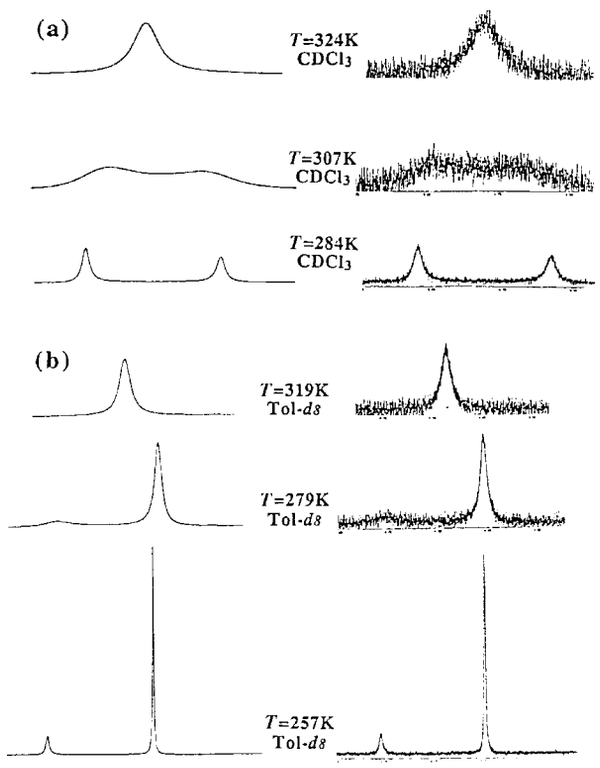


Fig. 1 Calculated and recorded spectra of the 5-methine proton of 5-amino-5*H*-dibenzo[*a*,*d*]cycloheptene **1b** in $CDCl_3$ (a) and toluene-d_8 (b).

A simple PM3 calculation performed with two different solvation models (hexadecane and water), did not point towards any special conformational change (see Table 4). To see if this change in conformational preference was an effect of aromatic–aromatic interactions between the solvent and the substrate, the amine was dissolved in cyclohexane-d_{12}. The conformational preference was still for the pseudo-equatorial position, hence ruling out the aromatic effect as a cause. A more likely reason would be that the amino group is more accessible for hydrogen-bonding to chloroform in the pseudo-axial position.

N-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-yl)benzylideneamine (1c)

Transforming the amino group to a simple benzylidene amino group (**1c**), showed yet another anomaly to what has been reported earlier regarding the conformational preference in the dibenzocycloheptene system. The chemical shift of the 5-proton of *N*-benzylidene-5*H*-dibenzo[*a*,*d*]cyclohepten-5-amine (**1c**) implied a strong preference towards having the imino moiety in the pseudo-equatorial position (93% in $CDCl_3$). This conformational preference, with imino group

Table 4 Calculated (PM3) solvent effects on the conformational energy/kcal mol^{-1} for 5-amino-5*H*-dibenzo[*a*,*d*]cycloheptene

Solvent model	Pseudo-axial-NH_2	Pseudo-equatorial-NH_2
hexadecane	56.03	57.79
water	59.24	60.89

pointing in the pseudo-equatorial position, was confirmed by NOESY (recorded at −75 °C in CD_2Cl_2). This is somewhat surprising, since the benzylidene moiety is more sterically demanding than an amino group. These findings also contradicted the calculations (PM3), which clearly showed that the preferred conformation would be with the imino substituent in the pseudo-axial position. Switching solvent to toluene-d_8 did not alter the balance in the populations. In view of transamination *via* hydride transfer, this conformational preference should favour donation of a hydride to a suitable acceptor, since the planarity to stabilise the developing cation is inherent in the most favoured conformation. The rearranged analogue of *N*-benzylidene-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-amine (**1c**), *N*-benzyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (**2**), has no 5-proton but instead a pair of benzylic protons. The NMR-spectrum of this compound showed a clear AB-quartet centred at 4.64 ppm (22 °C). This non-equivalence of the methylenic protons stems from the fact that the molecule is chiral. Since the interaction of the benzyl methylene group and the 4-, 6-protons of the dibenzocycloheptene ring system is relatively large in the transition state compared to the other compounds studied, it also yielded the largest barrier to inversion.

5-Hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (1d)

A compound isoelectronic to the amine is 5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene **1d**. It could be expected that the alcohol would show a similar pattern in conformational preference to the amine (**1b**) on going from chloroform-*d* to toluene-d_8, since these two compounds are of approximately the same polarity, with the amine more basic than the alcohol group. Somewhat surprisingly, the alcohol displayed a conformational preference for the hydroxy group in the pseudo-equatorial position in $CDCl_3$ as well as in toluene-d_8. The only difference being that the population is shifted even more towards the conformation with the hydroxy group in the pseudo-equatorial position in going from $CDCl_3$ to toluene-d_8. Drake and Jones reported that the favoured geometry had the hydroxy group in the pseudo-axial position when complexed with Eu(fod)$_3$.[15] Another interesting feature was that the 5-methine proton in the pseudo-equatorial position showed a coupling (doublet, $J = 7.78$ Hz) to the hydroxy group. Such coupling could not be seen in the case with the pseudo-axial proton. This would hence indicate a Karplus relationship between the methine proton and the hydroxy proton (see Fig. 2). A maximum coupling effect in the conformation with the hydroxy group in the pseudo-axial position is corroborated by the PM3 calculations which show that the most favoured configuration of the hydroxy group in the pseudo-axial position is with the hydrogen pointing directly towards the double bond of the cycloheptene moiety. This in turn gives a dihedral angle of 180° in the H–C–O–H system. A similar calculation for the conformation with the hydroxy group in the pseudo-equatorial position, results in a dihedral angle of 65.5°. Furthermore, the NOESY-spectrum recorded at −55 °C, confirmed that the signal located at 5.20 ppm indeed belonged to the proton in the pseudo-axial position (showing no cross coupling), and the proton signal located at 5.79 ppm belonged to the conformation with the proton in the pseudo-equatorial position.

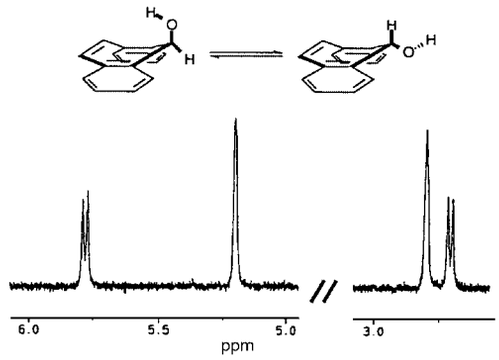


Fig. 2 The proton spectrum of 5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene **1d** in $CDCl_3$, recorded at $T = 213$ K. Left hand spectrum showing the NMR absorptions of the 5-methine proton, and the right hand side displaying the NMR absorptions of the hydroxy proton.

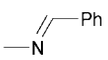
5-Chloro-5*H*-dibenzo[*a*,*d*]cycloheptene (1e)

For the sake of comparison we examined the behaviour of 5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene. At 25 °C the only detectable signal of the 5-methine proton in the NMR-spectrum was found at 5.98 ppm (toluene-d_8). On cooling the sample a decoalescence of the 5-methine proton signal could be observed and at −35 °C a small signal at 6.64 ppm emerged. This represented a mere 10% population with a pseudo-axial chlorine. Comparison with PM3 calculations of the two possible conformations showed that there was only a small difference between them ($\Delta H = 0.18$ kcal mol^{-1}, in favour of the conformation with the chlorine substituent residing in the pseudo-equatorial position). A possible explanation for this anomaly in conformation would be that the 5-chlorodibenzocycloheptene, like for example trityl chloride, has a cationic character in solution.[16] An equilibrium between a contact ion pair and a covalent species would complicate the situation, in addition to dealing with two different conformations of the covalent species. The considerations regarding whether we are dealing with two different species in solution or not, must be evaluated in the context of the spectra retrieved. If in fact lowering the temperature, and thereby increasing the concentration of a presumed cationic species, would result in at least three different signals (provided that all barriers are high); 5-methine proton (cationic species), 5-H (pseudo-equatorial) and 5-H (pseudo-axial). At the lowest temperature recorded (–80 °C), no such pattern could be seen. Furthermore, we could not observe any change in shift of any NMR-signal, which implies no occurance of cationic species. Furthermore, the study was made in toluene which in contrast to polar solvents, does not favour ionic species. Secondly, the populations between the two observed peaks does not vary with temperature, which is commonly seen when dealing with ionic species whose concentration grows when lowering the temperature. However we cannot completely rule out the possible existence of an ionic species, since the equilibrium between a cationic species and a covalent species is fast on the NMR-time scale. In order to fully investigate the identity of the two different 5-proton methine signals, a NOESY-spectrum was run at −80 °C. This indicated that the signal at 5.98 ppm belongs to the conformation with the chlorine atom pointing in the pseudo-equatorial position, since no clear cross coupling to other protons could be observed. However this conclusion relies on negative evidence. Since the population is very unequally distributed, the signal at 6.67 ppm is too small to permit observation of any cross coupling to the 4,6-protons.

5-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (1f)

A protonated analogue of the amine **1b** could sterically be represented by 5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene.[17] Earlier investigations report an inversion barrier of $\Delta G^{\ddagger}_{348\,K} = 72.5$ kJ

Table 5 Experimental populations and free energy difference on going from conformation *a* to conformation *e* according to Scheme 3

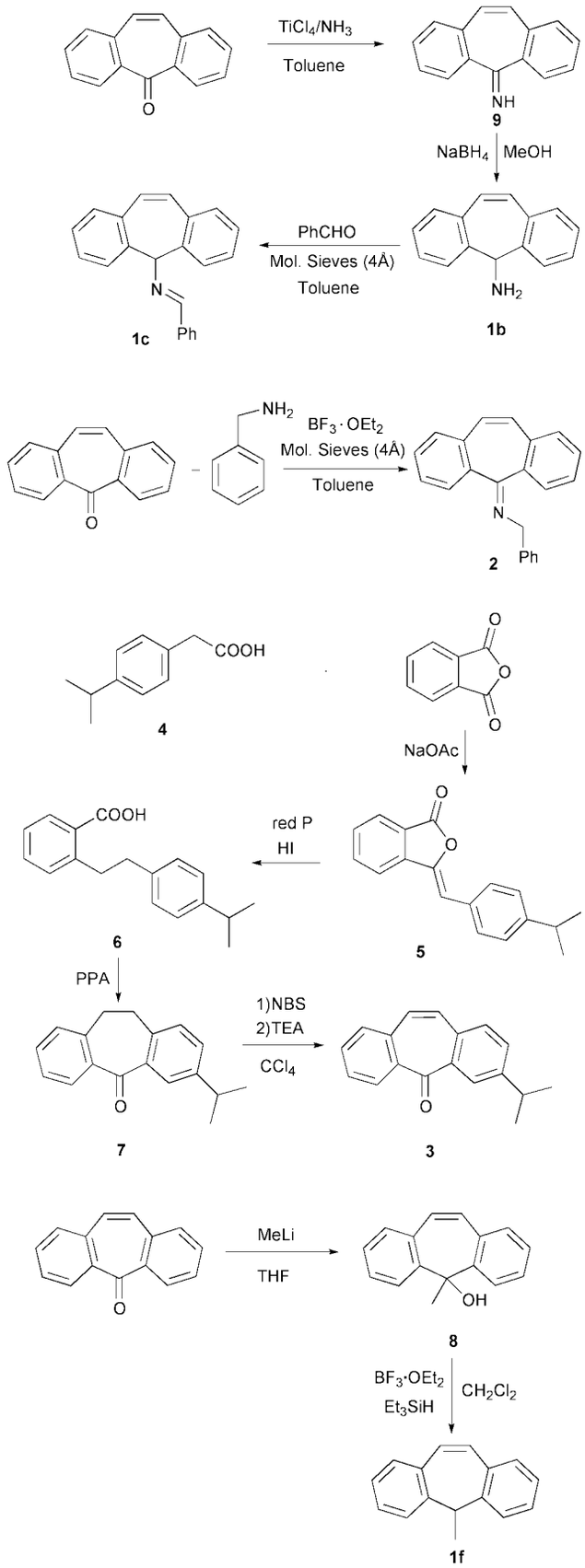
Substituent	Solvent	Fraction pseudo-axial	*T*/K	ΔG^0/kcal mol^{-1}
-OH	$CDCl_3$	0.40	218	0.17
$-CH_3$	$C_6D_5CD_3$	0.60	298	0.24
$-NH_2$	CD_3OD	0.64	258	−0.29
$-NH_2$	$CDCl_3$	0.54	223	−0.07
$-NH_2$	$C_6D_5CD_3$	0.20	278	0.76
$-NH_2$	C_6D_{12}	0.20	283	0.79
-Cl	$CDCl_3$	0.97	218	−1.50
-Cl	$C_6D_5CD_3$	0.14	238	0.86
	$CDCl_3$	0.07	223	1.15

mol^{-1}, which is well in accordance with our findings. In toluene-d_8 the methyl group resides primarily in the pseudo-axial position.

Table 5 summarises the experimental populations and free energy difference on going from conformation *a* to *e* for compounds **1b**–**1f**.

Synthesis

The synthesis of the key amine **1b** was made from the comercially available dibenzosuberenone (Acros) (see Scheme 5). The ketone was converted to its imine with ammonia and $TiCl_4$, in dry toluene. The afforded imine proved to be stable enough to permit isolation. The desired key amine could easily be produced by reduction of the imine with $NaBH_4$ in methanol. The investigated *N*-benzyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (**2**) was synthesised using both $BF_3{\cdot}OEt_2$ and activated molecular sieves in boiling dry toluene. The reaction proved to require more vigorous conditions than synthesis of the corresponding rearranged imine, *N*-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)benzylideneamine (**1c**), as the yield was lower. Benzylideneamine (**1c**) was synthesised from the key amine together with freshly distilled benzaldehyde, and boiled in dry toluene over activated molecular sieves (4 Å). 5-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (**1f**) was synthesised from 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one and methyllithium. The remaining hydroxy group on 5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (**8**) was eliminated by treatment with $BF_3{\cdot}OEt_2$, and quenching with Et_3SiH. 5-Chloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1e**) was produced by boiling 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (**1d**) with $SOCl_2$, which upon completion of the reaction was eliminated by evaporation *in vacuo*. The remaining red crystalline mass was recrystallised twice from hexane to afford white needles. The mother compound, 5*H*-dibenzo[*a*,*d*]cycloheptene (**1a**), was synthesised by reduction of the alcohol (**1d**) with $LiAlH_4$–$AlCl_3$. 3-Isopropyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**3**) was synthesised according to the method used by Ebnöther *et al.*[18]

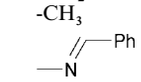
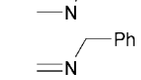


Scheme 5

Summary

It has been found that the conformational preference of simple 5-substituted dibenzocycloheptenes is very sensitive towards both the character of the solvent (polarity) and the substituent itself. The reason for this behaviour does not seem to solely depend upon either the steric size or the polarity of the substituent. It can be speculated that the findings in this report are a product of the presence of oligomeric species in some of the solvents used. The techniques used in this investigation cannot fully rule out the possibility of the presence of oligomeric species, but using compound (**1b**) as a model for this argument would yield the possibility of three different dimers as well as any monomers. Several scenarios could be contemplated. It has to be taken into account that we may have an equilibrium between the dimeric and monomeric species. However, we examined the concentration dependence of the amine in $CDCl_3$. Varying the concentration from 0.69 M to 0.38 mM did not result in any change in either NMR-spectra or UV-spectra. This would in part sustain the theory that we are not dealing with any dimeric species in solution. Comparison between the theoretically retrieved results and the experimental results deserves some comment. It can clearly be seen that regardless

Table 6 MM3 molecular mechanics conformational energy (kcal mol^{-1}) of 5-substituted dibenzocycloheptenes in the gas phase, going from conformation *a* to *e* according to Scheme 3

Substituent (-X)	ΔE^0
-H	0.00
-Cl	1.28
-OH	0.21
$-NH_2$	3.88
$-CH_3$	2.52
	0.08
	0.00

of the computational method used the calculated energies do not correlate well to the experimental results. During the investigation we decided to use MM3 molecular mechanics (Table 6) to achieve better correlation, but no such correlation could be seen. The calculated geometries of the transition states were all started from a planar structure. In all cases, but for compounds (**1a**) and (**4**), the resulting calculated geometry of the transition state turned out to be non-planar. All calculated transition states were analysed with normal mode analysis to assure the occurrence of strictly one imaginary vibrational frequency. The experimental results indicate that the imine (**1c**) prefers the conformation with the benzylidene imino group in a pseudo-equatorial position in both chloroform and toluene solution. This conformation should favour a hydride transfer reaction.

Experimental

NMR (^1H, ^{13}C) was performed on a Bruker DRX spectrometer operating at 400 MHz and 100 MHz respectively. FT-IR spectra were obtained on a Nicolet Impact 410 spectrometer. Melting points were recorded on a Gallenkamp melting point apparatus (and reported herein as uncorrected melting points). HRMS-analysis was carried out on a JEOL SX102 spectrometer. $TiCl_4$ was purchased from Riedel and used without further purification. Toluene and CH_2Cl_2 were dried and distilled over CaH_2 and stored under argon, over activated molecular sieves (4 Å). THF was dried and distilled over Na–benzophenone and used directly thereafter. All eluents used for chromatography were distilled prior to use. Thin layer chromatography was performed on silica gel plates with aluminium supports (Merck 60 PF_{254}). All other chemicals were used as received, unless otherwise noted. Deuterated solvents were used as received. Temperature calibration of the NMR-instrument was made by the method of van Geet,[19] using methanol-d_4. Adaptation of the NMR-spectra was made by the visual matching of calculated spectra according to literature procedure.[20] The derived rate constants were plotted against temperature according to the Eyring equation,[21] to afford the rate constants and thereof the relevant thermodynamic parameters. The semi-empirical and *ab initio* calculations were performed on a Silicon Graphics O_2-work station with R-10000 processor using the SPARTAN 5.0.3 program.[22] The geometries were evaluated with full optimization at the RHF level without symmetry restriction, employing the basis sets 3-21G and 6-31G*. Default convergence criteria for SCF and geometry optimization were used. The molecular mechanics calculations were performed using the MM3 force field implemented in the MacMimic program package.[23]

5*H*-Dibenzo[*a*,*d*]cycloheptene (1a)

5*H*-Dibenzo[*a*,*d*]cycloheptene (**1a**) was prepared according to literature procedures.[24]

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-imine (9)

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-imine (**9**) was prepared according to literature procedures.[25]

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-amine (1b)

To a solution of dibenzo[*a*,*d*]cyclohepten-5-imine (0.014 mol, 2.9 g) in abs. MeOH (65 ml), was added $NaBH_4$ (0.084 mol, 3.2 g) in small portions. The reaction mixture was stirred at room temperature for 20 h, whereupon the solvent was removed *in vacuo*. Water was added to the solid residue, and the aqueous phase was extracted with diethyl ether (4 × 50 ml). The combined etherial layers were dried over Na_2SO_4. The drying agent was filtered off and the solvent evaporated to afford a yellow oil which crystallised upon standing. The crude material was recrystallised from hexane to yield white crystals. Yield: 1.5 g, 52%. Mp 68–70 °C. $\delta_H(CDCl_3, T = 223\ K)$; 7.74 (1H, s), 7.72 (1H, s), 7.49–7.26 (6H, m), 7.18 (1H, s), 7.11 (1H, s), 5.09 (1H, s), 4.58 (1H, s), 1.95 (2H, br s). $\delta_C(CDCl_3, T = 223\ K)$; 141.21, 140.87, 133.38, 132.78, 131.26, 130.61, 130.08, 129.00, 128.67, 128.60, 127.70, 127.16, 125.93, 121.81, 62.79, 53.27. ν_{max}(KBr)/cm^{-1}; 3370 (N–H), 3306 (N–H). MS (EI+), 207.1054. $C_{15}H_{13}N$ Requires 207.1049. *m*/*z* 207 (45%, M), 191 (100).

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ol (1d)

5*H*-Dibenzo[*a*,*d*]cyclohepen-5-ol (**1d**) was prepared according to literature procedures.[26]

N-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-yl)benzylideneamine (1c)

To a solution of dibenzo[*a*,*d*]cyclohepten-5-amine (2.41 mmol, 0.5 g) in dry toluene (8 ml), was added activated molecular sieves (4 Å, 1.5 g). Freshly distilled benzaldehyde (2.41 mmol, 0.26 g) was added and the reaction mixture was refluxed under argon for 16 h. The flask was then allowed to cool to ambient temperature, and the molecular sieves were filtered off, and washed with several portions of diethyl ether. The organic phases were combined and the solvent was removed *in vacuo* to afford a yellow oil which crystallised spontaneously. The crude material was crystallised from MeOH–toluene. Mp 126–128 °C. Yield: 0.20 g, 28%. $\delta_H(CDCl_3)$; 8.40 (1H, s), 8.04 (2H, s), 7.83 (2H, *J* 7.8, d), 7.55 (2H, s), 7.41 (5H, m), 7.27 (2H, *J* 8.3, t), 7.22 (2H, s), 5.81 (1H, s), 4.89 (1H, s). $\delta_C(CDCl_3)$; 161.79, 141.29, 135.88, 132.84, 131.35, 131.19, 128.82, 128.58, 127.64, 125.97, 124.15, 71.58. ν_{max}(KBr)/cm^{-1}; 1643 (C=N). MS (EI+), 295.1364. $C_{22}H_{17}N$ requires 295.1362. *m*/*z* 295 (75%, M), 191 (100), 104 (35).

N-Benzyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (2)

To a solution of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (2.5 mmol, 0.5 g) in dry toluene (7.5 ml), was added activated molecular sieves (4 Å, 1.5 g). The reaction solution was heated to reflux under an argon atmosphere. Benzylamine (5.5 mmol, 0.59 g, 0.6 ml) and $BF_3{\cdot}OEt_2$ (2.0 mmol, 0.25 ml) was then added dropwise. The reaction was refluxed for 20 h, and thereafter allowed to cool to room temperature. The molecular sieves were filtered off and washed with several portions of diethyl ether. The combined organic phases were washed with 10% $NaHCO_3$ (20 ml) and water (20 ml) and finally dried over Na_2SO_4. The solvent was removed by evaporation to afford a yellow oil. The crude product was allowed to crystallise and purified by passing a solution of the crude material dissolved in 20% EtOAc in heptane through a short silica column. The solvent was again evaporated and recrystallised from hexane–MeOH to yield the desired imine. Yield: 90 mg, 13%. Mp 63–65 °C. $\delta_H(CDCl_3)$; 7.69 (1H, *J* 7.6, d), 7.47–7.19 (12H, m), 6.97 (2H, *J* 12, q), 4.69 (2H, *J* 14.6, q). $\delta_C(CDCl_3)$; 168.82, 141.62, 140.40, 134.25, 133.95, 133.09, 131.61, 130.19, 129.35, 129.15, 128.73, 128.60, 128.58, 128.48, 127.79, 127.16, 127.03, 126.78, 56.61.

ν_{max}(KBr)/cm^{-1}; 1634 (C=N). MS (EI+) 295.1365. $C_{22}H_{17}N$ requires 295.1362. *m*/*z* 295 (57%, M).

5-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (1f)

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one (24.2 mmol, 5 g) was dissolved in dry THF (25 ml). The reaction flask was cooled on an ice–salt bath and MeLi (25 mmol, 16.4 ml, 1.52 M in hexane) was added. The solution was stirred for 30 min, and then quenched with sat. NH_4Cl solution. The organic phase was separated and dried over Na_2SO_4. The solvent was removed by evaporation *in vacuo*. The intermediate compound 5-methyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (**8**) was used without further purification. 5-Methyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]-cycloheptene (16.2 mmol, 3.59 g) was dissolved in dry CH_2Cl_2 (30 ml) and cooled to −20 °C. $BF_3{\cdot}OEt_2$ (24.2 mmol, 3.1 ml, 1.5 equiv.) was added, and the red solution was allowed to stir for 20 min. $HSiEt_3$ (24.2 mmol, 3.9 ml, 1.5 equiv.) was added and the reaction flask was warmed to ambient temperature. The reaction was quenched with water. The organic layer was separated, and washed with sat. $NaHCO_3$ solution, and finally dried over Na_2SO_4. The solvent was removed *in vacuo*, to afford a pale yellow oil which crystallised upon standing. The crude product was purified by passing the raw material (dissolved in hexane) through a short silica column. Yield: 52%. $\delta_H(CDCl_3)$; 7.41–7.16 (8H, m), 7.12 (2H, s), 6.91 (2H, s), 4.14 (1H, *J* 7.3, q), 3.47 (1H, *J* 7.8, q), 1.87 (3H, *J* 7.3, d), 1.31 (3H, *J* 7.3, d). $\delta_C(CDCl_3)$; 142.88, 141.93, 135.57, 134.14, 131.68, 131.07, 130.11, 129.06, 129.03, 128.56, 127.81, 126.44, 125.55, 123.34, 49.50, 38.25, 17.44, 15.60.

5-Chloro-5*H*-dibenzo[*a*,*d*]cycloheptene (1e)

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ol (9.6 mmol, 2.0 g) was placed in a round bottomed flask. $SOCl_2$ (25 ml) was added and the deep red solution was set to reflux for 3 h. The reaction flask was thereafter allowed to cool to ambient temperature, and the remaining $SOCl_2$ was removed by evaporation *in vacuo*. The red crystalline mass was recrystallised twice from hexane to afford white needles. Yield: 70%. Mp = 87–90 °C. $\delta_H(CDCl_3,\ T = 218$ K); 7.54 (4H, m), 7.46 (4H, m), 7.22 (2H, s), 6.36 (1H, s), 5.52 (1H, s). $\delta_C(CDCl_3,\ T = 218$ K); 136.12, 134.30, 131.60, 130.59, 128.90, 128.87, 128.56, 67.97. ν_{max}(KBr)/cm^{-1}; 624 (C–Cl). MS (CI, isobutane) 226.0559. $C_{15}H_{11}Cl$ requires 226.0550. *m*/*z* 226 (35%, M), 191 (100).

4-Isopropylbenzyl chloride

4-Isopropylbenzyl alcohol (0.071 mol, 10.6 g, 10.8 ml) was added dropwise to $SOCl_2$ (0.21 mol, 25.2 g, 15.4 ml) under argon. The reaction mixture was refluxed for 1 h, and thereafter distilled under reduced pressure (15 mmHg). The product was collected at 105 °C as a colourless oil. Yield: 87%. δ_H ($CDCl_3$); 7.36 (2H, *J* 1.99, *J* 8.18, dd), 7.27 (2H, *J* 2.02, *J* 8.14, dd), 4.62 (2H, s), 2.96 (1H, *J* 6.92, septet), 1.30 (6H, *J* 6.93, d).

4-Isopropylbenzyl cyanide

4-Isopropylbenzyl chloride (0.056 mol, 9.5 g) was dissolved in methylene chloride (8.5 ml). Tetrabutylammonium hydrogen sulfate [$(n\text{-Bu})_4NHSO_4$] (2.8 mmol, 0.96 g) and NaOH (2.8 mmol, 0.11 g) were dissolved in water (8.5 ml). NaCN (0.062 mol, 3.04 g) was added and the two solutions were mixed, and refluxed for 1 h with stirring. The layers were separated and the organic phase was washed with water (10 ml) and made slightly acidic with HCl (pH = 5). The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo* to afford a colourless oil. The product was used without further purification. Yield: 92%. $\delta_H(CDCl_3)$; 7.27 (4H, s), 3.73 (2H, s), 2.94 (1H, *J* 6.92, septet), 1.28 (6H, *J* 6.93, d).

4-Isopropylphenylacetic acid (4)

4-Isopropylbenzyl cyanide (0.055 mol, 8.82 g), water (10 ml), conc. sulfuric acid (10 ml) and glacial acetic acid (10 ml) were mixed and refluxed with stirring for 5 h. Water (30 ml) was added and the mixture was mildly basified with saturated $NaHCO_3$, and washed with ether (3 × 20 ml). The remaining aqueous phase was made acidic with HCl and extracted with ether (3 × 20 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The resulting yellow oil was purified *via* distillation under reduced pressure. The product acid was collected at 167 °C/15 mmHg, which crystallised spontaneously to afford white needles. Yield: 62%. Mp 43–45 °C. $\delta_H(CDCl_3)$; 7.23 (4H, s), 3.64 (2H, s), 2.92 (1H, *J* 6.93, septet), 1.26 (6H, *J* 6.93, d). $\delta_C(CDCl_3)$; 178.18, 147.94, 130.51, 129.26, 126.72, 40.63, 33.74, 23.94. ν_{max}(KBr)/cm^{-1}; 3100 (OH), 1698 (C=O). MS (EI+) 178.0993. $C_{11}H_{14}O_2$ requires 178.0994. *m*/*z* 178 (45%, M).

3-(4-Isopropylbenzylidene)phthalide (5)

4-Isopropylphenylacetic acid (0.034 mol, 6.05 g), phthalic anhydride (0.034 mol, 5.04 g) and NaOAc (1.35 mmol, 0.089 g) were heated with stirring at 240 °C for 6 h. The water formed during the reaction was distilled off. The reaction mixture was allowed to cool to ambient temperature, and the crude material was recrystallised from abs. EtOH to afford yellow prisms. Yield: 58%. Mp 62–64 °C. $\delta_H(CDCl_3)$; 7.96 (1H, *J* 0.96, *J* 7.71, dt), 7.81 (2H, m), 7.78 (1H, m), 7.74 (1H, *J* 1.06, *J* 7.06, td), 7.56 (1H, *J* 1.05, *J* 7.03, td), 7.30 (2H, *J* 1.86, *J* 8.29, dd), 6.44 (1H, s), 2.96 (1H, *J* 6.99, septet), 1.29 (6H, *J* 6.92, d). $\delta_C(CDCl_3)$; 167.39, 149.74, 144.20, 140.89, 134.59, 130.86, 130.40, 129.72, 127.09, 125.71, 123.48, 119.90, 107.37, 34.30, 24.01. MS (EI+) 264.1151. $C_{18}H_{16}O_2$ requires 264.1151. *m*/*z* 264 (100%, M). ν_{max}(KBr)/cm^{-1}; 1781 (C=O).

2-[2-(4-Isopropylphenyl)ethyl]benzoic acid (6)

3-(4-Isopropylbenzylidene)phthalide (0.015 mol, 4 g) and red phosphorous (0.069 mol, 2.14 g) were placed in a 25 ml round bottomed flask equipped with a condenser and a magnetic stirrer bar. HI (15 ml, 57% aq. solution) was added and the reaction flask was heated to 120 °C for 15 h. The mixture was allowed to cool to room temperature and a solution of toluene–EtOAc (80 : 20) was added and the red phosphorous was filtered off. The solution was then basified with an aqueous KOH solution (10%), and extracted with toluene. The remaining aqueous phase was made acidic by addition of conc. HCl, and again extracted with toluene. The organic layer was washed with $Na_2S_2O_3$ (10%) and water. Drying and evaporation of the solvent *in vacuo* afforded yellow crystals. Recrystallisation from hexane gave the pure acid as a white solid. Yield: 54%. Mp 74–76 °C. $\delta_H(CDCl_3)$; 8.12 (1H, *J* 7.73, d), 7.50 (1H, *J* 1.26, *J* 7.44, td), 7.26 (6H, m), 3.35 (2H, m), 2.91 (3H, m), 1.26 (6H, *J* 6.92, d). $\delta_C(CDCl_3)$; 172.73, 146.43, 144.99, 139.27, 133.00, 131.77, 131.46, 128.42, 128.02, 126.37, 126.16, 37.74, 37.15, 33.71, 24.07. MS (EI+) 268.1461. $C_{18}H_{20}O_2$ requires 268.1464. *m*/*z* 268 (76%, M) ν_{max}(KBr)/cm^{-1}; 3200 (OH), 1694 (C=O).

3-Isopropyl-10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one (7)

2-[2-(4-Isopropylphenyl)ethyl]benzoic acid (7.9 mmol, 2.13 g) was added to polyphosphoric acid (PPA) (9.2 g). The mixture was heated to 145–150 °C with stirring for 50 minutes under an argon atmosphere. After completion of the reaction, the mixture was poured into cold water, and extracted with EtOAc. The organic layer was washed with 10% $NaHCO_3$, brine and finally dried over Na_2SO_4. The solvent was removed by evaporation *in vacuo*. The crude product was purified by column chromatography using toluene as eluent ($R_f = 0.41$), and retrieved as a yellow oil. Yield: 67%. $\delta_H(CDCl_3)$; 8.00 (1H, *J* 1.22, *J* 7.85, dd), 7.90 (1H, *J* 2.04, d), 7.44 (1H, *J* 1.51, *J* 7.45, td), 7.33 (2H, *J* 1.57, *J* 7.71, td), 7.23 (1H, *J* 0.81, *J* 8.36, dd), 7.17 (1H, *J* 7.79, d), 3.20 (4H, s), 2.97 (1H, *J* 6.9, septet), 1.29 (6H, *J* 6.94, d).

$\delta_C(CDCl_3)$; 196.52, 147.63, 142.29, 139.96, 139.38, 138.76, 132.66, 131.13, 130.88, 129.94, 129.60, 128.85, 127.01, 35.37, 35.00, 34.15, 24.32. MS (EI+) 250.1368. $C_{18}H_{18}O$ requires 250.1358. *m*/*z* 250 (100%, M). ν_{max}(NaCl)/cm^{-1}; 1643 (C=O).

3-Isopropyldibenzo[*a*,*d*]cyclohepten-5-one (3)

3-Isopropyl-10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one **7** (5.3 mmol, 1.33 g) was dissolved in CCl_4 (42.5 ml). To the solution was added NBS (5.8 mmol, 1.05 g) and the reaction mixture was refluxed for 16 h. The reaction mixture was then filtered and the filtrate was evaporated (*in vacuo*). The residual oil was dissolved in triethylamine (21.3 ml), and refluxed for 16 h. The solvent was then evaporated, and the residue was dissolved in EtOAc. The solution was washed with water, 3% HCl and brine. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by chromatography ($R_f = 0.32$, toluene), and retrieved as a pale yellow oil. Yield: 9.1%. $\delta_H(CDCl_3)$; 8.24 (1H, *J* 1.04, *J* 8.27, dd), 8.10 (1H, *J* 1.84, d), 7.63 (1H, m), 7.54 (4H, m), 7.04 (2H, *J* 12.03, q), 3.07 (1H, *J* 6.92, septet), 1.33 (6H, *J* 6.93, d). $\delta_C(CDCl_3)$; 193.24, 138.57, 138.48, 135.03, 131.78, 131.53, 131.00, 130.71, 130.59, 130.45, 130.15, 129.00, 128.57, 128.19, 127.74, 34.03, 23.75. MS (EI+) 248.1207. $C_{18}H_{16}O$ requires 248.1202. *m*/*z* 248 (100%, M). ν_{max}(NaCl)/cm^{-1}; 1639 (C=O), 1625 (C=C).

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