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THE CONFORMATIONAL ANALYSIS OF BENZOCYCLOALKANONES USING THE LANTHANIDE INDUCED SHIFT METHOD

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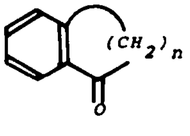
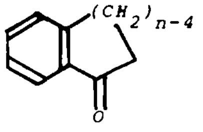
Abstract: The conformations of the benzocycloalkanones 1a - 1d in solution were estimated by the use of the lanthanide induced shift method (LIS of ^{1}H, ^{13}C NMR spectra). The starting geometry was obtained from MNDO calculations. The torsional angle of the carbonyl group with respect to the benzene ring is 0° for compound 1a, 3° for 1b, 56° for 1c and 67° for the eight-membered ring compound 1d. These results are compared with the data obtained by other methods for similar compounds and are discussed with regard to kinetic measurements for solvolysis of chlorobenzocycloalkanes and oxidation of benzocycloalkanols, respectively.

The consequence of steric interference between neighbouring groups is of great importance in chemistry[2]. This is reflected in extensive studies of chemical reactivity of sterically hindered centers and in unusual physical properties of these molecules. In aromatic molecules the steric interaction can lead to changes in conjugation of π-systems, which produce marked deviations from "normal" behaviour. In the present study of steric effects in substituted benzenes we are dealing with spectroscopic and conformational properties of benzocycloalkanones 1. The torsional angles ϕ (that is the angle between the C=O-group and the aromatic ring) can be used as a probe of steric inhibition of resonance for sp^2 hybridized carbon atom attached to an aromatic system. The compounds with the fixed structures (no free rotation) can provide good model systems to the problem under discussion by variation of the ring size.



1a - d

In the course of an attempt to obtain more insight into this problem and to give quantitative values of the angle Ø we decided to study benzocycloalkanones **1** capable to coordinate the lanthanide shift reagent. Thus, the simultaneous use of the ^1H and ^{13}C lanthanide induced shift technique[3] for the investigation of conformational problems in solution was adopted. The question of the torsional angle Ø in compounds **1** - **4** has been the subject of many investigations, utilizing chemical methods as pK_B measurements of 2-amino- and 2-hydroxy-derivatives[4] and physical methods including IR[5], UV[6], photoelectron spectroscopy[7] and force-field calculations[8].



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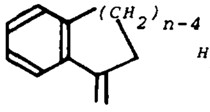

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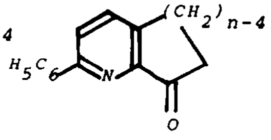

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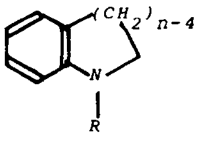

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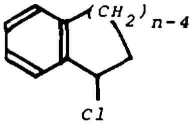

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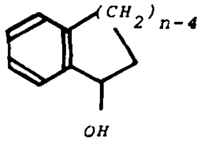


6

In compounds **1**, **2**, **3**, **4**, **5** and **6** a: n=5; b: n=6; c: n=7; d: n=8.

METHOD

The lanthanide-induced shift method (LIS-technique) for conformational analysis is well documented[3]. It is based on the McConnell-Robertson equation (1), where Δ is the pseudocontact contribution to the induced shift, r is the internuclear distance between lanthanide ion and the considered nucleus and ϑ is the angle between this distance vector and the principal magnetic axis. The use of equation (1) implies that contact contribution and nonaxial symmetry can be neglected. With a given geometry of the substrate, a specific complexation site and observed Δ_{LIS}-values one can calculate, according to equation (1), the best position of the

$$\Delta = K \frac{3\cos^2\vartheta - 1}{r^3} \qquad (1)$$

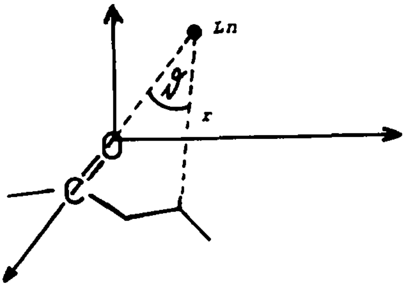


Fig. 1: Basic coordinate parameters for the calculation of LIS values

lanthanide ion by variation of the polar coordinates of the lanthanide ion. This is best done by a computer program (Lanthan-program[9]*), which calculates Δ -values and scales them (K is the scale factor) against the observed shifts Δ_{obs}. According to equation (2) an agreement factor R is then evaluated, which is a measure of the quality of the fit. It is obvious that one should use as*

$$R = \sqrt{\frac{\sum(\Delta_{obs} - \Delta_{calc})^2}{\sum \Delta^2_{obs}}}$$

many Δ_{obs} values as possible to ascertain a special geometry of the substrate. Therefore the combined use of ^1H- and ^{13}C-chemical shifts is highly recommended[10]*. An agreement factor less than 0.05 (5%) is accepted to be reliable. That means, that the choosen geometry of the substrate is reasonable. The starting geometry (cartesian coordinates; if only bond-distances, -angles and dihedral angles are available, the computer program KOORD calculates from these values the cartesian coordinates*[9]*) of the substrate should be the best possible one, therefore data from X-ray analysis, force field calculations or, as in the present paper, from MNDO calculations are used. The Lanthan-program has the option to vary dihedral angle with respect to certain bonds and plots the agreement factor versus the rotational angle. So the conformation of the complex can be further optimized. The use of equation (1) for conformational analysis requires the consideration of the following points*[10]*:*

1) *The contact shift is negligible for protons with europium shifts reagents, but not for carbon nuclei. Ytterbium shift reagents cause no contact contribution except for the adjacent atoms. The LIS-value of the atoms, which are very close to the complexation site should be omitted in the calculation.*

2) *The substrate conformation determined by this method is that in the complex. This geometry may differ from that in the free molecule.*

There are some possiblities to extract the Δ_{obs} values from the shifted spectra[11]*. We prefer the "relative shifts": that is to plot the induced shifts of each nuclei versus the shifts of an arbitrarly chosen nuclei. The slopes, calculated by linear regression analysis, are than used as Δ_{obs} values. This procedure reduces the experimental errors*[10]*.*

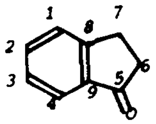
RESULTS AND DISCUSSIONS

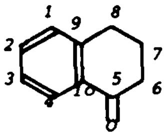
a) Carbon 13 NMR Spectra:

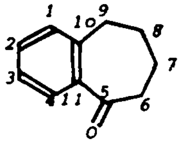
The carbon-13 chemical shifts are given in Table 1, also included are the Δ_{LIS}-values (see above). The assignment of the quaternary carbon atoms is straightforward by inspection of the chemical shift. The carbonyl groups absorb at lowest field, as expected. From six-membered to the eigth-membered ring this shift increases due to noncoplanarity of the carbonyl group (see conformation of the benzocycloalkanones

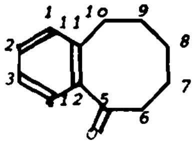
The δ_{CO} value for the indanone (**1a**) is higher than that for the tetralone (**1b**). This is also observed in cyclopentanone ($\delta_{C=O}$ = 219.6) in comparison to cyclohexanone ($\delta_{C=O}$ = 209.7)[12] and can be rationalized by the different bond angles of the carbonyl groups, which are approximately 117° and 121°, respectively. In the series **1a** - **1d** carbon atoms C-8, C-9, C-10 and C-11 (ortho position to the carbonyl group) show an upfield shift, which can be explained by the increase of the torsion angle of the carbonyl group with respect to the benzene ring. The mesomeric effect of the carbonyl decreases going from **1a** - **1d**. The other sp^2-carbon atoms were assigned by comparison of the lanthanide induced shift values Δ_{LIS} (see above) and the chemical shifts themselves. For example C-4 has the largest Δ_{LIS} value of all aromatic C-H-groups because it is close to the complexation site. It is interesting to note,

Table 1: ^{13}C and ^{1}H Chemical shifts (relative to internal TMS) at 29° C in $CDCl_3$ as solvent and relative LIS-values Δ_{LIS} of the benzocycloalkanones **1a** - **1d**, obtained with $Yb(fod)_3$ (see text).









	δ_C	Δ_{LIS}	δ_C	Δ_{LIS}	δ_C	Δ_{LIS}	δ_C	Δ_{LIS}
1	126.67	0.647	128.74	0.661	129.66	0.707	130.98	0.655
2	134.37	0.589	133.22	0.608	132.06	0.649	131.47	0.593
3	127.07	0.622	126.47	0.708	126.50	0.753	126.26	0.675
4[a]	123.25	1.274	126.94	1.623	128.47	1.750	127.57	1.682
5[b]	206.25	4.784	197.52	4.950	205.28	5.289	206.81	4.710
6	35.98	1.985	23.26	1.000	25.21	0.761	34.27	0.789
7	25.66	1.000	29.56	0.836	32.38	0.869	24.99	0.716
8	155.01	1.098	39.00	2.207	20.87	1.000	27.87	0.634
9	136.92	1.987	144.36	1.087	40.73	2.298	24.03	1.000
10			132.56	2.143	141.24	1.162	44.03	2.084
11					138.78	2.254	139.80	1.091
12							139.93	2.137
	δ_H	Δ_{LIS}	δ_H	Δ_{LIS}	δ_H	Δ_{LIS}	δ_H	Δ_{LIS}
$(C-6)H_2$	2.40	1.405	2.50	1.571	2.57	1.605	2.84	1.577
$(C-7)H_2$	2.90	0.703	1.97	0.687	1.70	0.678	1.70	0.477
$(C-8)H_2$			2.80	0.605	1.70	0.594	1.48	0.729
$(C-9)H_2$					2.76	0.713	1.70	0.477
$(C-10)H_2$							2.90	0.659
$(C-4)-H$[a]	7.43	1.136	7.84	1.739	7.50	1.947	7.56	1.911
other H	6.85-7.40		6.60-7.60		6.60-7.40		6.60-7.40	

[a] These signals show a significant line broadening upon addition of small amounts of $Yb(fod)_3$, the Δ_{LIS} values were not considered in the calculations

that the carbon atom C-4, which is, as that one discussed above, in ortho position to the carbonyl group, shows a different behaviour. First there is a downfield shift (**1a**→**1b**→**1c**), but for the next compound **1d** an upfield shift is observed. This can be explained in terms of two operating effects: the mesomeric effect of the carbonyl group, which leads to an upfield shift, if the torsional angle is increased, and a steric effect, which is largest for indanone **1a**, where the carbonyl group is coplanar with the C-H bond of carbon atom C-4. This interaction causes a large upfield shift[12], which decreases, if the torsional angle increases. Carbon atom C-2, on which only the mesomeric effect of the carbonyl group is acting, shows an upfield shift in going from **1a** to **1d**. This behaviour reflects, at least qualitatively, the increasing torsional angle of the carbonyl group with respect to the aromatic system (for the quantitative correlation see section d). The assignment of the sp^3-carbon atoms was performed in the same way as for the sp^2 carbon atoms. The CH_2-group in α-position to the carbonyl group has the largest shift. All other were assigned by inspection of their Δ_{LIS}-values. Finally it should be noted, that there is a complete agreement of the data for indanone **1** (δ_C- and Δ_{LIS}-values) with those reported in the literature[13].

b) ^1H NMR Spectra:

The 100 MHz ^1H NMR spectra of compounds **1a** - **1d** cannot be discussed according to first order rules. Apparently they are all of higher order. The individual CH_2-groups could be assigned with the aid of the Δ_{LIS} values (see Table 1).

c) UV Spectra

It is well known that UV data reflect the conjugation ability of chromophores[14]. So we recorded the UV spectra of the compounds **1a** - **1d** in dioxane. The following λ_{max} and ε-values for $\pi-\pi^*$transition were obtained: **1a**: λ_{max} = 240 nm, ε = 12240; **1b**: λ_{max} = 245 nm, ε = 10030; **1c**: λ_{max} = 243 nm, ε = 8700; **1d**: λ_{max} = 245 nm, ε = 5800. The UV estimations for the torsional angle ϕ by means of the widely used equation (3)[14] were obtained with accepting for ε_o the values for

$$\varepsilon = \varepsilon_o \cos^2\phi$$

benzaldehyde[15] which has a carbonyl group coplanar to the aromatic ring (see Table 2)

d) Conformations of the benzocycloalkanones **1a** - **1d**

As mentioned above the Lanthan-program requires as input the x,y,z coordinates of each nuclei of the subtrate. We calculated them with the MNDO-program of M.J.S. Dewar and W. Thiel[16]. The MNDO-method is known to give excellent results for the geometry of molecules[17]. With these coordinates and the "relative shifts" given in Table 1 the best positions of the Yb-ion was calculated, varying the torsional angle ϕ as well. The results are given in Table 2 and in the Fig. **2a** - **d**, which show the conformation of the complexes between the lanthanide ion and the benzocycloalkanones **1a** - **1d**. It turns out, that with increasing ring size the torsion of the CO-group increases with respect to the benzene ring. The agreement factors are in all cases less that 4%. The eight-membered ring compound **1d** has a slightly

*Table 2: Results of the calculation of the best position of the ytterbium ion in the complexes of compounds **1a** - **1d** and torsion angles obtained by other methods*

Compound	Distance Å	Agreement factor	Torsional angle of CO-group		
			LIS	MNDO	UV
1a	2.55	0.015	0°	0°	22°
1b	2.60	0.019	3°	13°	33°
1c	2.60	0.021	56°	64°	38°
1d	2.60	0.032	67°	79°	50°

INDANONE

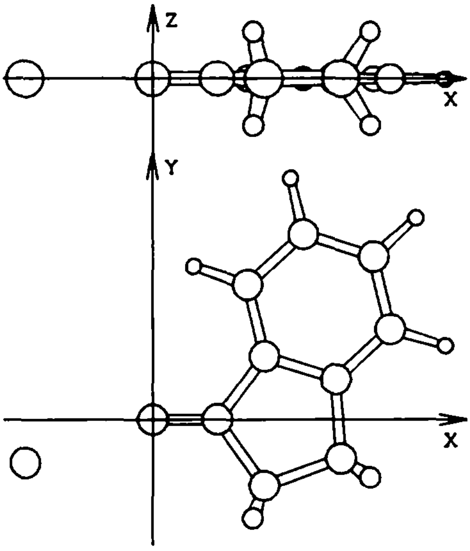


Fig. 2a

TETRALONE

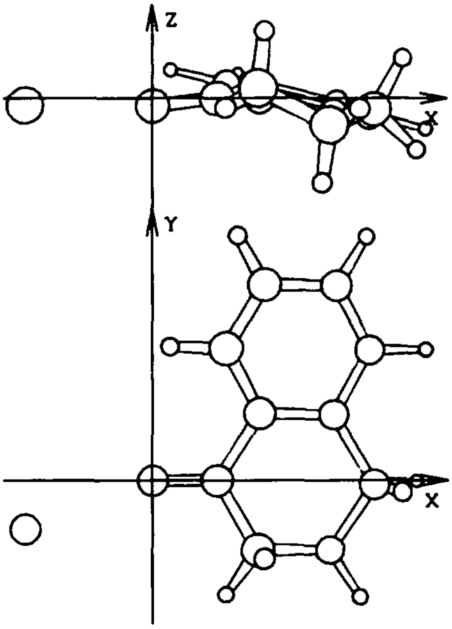


Fig. 2b

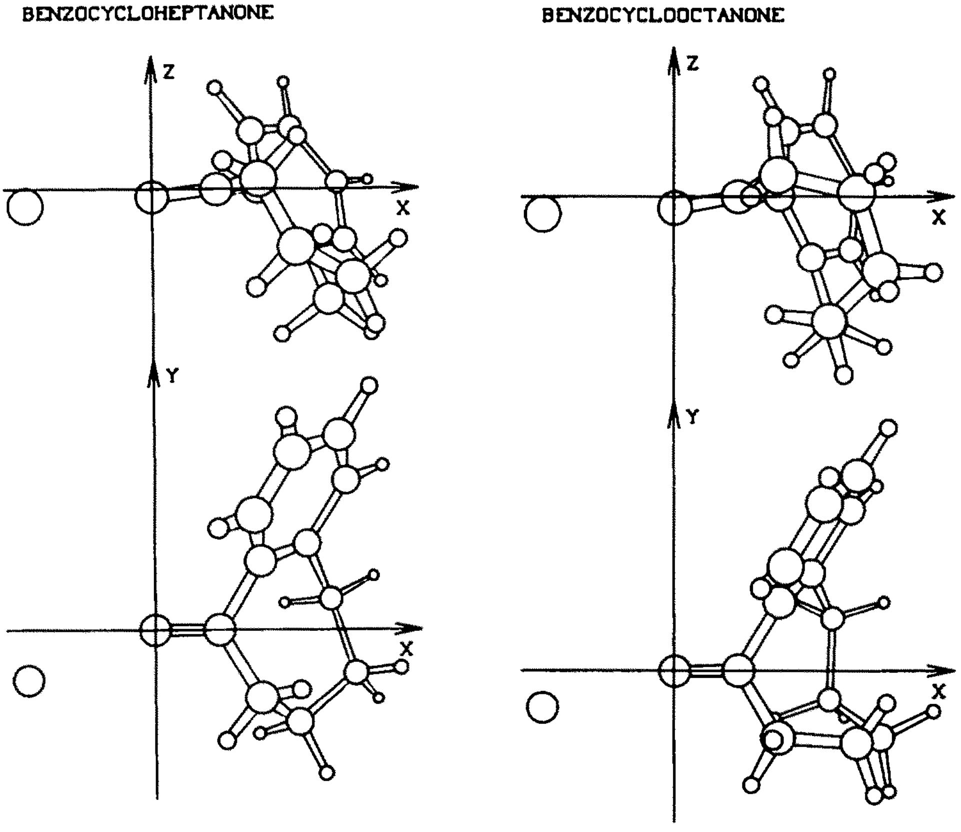


Fig. 2c

Fig. 2d

Figure 2a - d:
The prefered complex conformations of 1a, 1b, 1c and 1d obtained by the LIS method.

higher agreementfactor than the other compounds (0.032) and we believe that is due to the greater flexibility of this ring system. That means, that other conformations are in quielibrium with the conformation shown in Figure 2d but the agreement factor is still in an range, in which the shown conformation can be accepted to be the preferred one. Figure 3 shows the agreementfactor as a function of the torsional angle for compound 1d. The minimum is found at -12°, starting with the MNDO geometry (torsional/angle 79°, see Table 2). The torsional angles of the other compounds 1a, 1b, 1c were evaluated in the same way. Ringpuckering or ring inversion in the studied system is fast on the NMR-time scale. This was considered in the calculation by averaging the calculated induced shifts of the protons in each CH_2-group. By inspection of Figure 2a - d it turns out that the five- and six-membered ring are planar or nearly planar. The seven-membered ring 1c adopts a chair conformation, compound 1d boat-chair conformation. There is only a poor

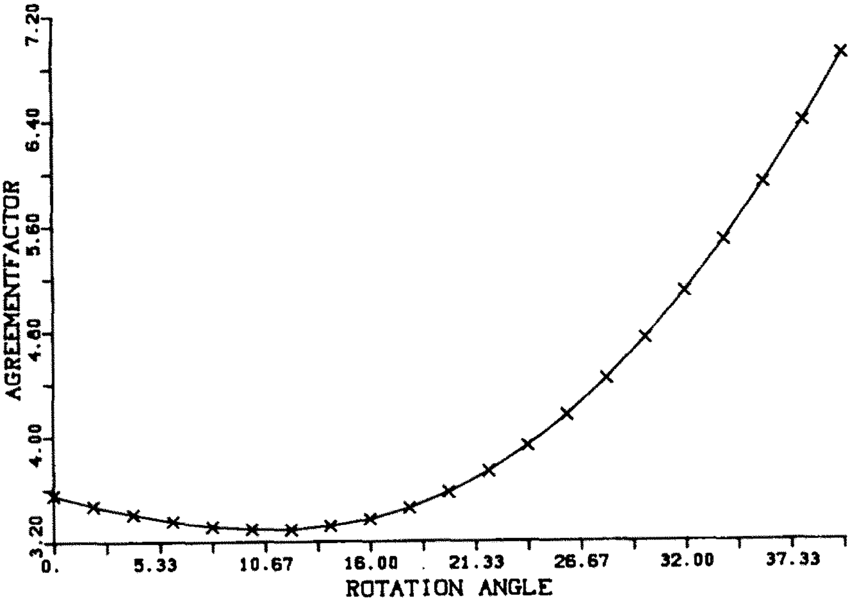


Fig. 6: Agreement factor versus torsional angle for compound 1d

agreement between the torsional angle values obtained by the LIS method and UV data (Table 2). To our opinion this is due to equation (3), which has some simplification like using ε of benzaldehyde for all the calculations. Equation (3) is used in ^{13}C NMR spectroscopy in a similar way like (4)[18].

$$\cos^2 \phi = \frac{\delta - \delta^{90^\circ}}{\delta^{0^\circ} - \delta^{90^\circ}} \qquad (4)$$

But there is again a poor linear correlation (correlation coefficient: 0.929; slope: 2.67; intercept: 131.13) between $\cos^2 \phi$ values obtained by the LIS-method and the chemical shifts δ_{C-2} (Table 1). δ^{0} and δ^{90° are the chemical shifts in compounds with a torsion angle of 0° and 90° respectively. The use of equations (3) and (4) implies that the observed effect (ε -, δ -values) arises solely from conjugation. This assumption is to simple to give reliable quantitative results.

e) Final remarks

The reliability of our estimated geometries (torsional angles ϕ) of benzoecycloalkanones 1a - 1d, presented in Table 3, is shown by the agreement with data from other techniques and related compounds. In fact, the data collected in Table 3 reveal good correlation with force-field calculations of the molecular geometries of exo-methylenebenzocycloalkenones 2[8], X-ray data of pyridino[b]cycloalkenones 3[19] and variations of twist angle (the angle between the lone pair and the aromatic π-orbitals) of aniline derivatives 4[20] estimated from the chemical shift of the para-carbon-atom. It is evident that the observed increase of torsional angle for those compounds in which $n > 6$ is chaused by the repulsive transannular H...H nonbonding interaction between hydrogens of the carbons 6...9 and 6...10, respectively. Attempts have been made to correlate rates of reactions involving hybridization changes from sp^3 to sp^2; i. e. solvolysis (namely generation of the corresponding carboniumion) of benzocycloalkeno chlorides 5[6] and chromium (VI)-

Table 3: Comparison of the torsional angles ∅ of compound **1**, **2**, **3** and **4** and relative rates of the selected reactions

Ring-size	**1**[a]	**2**[b]	**3**[c]	**4**[d]		Solvolysis of **5**[e]	Chromium (VI)-oxidation of **6**[f]
				R=H	R=Me		
5	0°	1.4°(0°)	1.1°	33°	32°	1016	14.8
6	3°	1.8°(0°)	1.4°	0°	13°	213(94.5)	23.4
7	56°	59.0°(60°)	32.1°	53°	58°	7.9(25.9)	4.6
8	67°	84.4°	64.8°	64°	80°	1.0(1.0)	1.0

[a] This work

[b] Force-field calculation[8]. Data in parentheses from PE spectroscopy[7]

[c] X-ray data[19]

[d] Estimated from variation in the ^{13}C chemical shift of the para-carbon atom[20]. For the discussion concerned to the unexpected value of **4a** see original work, ref.[20].

[e] In ethanol at 40°C[6b]. Data in parentheses represent relative rates in ethanol at 25°C [23].

[f] In 90% of acetic acid at 25°C [21]. The observed decreased value of **6a** was sufficiently discussed on the original work, ref.[21].

-oxidation of benzocycloalkenols **6**[21] (in this case the carbonyl character of the transition state has been demonstrated[22]). An examination of the data (collected in Table 3) reveals same regular behaviour between variation of the torsional angle ∅ and k_{rel}. This indicates that the benzocycloalkenes of type **1** and **2** are good model systems giving a background for the ground as well as for the transition state.

EXPERIMENTAL:

All compounds were purifield by distillation, chromatography on alumina (C_6H_6) and redistillation. Indanone (**1a**), tetralone (**1b**) and 5-6,7,8,9-tetrahydrobenzocycloheptanone (benzosuberone) (**1c**) were commercially available. 5-(6H)-6,7,8,9-Tetrahydrobenzocyclooctanone (**1d**) was prepared by the procedure of Huisgen and Rapp[24]. The UV spectra were recorded in dioxane using a Unicam SP 1700 spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained with a Jeol JNM MH-100 and a Varian XL-100/12 spectrometer. Commercially available Yb(fod)$_3$ was added in incremental quantities to the $CDCl_3$ solutions of the benzocycloalkanones **1a** - **1d**. After each addition the spectra were recorded. The linear regression analysis, the MNDO-calculation and the computations with the program Lanthan were performed at the computer center of the University of Gießen.

We thank the Hochschulrechenzentrum at Gießen for computer time.

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