was attached to the outflow of the detector. The GLC analyses were carried out at 85 °C with He as the carrier gas on a 6 ft × $^1/_8$ in. aluminum column packed with 50–80 mesh Porapak Q (Waters) installed in a Varian Aerograph Model 2700 chromatograph (thermal conductivity detection). Both HPLC and GLC quantitations were performed on a Hewlett-Packard Model 3390A reporting integrator. HPLC grade H_2O and MeCN (J. T. Baker) were used for all reactions. 1 (Aldrich) was recrystallized from EtOH, mp 76–77 °C (lit.[14a] mp 79.5–80 °C), and 2 was prepared by the literature procedure, bp 140–145 °C (ca. 20 mmHg) [lit.[14b] bp 174–175 °C (10 mmHg)].

HPLC Kinetic Measurements. Reactions were performed at room temperature (23 ± 1 °C) with the procedures given in the text. The extent of reaction was determined by comparison of the peak area for unreacted ester with that for ester in a blank.[4] Rate constants were obtained with least-squares analysis as described in the text, and the limits of error were estimated with the use of the Student's *t* test.[15] Even though the volume of the NaOH aliquot will increase as it moves through the column due to dilution by the eluant, the initial volume was used in calculations. It is likely, at least for runs where little or no MeCN was used in the equilibration, that ester was sorbed by the polymer at or near the head of the column, where minimal dilution of the aliquot has occurred. The volume of the line between the injector and column inlet was 0.02 mL. The results are summarized in Tables I and II. Comparable results for selected entries were obtained on a second, identical column.

The pump pressure did not exceed 2000 psi. The activation volume for the ^-OH-catalyzed hydrolysis of 1 in H_2O at 24.5 °C is -3 cm^3/mol.[16] At 2000 psi, k_ψ in H_2O would experience about a 2% increase compared to atmospheric pressure. Thus, it is unlikely that the lesser reactivity for 1 under the HPLC reaction conditions as compared to homogeneous conditions[5] resulted from the elevated pressure, and the same is assumed for **2**.

GLC Eluant Analyses. The procedures given in the text were used. The retention times for H_2O and MeCN were 1.0 and 5.8 min, respectively. The MeCN content was calculated from the peak area ratios for the sample and 5:95 (v/v) MeCN–H_2O. The results are summarized in Table III and Figure 3. With literature data[17] the pseudo-first-order rate constant for hydrolysis of MeCN in 0.5 M NaOH at 25 °C is calculated to be 7.7×10^{-9} s^{-1}. Thus, MeCN was effectively inert during the reaction procedure.

Acknowledgment is made to the U.S. Army Research Office for support of this research and to Dr. Warren T. Ford for helpful discussions.

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Conformation and Internal Mobility of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene Derivatives in Solution. Conformational Analysis of Highly Flexible Structures

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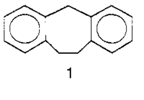
The ground-state conformations and internal mobilities of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**), of the 5-hydroxy derivative **2**, and of 10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one (**3**) as well as of their mono tricarbonylchromium complexes **1m**–**3m** are analyzed. It is shown that with use of the lanthanide induced shift method, together with empirical force-field calculations (**1**–**3**) and X-ray analysis (**1m**–**3m**), the conformations and interconversion modes of these highly flexible structures (with interconversion barriers less than 29 kJ mol^{-1}) can be analyzed. In solution, **2** and **3** adopt at room temperature a conformation similar to that of **1** and **3**, respectively, in the solid state. π-Complexation with tricarbonylchromium does not change the structure of the tricyclic system to a very significant degree, although the $Cr(CO)_3$ unit is located either on the convex (**1**, **3**) or on the concave (**2**) face of the ligand. In solution, a predominant conformation of **2m** with the tricarbonylchromium unit on the concave face is found.

This paper reports the results of a conformational analysis whose aim was to study the conformations of **1**–**3** in solution and to quantify the effects induced by π-complexation on the ground-state conformations and internal mobility of the tricyclic cycloheptene system. 5*H*-Dibenzo[*a*,*d*]cycloheptene (**4a**) and 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**) are common substructures of a variety of pharmacologically and clinically active compounds[1] such as protryptyline (**5**) or butaclamol (**6**). In order to investigate structure–activity relationships, systematic conformational analyses have been previously reported using X-ray spectroscopy,[2] quantum mechanical calculations,[1b] and other methods.[3] Models,[4] including



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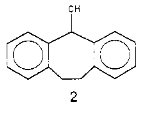

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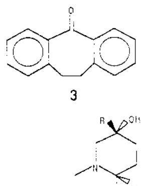

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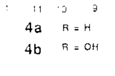
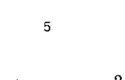


4a R = H
4b R = OH



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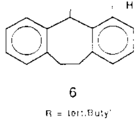

6
R = tert.Butyl

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Table I. Symmetry and Relative Steric Energy (kJ/mol) of the Transition-State Structures of 1–3

	ground state		transition state reached by mode			
	energy	symmetry	a		b	
1	0	C_1	19.7	C_2	16.9	C_s
2	0(2.2)[a]	C_1	25.2 (23.2)[b]	C_1	15.4 (14.0)[c]	C_1 (C_s)[d]
3	0	C_1	13.2	C_2	28.6	C_s

[a] The steric energy of **2** with the hydroxyl group pseudoaxial (**2**-ax) is set to zero. The relative steric energy of **2**-eq (the hydroxyl group pseudoequatorial) with respect to **2**-ax is given in parentheses. [b] Transition-state energy relative to the ground-state energy of **2**-ax and **2**-eq (in parentheses). [c] Relative steric energy of the transition-state structures connecting the two enantiomeric conformations of **2**-ax and **2**-eq (in parentheses). [d] Small deviations from a perfect C_s symmetry are caused by the hydroxyl hydrogen.

a geometrical model of the drug–receptor interaction, have been deduced.[5] Drug receptor binding is believed to involve several intermolecular interactions: π–π stacking of a drug–aromatic moiety with a receptor–aromatic amino acid residue, ionic interactions between a basic amino group (5–7 Å distant from the aromatic ring) and an acidic amino acid residue, and finally, hydrophobic and hydrophilic forces. This model has proved to be very powerful in designing new drugs,[5] but still relatively little is known about the conformations of such drugs in solution and about the influence of π-complexation on the preferred conformations.

We chose as our models the parent compound 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**), the alcohol **2**, and the ketone **3**. As π-complexation unit we used the tricarbonylchromium moiety. This sterically demanding unit certainly does not mimic an actual receptor site, but allows the study of the influence of nonbonding interactions, resulting from π-complexation, on the ligand conformations.

To determine the conformations in solution of the ligands **1**–**3** and their mono tricarbonylchromium complexes, we have used primarily the lanthanide induced shift (LIS) NMR technique, accompanied by empirical force-field calculations and X-ray structure analysis. We also compare our results with the already reported X-ray structures of **1**, **3**, and related compounds.

Results and Discussion

Empirical Force-Field Calculations. It is well established[6] that in solution seven-membered ring systems may adopt several distinct geometries of similar energy which can interconvert by different modes. To explore such conformational possibilities we resorted to empirical force-field calculations which have already proved to be highly successful in modelling the structures of hydrocarbons.[7] Using Allinger's MM2 force field and the program BIGSTRN-3 (for details on the calculations, see supplementary material), we found one asymmetric biplanar minimum-energy structure and two additional statiomers of C_2 and C_s symmetry (Figure 1) characterized as transition states for **1**. Very similar results were obtained for the ketone **3**. MMP2 calculations again gave a minimum-energy structure of C_1 symmetry as well as C_2 and C_s structures of higher energy (Table I). According to the MM2 calculations, the alcohol **2** adopts two minimum-energy conformations of C_1 symmetry, the hydroxyl group occupying either a pseudoequatorial or a pseudoaxial position. The pseudoaxial arrangement is calculated to be lower in energy by 2.2 kJ/mol. In addition, two transition states of C_1 and C_s symmetry respectively have been characterized (single partial maxima with one negative eigenvalue) for **2**.

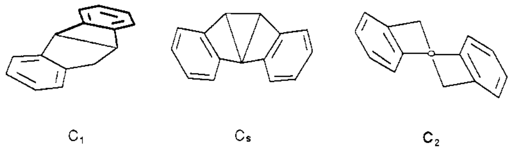

Figure 1. Ground-state and transition-state structures of the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene skeleton.

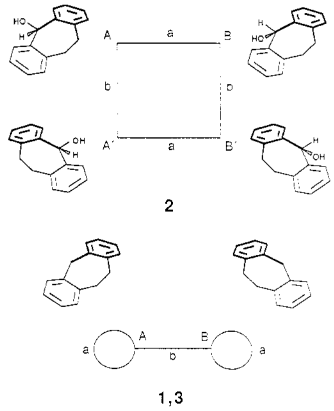

Figure 2. Interconversion scheme of **2** (top) and **1** and **3** (bottom).

Since both minimum-energy conformations for **2** are asymmetric, their enantiomeric conformations will also be part of any interconversion scheme. Indeed, eigenvector distortion of all transition states of **1** and **2** shows that there exist two independent interconversion modes: mode a associated with isomerization which interconverts diastereomeric conformations (**2**), or with homomerization (**1** and **3**) which involves the C_1 (**2**) and C_2 (**1**, **3**) symmetrical transition states; mode b associated with enantiomerization and a C_s-symmetrical transition state (**1**–**3**). A graphical representation is given in Figure 2. For example, assume that alcohol **2** is in conformation A with the hydroxyl group pseudoequatorial. Mode a will interconvert conformation A via a C_1-symmetrical transition state into the diastereomeric conformation B (with the hydroxyl group now pseudoaxial). B is interconverted by mode b into its enantiomer B′ (via a C_s-symmetrical transition state) and so on. However, the ground-state structure of **1** and by

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Table II. Conformational Parameters of 1–3, 1m–3m, and Related Structures

	$\alpha1^a$	$\alpha2^a$	$\alpha3^a$	$d1^b$	$d2^b$	$d3^b$
1 calcd	119.1	53.7	70.3	59.8	176.3	107.6
1	123.0	52.8	66.8	58.0	177.0	109.7
1m	133.1	43.0	62.1	71.9	163.6	110.6
2 calcd	115.9	56.9	73.0	56.1	-179.9	108.1
2m	119.4	49.6	69.3	61.1	175.4	104.6
3 calcd	128.2	40.1	60.1	70.1	164.8	107.2
3	145.2	14.1	39.6	81.8	143.7	119.0
3m	142.5	20.9	41.2	76.3	150.9	114.4
set A[c]	142.4	16.7	41.3	82.5	145.8	115.1
set B[d]	122.8 (4.8)	53.3 (10.2)	67.7 (6.1)	60.9 (4.2)	173.2 (5.3)	110.3 (2.5)

[a] Angles of intersection of planes A and B ($\alpha1$), A and C ($\alpha2$), B and C ($\alpha3$). A, B, C: best least-squares planes, defined by C4,C5,C6,C7,C8,C9 (A), C12,C13,C14,C15,C16,C17 (B), and C4,C17,C18 (C) for **1m**, **2m**, and set B and by C4,C17,C18,O4 (C) for **3m** and set A. The numbering system is given in Figure 5. [b] Dihedral angles: d1, C9,C10,C11,C12; d2, C8,C9,C10,C11; d3, C10,C11,C12,C13. [c] Mean values. [d] Mean values, standard deviations in parentheses.

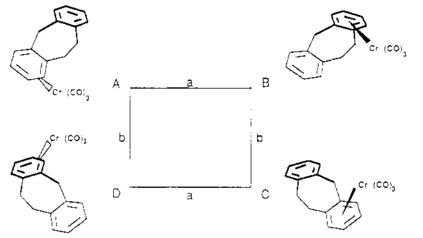

Figure 3. Interconversion scheme of one enantiomer of **1m**.

analogy of **3** will be interconverted by mode a into a structure that is indistuinguishable from the starting structure, but action of mode b again results in enantiomerization. The calculated interconversion barriers are given in Table I and are significantly lower than those of the related dibenzo[*a*,*d*]cycloheptene derivatives.[6b]

If asymmetric structures like **1** and **3** with four different (non symmetry equivalent) complexation sites form π-complexes, a maximum number of four diastereomeric complexes (pairs of enantiomers) may result. However, if interconversions by modes a and b are fast on a particular time scale, only one isomer (residual enantiomers[8]) is detectable under achiral conditions. Figure 3 shows the interconversion scheme of one enantiomer of the mono tricarbonylchromium complex **1m**.

Syntheses and X-ray Structures of the Mono Tricarbonylchromium Complexes 1m–3m. The mono tricarbonylchromium complexes **1m** and **3m** were synthesized by standard procedures,[9] and from each reaction mixtures was isolated only one racemic mono complex. Contrary to **1** and **3**, complexation of **2** should give at least two diastereomers, even if both interconversion modes are fast on a particular time scale. One diastereomer is characterized by a syn relationship of the tricarbonylchromium unit and the hydroxyl group whereas in the second diastereomer this relationship is anti.

However, complexation of **2** with hexacarbonylchromium gave exclusively one mono complex, which was shown to be the syn isomer (**2m**, Figure 4). The same isomer was formed by the reduction of complex **3m** with diborane in THF. By analogy with previous reports, it is plausible that in **2** the hydroxyl group acts as a directing group[10] whereas in **3** the reducing agent approaches the ketone carbonyl from a position opposite to the tricarbonyl unit,[11] both reactions giving the same isomer.

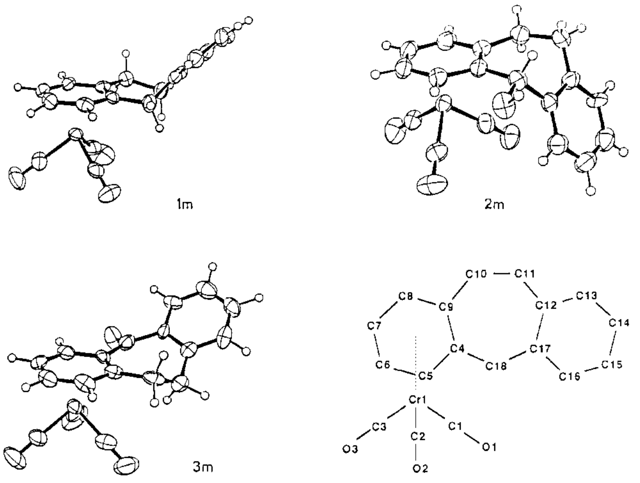

Figure 4. ORTEP plots and numbering scheme of the X-ray structures of **1m–3m**.

The structures of **1m–3m** were determined by X-ray crystallography. Crystals of **1m** and **3m** belong to the monoclinic system, space groups $P2_1/n$ and C_c, respectively. Crystals of **2m** are triclinic, space group $P\bar{1}$. ORTEP plots of **1m–3m** are shown in Figure 4. Final atomic coordinates and the hydrogen positions are given in supplementary material.

Inspection of Figure 4 shows that complexes **1m** and **3m** differ markedly from **2m**. In **1m** and **3m**, the tricarbonyl unit is located on the convex face of the ligand, but it is located on the concave face in **2m**. From steric arguments alone, one would expect the tricarbonyl unit to be located on the convex face of the molecule and thus minimize steric interactions. Complexation on concave faces (like tripticene) should cause considerable intramolecular strain.[12]

It is therefore surprising that **2m** adopts, at least in the solid state, a minimum-energy conformation with the tricarbonylchromium unit on the concave face, particularly since interconversion of this structure by mode a results in a conformation with the chromium tripod on the convex face.

In the next section the structures of **1m–3m** are analyzed in more detail and compared with the calculated structures of **1–3** as well as with the X-ray data of **1**, **3**, and related structures.

A search of the Cambridge Crystallographic Data Base reveals 25 structures with the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene skeleton as a substructure. For our analysis we selected only those structures in which the central seven-membered ring is not part of an additional ring system as, e.g., in butaclamol (**6**).[13] The remaining

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Table III. ^{1}H Chemical Shifts and Selected Coupling Constants of 1–3 and 1m–3m

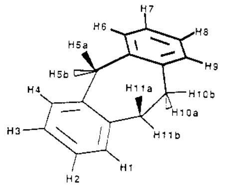
	chemical shifts,[a] δ													
	H1	H2	H3	H4	H6	H7	H8	H9	H5a	H5b	H10a	H10b	H11a	H11b
1	7.07–7.15								4.06		3.12			
2		7.16		7.41	7.41		7.16		5.94	2.28[f]	3.10	3.42	3.42	3.10
3	7.22	7.32	7.43	8.00	8.00	7.43	7.43	7.22			3.22			
1m	4.28[b]	4.38[c]	4.32[c]	4.52[b]	6.79[d]	6.96[e]	7.01[e]	6.83[d]	3.93	2.79	2.83	2.42	2.06	2.76
2m	4.01	4.58	4.12	5.33	7.25	7.18	7.21	6.85	5.33	1.64[f]	2.46	2.79	3.09	2.09
3m	4.03	4.63	4.32	6.20	7.94	6.94	7.00	6.65			2.63	2.39	2.19	2.41

	coupling constants, Hz					
	^2J		^3J			
	10a–10b	11a–11b	10a–11a	10a–11b	10b–11a	10b–11b
1m	−15.4	−16.2	8.8	4.3	4.4	10.4
2m[g]	−15.5	−16.3	12.2	4.8	4.8	5.0
3m	−15.0	−16.7	10.2	1.0	1.0	9.7

[a] Solvent $CDCl_3$ for **1–3**, C_6D_6 for **1m–3m**. [b–e] Assignments interchangeable. [f] Hydroxyl proton. [g] Coupling constants are identical within ±0.3 Hz if the solvent is $CDCl_3$.

13 structures fall into two classes: (i) structures related to **1**[14] with different substituents on an sp^3-hybridized C18 (the numbering system given in Figure 4 is used) and (ii) structures related to **3**[15] with different substituents on an sp^2-hybridized C18. (A list of REFCODEs is given in the Experimental Section.) To compare these structures, we used the following conformational parameters: α1–α3, the angles of intersection of planes A, B, and C; d1–d3, torsional angles. A definition of these parameters is given in Table II. Comparison of the conformational parameters shows that the structures of **3** and the closely related 2,3-dimethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (MXBSUB) differ significantly from all others in classes i and ii. For these two compounds the angle of intersection α1 (angle between the best planes A and B, defined by the benzene ring carbons) is about 20° larger than that of all other structures, whereas α2 and α3 are smaller by about 37° and 26°, respectively. It has been noted previously[15] that replacement of the carbonyl oxygen O4 in **3** by a =CHR substituent significantly reduces α1. This is also true for =NR[16] and even =MnR[17] substituents. Except for **3** and MXBSUB, the overall shape of the tricyclic system of all compounds of classes i and ii is very similar. Thus we may partition all structures into two sets: set A including **3** and MXBSUB and set B including all other structures (Table II).

The structures of **1m–3m** show some similarities: the benzene rings are almost planar with a maximum deviation from the least-squares planes of 0.01 Å. The chromium tripod is bonded to that benzene ring which defines plane A (Table II) and the torsional angle d1 (in **7**, plane A is defined by the benzene ring with protons 1–4). The carbonyls of the $Cr(CO)_3$ unit adopt a conformation with one carbonyl located above the bond vector C9–C10. The deviations from the staggered conformation as described by the dihedral angle of two vectors, one pointing from the benzene ring centroid to C9 and the other one pointing from chromium to the carbonyl carbon, are 19.3° for **1m**, 4.6° for **2m**, and 16.5° for **3m**.



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The conformational properties of the individual compounds **1m–3m** and **1–3** are listed in Table II together with the calculated data for **1–3** as well as the mean values for set A and set B. The X-ray data for **3m**, **3**, and set A are almost identical. In addition, the structure of **2m** is also very similar to those of **1** and set B and to the calculated structures of **1** and **2**. Apparently, complexation of **3** and **2** has no influence on the conformation of the tricyclic system, despite the fact that the $Cr(CO)_3$ unit is located on the convex face of **3** but on the concave face of **2**. However, the structure of **1m** deviates to some degree from that of **1** as reflected, e.g., by enhanced values of d1 and α1 (Table II). One reason for this distortion might be that complexation of **1** on the convex face results in nonbonding interaction (repulsion) between one tripod carbonyl and proton H11b (**7**). Increase of d1 and consequently of α1 minimizes such an interaction. It should be noted, however, that this distortion in the solid state is not reflected by the NMR data (see below). In summary, in the solid state the influence of π-complexation with $Cr(CO)_3$ on the overall structure of the tricyclic system is relatively small. Moreover, the calculated data for **1** and **2** are in good overall agreement with the X-ray structures, whereas the MMP2 calculations for **3** deviate significantly from the X-ray data and will be discussed below.

Conformation and Internal Mobility of 1–3 and 1m–3m in Solution. The analysis is based on proton NMR spectroscopy, especially by the lanthanide induced shift (LIS) technique.[18] Table III lists chemical shifts and selected coupling constants for **1–3** and **1m–3m**. The proton numbering is given in formula **7**. Shift assignments for the bridge protons H10a, H10b, H11a, and H11b are based primarily on NOE measurements and on the assumption that the geminal coupling constants of protons next to the complexed aryl ring (H11a, H11b) are more negative than those for protons next to the uncomplexed ring (H10a, H10b). The coupling constants for these bridge protons were calculated by standard software (see Experimental Section).

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According to our calculations, the ligands **1**–**3** are expected to adopt ground-state conformations of C_1 symmetry which interconvert rapidly by modes a and b (Figure 2), resulting in time-averaged NMR spectra in solution at room temperature. Furthermore, both diastereomers of **2** should be present to a significant amount. By analogy, the diastereomers of **1m**–**3m** are also expected to interconvert rapidly in solution (Figure 3), provided that complexation does not enhance the interconversion barriers to such a degree that the interconversion becomes slow on the NMR time scale. This assumption is based on previous studies showing a maximum experimentally observed change in rotational barriers on complexation of +32 kJ/mol.[19]

The observation of single $-CH_2CH_2-$ bridge proton NMR spectra for **1** and **3** indicates that both interconversion mechanisms are fast as the action of only one mode should result in apparent C_2 (a) or C_s (b) molecular symmetry, giving an AA′BB′ spin system. Symmetry arguments do not give an unequivocal answer for the alcohol **2**. An AA′BB′ system is observed for the $-CH_2CH_2-$ bridge protons of this compound. Mode a will result in an apparent C_1 structure and can therefore be excluded. However, mode b, as well as mode b followed by a, will result in the observed apparent C_s symmetry. Hence, these two latter possibilities cannot be distinguished by symmetry arguments.

For complexes **1m**–**3m**, any rapid interconversion still results in an apparent C_1 molecular symmetry, giving an ABCD spin system for the $-CH_2CH_2-$ bridge protons. However, to a first approximation modes a and b can be separated experimentally by the following procedure: As already noted, mode a interconverts ligands **1** and **3** into homomers. Thus the geometry of the starting and the final structure will be exactly the same. Nevertheless, this process causes an NMR exchange phenomenon. The ABCD spin system of the $-CH_2CH_2-$ bridge protons changes to an AA′BB′ system, since the axial protons H10a and H11a as well as the equatorial protons H10b and H11b become symmetry equivalent. This results in averaging of all coupling constants except for the vicinal ax–ax ($J_{H10a,H11a}$) and eq–eq ($J_{H10b,H11b}$) constants. It follows that these coupling constants do not depend on mode a and are only affected by mode b. This conclusion is more nearly valid for the homomerization process (**1** and **3**) but not for the interconversion of diastereomers like **2** and **1m**–**3m**. However, the X-ray structures of **1m**–**3m** show that neither complexation on the concave face nor complexation on the convex face changes the ligand conformations to a very significant degree, and it is reasonable to assume that to a first approximation the vicinal ax–ax and eq–eq coupling constants of the $-CH_2CH_2-$ protons remain effectively independent of mode a. Thus, spin-system analysis of the observed ABCD systems of **1m**–**3m** supplies information about interconversions caused by mode b (flips of the $-CH_2CH_2-$ bridge). These results are listed in Table III and will be discussed in detail together with the results of the LIS calculations. Internal mobility caused by modes a and b as well as more detailed structural information can be deduced from the LIS data.

However, before we discuss the LIS results for compounds **2**, **2m** and **3**, **3m** in detail, some general comments on the use of the LIS method for flexible structures seem necessary. Several problems may arise in the LIS simulation of flexible structures, depending on the course of the interconvesion: (i) homomerization or enantiomerization and (ii) interconversion of diastereomers.

(i) In the LIS simulation, the overall molecular symmetry caused by possible interconversion modes must be reflected in the substrate–lanthanide complex as well. The usual way to allow for flexibility is to average the so-called geometrical factors of corresponding atom positions of all possible conformers.

The geometrical factors, derived from the McConnell–Robertson equation,[20] represent the magnetic field strength of the Ln(III) point dipole at particular (usually proton) positions within the complex and are directly proportional to the experimental LIS.[21] The position of the coordinating Ln(III) ion is optimized in the computational procedure to give the best fit when the geometrical factors for the proton positions are scaled to the experimental LIS by a least-squares method (the quality of the fit is usually given by the crystallographic *R* factor,[22,23] with values <10 representing reasonable fits). In cases where there is only one possible substrate geometry with a rigid structure, this is no problem, and the fit may be further refined by reasonable variations in the suggested substrate geometry. For flexible molecules, however, all possible molecular geometries must be included in the calculation. This is a minor problem if the interconverion process produces either identical or enantiomeric structures since then all possible geometries are equally populated and no additional adjustable parameters must be introduced into the LIS calculation. The simplest way to simulate LIS data for this type of compound (e.g., **3** with interconversion modes a and b) is to average the geometrical factors of corresponding atom positions *before* scaling to the experimental LIS (which are of course also averaged values on the NMR time scale).

Note: If an interconversion process produces magnetically equivalent atom positions in *homomers* and/or *enantiomers*, these (equal) LIS values are simulated by *averaging of corresponding geometrical factors* in the calculation.

The time-averaged symmetries of the substrate and the substrate–lanthanide complex are thus assumed to be the same. Most LIS programs include this averaging option.[18]

(ii) If an interconversion process results in a diastereomeric structure (for instance, compound **2** with interconversion mode a), matters are more complicated. Then the expected LIS values (or geometrical factors) of two different molecular geometries must be calculated separately and mixed for corresponding atoms according to the population ratios of the two isomeric structures. If the flexible part of the substrate molecule is far away from the complexing site, this still represents a minor factor in the calculation, since only one further adjustable (population) parameter has to be introduced for each isomer in the LIS calculation. In our case, where the coordinating OH group is involved directly in the interconversion, we expect two further complications: (1) the complexation constants are usually not known for the individual isomeric complexes, and therefore, the population ratios obtained in the best fit of the mixing procedure can only be used as estimations of the true population ratios (e.g., if isomer X coordinates better than Y to a shift reagent, the population of X will be overestimated in the fit); (2) the Ln(III) positions in both interconverting isomers are expected to be different due to an entirely different environment in the vicinity of

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Table IV. Experimental and Calculated Lanthanide-Induced Shifts of 2/2m and 3/3m[a]

	2				2m						
		calcd				calcd		3		3m	
no.	exptl	ps-eq	ps-ax	eq:ax 64:36	exptl	ps-eq	eq:ax 97:3	exptl	calcd[c]	exptl	calcd[c]
1	0.25	0.19	0.22	0.24	0.20[d]	0.18	0.19	0.16	0.15	0.17[d]	0.18
2	0.20	0.15	0.13	0.17	0.14[d]	0.13	0.13	0.08	0.06	0.13[d]	0.13
3	0.20	0.20	0.13	0.21	0.14[d]	0.15	0.15	0.08	0.06	0.14[d]	0.15
4	1.00	1.12	0.34	1.00	1.00[d]	1.00	0.98	1.00	1.01	1.00[d]	1.00
5	0.77		–[e]		1.28		–[e]	–	–	–	–
6	1.00	1.12	0.34	1.00	0.82	0.85	0.83	1.00	1.01	0.80	0.78
7	0.20	0.20	0.13	0.21	0.13	0.14	0.14	0.08	0.06	–0.01	–0.01
8	0.20	0.15	0.13	0.17	0.13	0.11	0.11	0.08	0.06	0.03	0.03
9	0.25	0.19	0.22	0.24	0.20	0.17	0.17	0.16	0.15	0.12	0.11
10a	0.36	0.25	0.40	0.36	ax: 0.27	0.31	0.32	0.28	0.27	0.26	0.26[f]
10b	0.58	0.30	0.85	0.59	eq: 0.23	0.20	0.22	0.28	0.27	0.26	0.26[f]
11a	0.58	0.30	0.85	0.59	ax: 0.33[d]	0.23	0.32	0.28	0.27	0.25[d]	0.24[g]
11b	0.36	0.25	0.40	0.36	eq: 0.22[d]	0.21	0.23	0.28	0.27	0.25[d]	0.24[g]
R^h		26%	57%	2.7%		8.6%	4.9%		3.2%		1.9%

[a] Eu(fod)$_3$; for better comparison, relative values are listed, normalized to a value of 1.00 for H4 (ortho H); the numbering of the protons corresponds to formula **7**. [b] Identical with the X-ray structure. [c] TSM; the values for the OSM were very similar (see supplementary material). [d] Protons of the benchrotrene unit or CH$_2$ next to benchrotrene. [e] Not included in the fit (possibly contact shifts[18,28]). [f] Individual values 0.35 for 10a and 0.18 for 10b. [g] Individual values 0.27 for 11a and 0.21 for 11b. [h] For further details of the calculation (lanthanide ion positions, population ratios in the TSM, etc.), see supplementary material.

the complexing sites (for instance, the pseudoequatorial and pseudoaxial isomers of compound **2**, interconverting by mode a). In this case some knowledge of the complexing behavior of particular coordinating groups is required to predict expected Ln(III) positions and the expected geometrical factors (or LIS values) of individual isomeric conformers of the substrate molecule. For OH as a coordinating group, a simple geometrical model for the shift reagent "cavity" which gives good results for the prediction of complex geometries for a series of primary, secondary, and tertiary alcohols[24] has been described.

Note: If an interconversion process produces *diastereomers*, the expected *LIS values* (or geometrical factors) *of the isomers have to be mixed in proper population ratios.* The individual isomers may of course again possess a time-averaged structure of high overall symmetry in solution (e.g., interconversion mode b for **2**) which has to be accounted for by averaging the corresponding geometrical factors within the LIS calculation in the single isomers (vide supra, i).

On the basis of the principles outlined above, the LIS method may be used for the conformational analysis of molecular geometries of flexible structures if a limited number of conformers is present in solution. The method is therefore not suited for molecules with pseudorotational behavior, for example. In special cases, a change of substrate conformation may occur upon coordination with the shift reagent; however, this should be clearly indicated by changes in the coupling constants (which was not observed in our case). Any structural information obtained from independent methods should be used in the proposed substrate geometry. This includes the following: results from force-field calculations; X-ray structural analysis of the most favored conformer(s) in the solid state; information on magnetically equivalent proton positions on the NMR time scale, spin system simulation; NOE experiments; etc. In favorable circumstances, the LIS method may either help to solve stereochemical problems of molecules with limited flexibility or at least allow a decision on whether or not some model assumptions about interconversion systems are valid.

2m. The structure derived from the X-ray data—with the chromium tripod on the concave face—was also found to be strongly favored in solution. Using the assignments of the ^{1}H NMR resonances obtained from unambiguous decoupling experiments and NOE measurements, we obtained the best LIS fit for a geometry with OH in a pseudoequatorial position and with both methylene carbon atoms in the plane of the Cr(CO)$_3$-complexed aromatic ring (syn isomer, R = 8.6%). The other possibility with both methylene carbon atoms in the plane of the uncomplexed aromatic ring (a product of interconversion mode b) gave only a poor fit (R = 17%). For the isomeric structure with pseudoaxial OH (a product of interconversion mode a), an R factor of less than 35% was unobtainable. However, it is of interest to note that in the first case the largest difference between experimental and calculated LIS values is observed for the axial methylene proton close to the benchrotrene ring (H11a, **7**). Here, the calculated value is too low. Allowing interconversion by mode a brings this proton very close to the hydroxyl group, which now becomes axially orientated. Mixing 3% of this conformer with 97% of the X-ray derived geometry lowers the R factor in the LIS calculation from 8.6% to 4.9% (Table IV). That there might be some of the OH pseudoaxial conformer present in solution is further supported by the fact that upon irradiation at H1 the NOE effect is clearly stronger for the equatorial proton H11b than for the axial proton H11a. Both these experimental findings are consistent with a conformational equilibrium in solution with the presence of a small percentage of a conformer with a pseudoaxial hydroxyl group. H11a may thus on average be closer to OH (explaining the LIS data) while on the other hand the average distance H1–H11a increases since both effects are the result of the same geometry change in the molecule. (Axial and equatorial H refer to the assignment in the predominant conformer **7** which is identical with that found in the X-ray structure and which has the chromium tripod located on the benzene ring with protons H1–H4).

The fact that one diastereomer predominates in solution is also consistent with the spin-system analysis for protons H10 and H11. For an ABCD system resulting from a molecule with the torsional angle d1 = 61° (Table II), one large (ax–ax) and three smaller vicinal coupling constants are expected, in agreement with the experimental findings (Table III).

2. In the case of carbinol ligand **2** (conversion scheme Figure 2), neither the geometry with a pseudoequatorial OH group (A + A′ in Figure 2) nor that with a pseudoaxial

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OH (B + B′) gave a reasonable LIS fit. The best R factor obtained for the former case (LIS calculation of A + A′ by averaging of corresponding geometrical factors) was 26%, for the latter case 57% (Table IV). However, mixing both possible conformers gave a fit with $R = 2.7\%$ at a population ratio of 64% pseudoequatorial OH (A + A′) to 36% pseudoaxial OH (B + B′). It should be emphasized that this is only an estimation of populations since the complexing abilities of both isomers and the geometries of the two individual substrate–reagent complexes are not exactly known. However, it may be safely concluded from the LIS calculations that *both* conformers must play an important role in a conformational equilibrium in solution. This is consistent with the empirical force-field calculation, showing only a small difference in steric energy (2.2 kJ/mol) for both diastereomers.

3m. In the LIS calculations for this compound, two computational models were used. In the simpler one-site model, which allowed for one average lanthanide ion position in the substrate–reagent complex,[25] the fit using the X-ray-derived proton positions gave $R = 4.6\%$. The Eu(III) position was found to avoid both nonbonded interactions with the two aromatic ortho H adjacent to the carbonyl group [Eu(III) at the "convex side" of the saddle-like structure] and steric interaction with the $Cr(CO)_3$ moiety (see supplementary material). This result is even more apparent in the two-site model, which assumed two possible Eu(III) positions corresponding to the two free electron pairs in carbonyl compounds.[26,27] The best fit obtained was characterized by $R = 2.5\%$ at a population ratio of 85% for the Eu(III) position close to the benzene ring to only 15% close to the benchrotrene ring (Table IV). The usual planar arrangement $>C{=}O\cdots Eu$ gave a poor fit ($R = 22\%$), the best fit being obtained for a torsional $C_{aromatic}{-}C{=}O\cdots Eu$ angle of 40° [Eu(III) 40° off the $>C{=}O$ plane, away from the benzene ortho H; the calculation is rather less sensitive to the Eu(III) torsional angle of the second (less dominant) Eu position]. One requirement for a good fit of the experimental LIS data of the methylene protons was the averaging of the geometrical factors of the two protons within the individual methylene groups (H10a/H10b and H11a/H11b). This corresponds to interconversion modes a + b. All experimental methylene LIS values are within 25 and 26 units in the normalized scale (Table IV). Without averaging, values of 18, 21, 27, and 35 were expected, whereas averaging results in calculated values of 24 for the methylene protons H11 and 26 for H12 (Table IV). The saddle-like X-ray structure is therefore compatible with the LIS results in solution if one allows interconversions a + b.

This is in full agreement with the spin-system analysis (Table III). With a torsional angle d1 = 76° (Table II) the ax–eq (${}^3J_{H10a,H11b}$, ${}^3J_{H10b,H11a}$) coupling constants are expected to become significantly smaller than for **2m**, whereas the eq–eq coupling constant will be enhanced. In addition, mode b averages the ax–ax and eq–eq as well as the two ax–eq coupling constants, as observed.

3. The X-ray structure[15] used for the proton positions in the LIS calculation is again characterized by a saddle-like geometry (angle between the aromatic planes 145.2°). However, the simple ${}^1H$ NMR as well as the LIS data indicate that the average geometry in solution must be of higher symmetry (C_{2v}) due to interconversion modes a and b (homomers and enantiomers). Averaging proper geometrical factors for corresponding positions, the R factors are 2.2% in the one-site carbonyl LIS model (OSM) and 3.2% in the two-site model [TSM, 50% population for both Eu(III) positions]. On the basis of the geometry derived from the force-field calculation (angle between the aromatic planes 128.2°), the LIS simulation was less successful (R factor of 4.1% for the OSM and 5.6% for the TSM). Therefore, the conformation of **3** in solution seems to be similar to that observed in the solid state.

Since the structures of **3** and **3m** are similar in both the solid state and solution but significantly different from the calculated structure (**3**, Table II), MMP2 calculations for compounds of type **3** are expected to be less accurate than MM2 calculations for compounds related to **1**. Nevertheless, the calculated transition-state energies (Table I) should be good estimates.

1m. For **1m** no LIS data are available, but an ABCD spin system analysis of the methylene proton subspectrum was possible. On the basis of the X-ray structure of **1m** with a torsion angle d1 = 72°, the ax–eq coupling constants should be similar to those of **3m** (Table III). However, the experimental ax–eq coupling constants are almost identical with those of **2m**, indicating that in solution the structure of the tricyclic system differs less from **1** and **2** than in the solid state. The averaged ax–ax and eq–eq coupling constants are the result of the action of mode b. The interconversion by mode b results also in an Overhauser enhancement of protons H11b and H10a if H5b is irradiated. For **1m** we have no conclusive data showing the presence or absence of interconversion by mode a.

Summary

From empirical force-field calculations, X-ray structure analysis, and NMR studies, we find that in solution compounds **1**–**3** interconvert rapidly by two distinct interconversion modes with calculated transition-state energies smaller than 29 kJ/mol. As deduced from lanthanide induced shift (LIS) studies, the ground-state structure of **3** in solution agrees well with the solid-state structure and to a lesser degree with the MMP2 calculations. LIS calculations also show that both diastereomers of **2** (the OH group pseudoequatorial or pseudoaxial) must play an important role in the conformational equilibrium. This differs from the case of **4b**, where as predominant conformation with the OH pseudoaxial has been found in solution.[3c]

The effects of π-complexation on the ground-state structures of **2** and **3** are small in solution as well as in the solid state. In the solid state, the structure of **1m** does show some deviation from that of **1**, but in solution, the conformation of its tricyclic system is apparently similar to the solid-state structure of **1**. The most striking observation is, however, that in the ground-state conformations the $Cr(CO)_3$ unit can be located either on the concave (**2m**) or on the convex (**1m**, **3m**) face of the tricyclic system both in the solid state and in solution.

The influence of complexation on the internal mobility differs for **2m** as compared to **1m** and **3m**. For **1m** and **3m**, no predominant conformation in solution was found, and hence, all four diastereomers of **3m** must be present to a significant amount in a conformational equilibrium. For **1m**, interconversion by one mode can be shown conclusively although the other mode cannot be excluded and may also be present. At least two diastereomers are therefore present in equilibrium. In contrast, for **2m**, a single conformation, almost identical with that found in the solid state [with the $Cr(CO)_3$ unit on the concave face of the tricyclic system and the OH pseudoequatorial] predominates in solution. The LIS data show that at most

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Table V. Crystallographic Data of 1m-3m

	1m	2m	3m
lattice constants			
a, pm	1073.9 (7)	744.8 (1)	2551.1 (4)
b, pm	825.1 (5)	918.9 (2)	827.7 (1)
c, pm	1704.6 (19)	1262.9 (2)	1553.0 (2)
α, deg	90.00 (4)	97.01 (1)	90.00 (1)
β, deg	78.09 (4)	104.69 (1)	110.97 (1)
γ, deg	90.00 (4)	112.35 (1)	90.00 (1)
space group	$P2_1/n$	$P\bar{1}$	C_c
molecules/unit cell	4	2	4
calcd density, g cm^{-3}	1.484	1.53	1.495
exptl density, g cm^{-3}	1.483	-	1.493
cryst dimens, mm^3	0.3 × 0.3 × 0.05	0.38 × 0.35 × 0.25	0.25 × 0.25 × 0.3
collected data	2232	2859	4726
2θ(max), deg	45	50	45
unique data	2153	2632	2192
obsd data $F > 4\sigma(F)$	1299	2467[a]	1188
largest peak in final diff Fourier	0.11	0.26	0.15
final residual *R*, %	5.3	3.0	8.2
R_w, %	4.8	3.4	5.6

[a] $F > 3\sigma(F)$.

about 5% of a second diastereomer (with OH pseudoaxial) is present in a conformational equilibrium.

We conclude that a combination of the lanthanide induced shift method combined with other methods for structure analysis, such as empirical or semiempirical calculations and X-ray analysis, can give information concerning the structures of highly flexible and complex molecules in solution under room-temperature conditions. We are therefore confident that by using these combined methods other flexible structures like the related pharmacologically active compounds can be studied.

Experimental Section

Proton NMR spectra were recorded with a Bruker WM-250 spectrometer, operating at 250.13 MHz. The Bruker-supplied program PANIC was used for spin-system analyses. Mass spectra were recorded with a MAT-CH7 instrument. Melting points were determined on a Kofler microscope and are uncorrected. Medium-pressure chromatography was carried out at a pressure of 3 bar using silica gel (Merck 60, 0.04–0.006).

Compounds **1–3** were purchased from Aldrich and used without further purification.

Complexation of Ligands 1–3 to Tricarbonyl(η^6-aryl)chromium Complexes: General Procedure. The ligand was refluxed with a 4-fold molar amount of $Cr(CO)_6$ in dry di-*n*-butyl ether/heptane (2:1) (20 mL for 1 mmol of ligand) for 48 h. The reaction mixture was filtered, the solvent and excess of $Cr(CO)_6$ were removed under reduced pressure, and the residue was purified by chromatography (MPLC) on silica gel.

Complexation of 1. Complexation of 1 g (5.1 mmol) of **1** gave 0.95 g (57%) of **1m**, mp 124 °C (chromatography: eluent, petroleum ether/15% ethyl acetate): mass spectrum, *m/e* 330 (M^+), 274, 246, 52 (100); ^1H NMR spectrum (Table III).

Complexation of 2. Complexation of 1 g (4.8 mmol) of **2** gave 0.81 g (49%) of **2m**, mp 134–135 °C (chromatography: eluent, petroleum ether/30% ethyl acetate): mass spectrum, *m/e* 346 (M^+), 262, 244, 210, 192; ^1H NMR spectrum (Table III).

Complexation of 3. Complexation of 1 g (4.8 mmol) of **3** gave 0.97 g (59%) of **3m**, mp 135–137 °C (chromatography: eluent, petroleum ether/30% ethyl acetate): mass spectrum, *m/e* 344 (M^+), 288, 260, 52 (100); ^1H NMR spectrum (Table III).

Crystallography. The intensity data of **1m** and **3m** were measured at room temperature on a modified four-circle STOE diffractometer, the data of **2m** on a Nicolet R3m diffractometer using graphite-monochromated Mo Kα irradiation (λ = 0.71069 Å). The structures were solved either by the heavy-atom method (**2m**) or by direct methods (**1m**, **3m**).[29] For details, see supplementary material. Crystal data and structural parameters are given in Table V.

Empirical Force-Field Calculations. The structures of **3** were minimized with use of the original MMP2[30] program. For **1** and **2** the program BIGSTRN-3[31] with the MM2 force field was used.

Cambridge Crystallographic Data Base Search. The REFCODEs of the retrieved 13 hits are as follows: HBZCHP,[14] BERWOK,[32] CIKVEX,[33] CIKVIB,[33] BCHMPY,[34] PIRHMB,[35] BMBZCH,[36] BUTCUO,[17] CERJIS,[16] CERJIS10,[37] CERJOY,[16] BUFDOV,[15] MXBSUB.[38]

Lanthanide-Induced Shifts. The LIS values were determined by adding increasing amounts of tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato]europium (Merck) to a solution of 5–10 mg of substrate in 0.5 mL of $CDCl_3$ (**2**, **2m**, **3**) or C_6D_6 (**3m**). The spectra were recorded at four to six different reagent concentrations up to a molar ratio of reagent:substrate = 0.7; the LIS for the 1:1 complex were obtained by extrapolation. However, in Table IV relative values are listed to allow a better comparison of data within the series; factors of 5.9 for **2**, 0.35 for **2m**, 10.0 for **3**, and 6.1 for **3m** may be used to convert the relative values of Table IV into the usually given so-called 1:1 values in parts per million (e.g., 5.9 ppm for H4 of **2** and only 0.35 ppm for **2m**). As usual, the Cr complexes show a weaker complexing ability in comparison with their ligands[39] (however, one should be careful in quantitative interpretations of complex formation constants, since for weakly complexing substrates the values obtained by extrapolation to the 1:1 value are not identical with the true lanthanide-induced shifts of the 1:1 substrate–reagent complex[18,40]). For the LIS calculations, a modified program of

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the PDIGM type[21,22] was used (written in BASIC for an Apple Macintosh PC).

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Registry No. 1, 833-48-7; **1m**, 75969-44-7; **2**, 1210-34-0; **2m**, 114818-63-2; **3**, 1210-35-1; **3m**, 86324-68-7.

Supplementary Material Available: Experimental details on crystallography, empirical force-field calculations, the Cambridge Data Base search, and the lanthanide induced shift experiments, the final atomic coordinates and isotropic thermal parameters (Table VI), and the proton coordinates (Table VII) (8 pages). Ordering information is given on any current masthead page.

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Response of Tricyclo[5.5.0.0^{2,8}]dodecatetraene, Tricyclo[5.3.0.0^{2,8}]deca-3,5,9-triene, and 9,10-Dimethylenetricyclo[5.3.0.0^{2,8}]deca-3,5-diene to Thermal and Photochemical Activation

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The light-sensitive tetraene **1** is relatively stable at room temperature in diluted form. Dimerization/polymerization does, however, occur slowly when **1** is stored in neat condition. At temperatures in the vicinity of 100 °C, **1** rearranges smoothly to Kukla's hydrocarbon (**7**) by a concerted [1,3] carbon migration. Irradiation with long wavelength light (366 nm) also leads to **7** and, to a lesser extent, bicyclo[6.4.0]pentaene (**12**). In contrast, **2** rearranges at 20 °C and below via isobullvalene (**14**) to lumibullvalene (**15**). Appropriate deuterium labeling has shown this rearrangement to proceed via biradical **18**. When heated to 80 °C in benzene, **3** undergoes smooth first-order isomerization to **22** with a half-life of 65 min. The underlying causes of this divergent behavior are discussed in terms of orbital symmetry allowedness.

As in spiroconjugated systems, the level and consequences of through-bond interaction between two π-ribbons linked orthogonally across a cyclobutane ring is intimately related to the total number of electrons involved.[2] Whereas the split between the first two photoelectron (PE) bands of **1**[3,4] amounts to 1.44 eV and points to a strong through-bond interaction between the cyclobutane relay and the peripheral π-systems,[5] the PE spectra recorded for **2**[4,6] reveal a lack of interaction between its two olefinic fragments. The PE spectrum of **3**[4,7] has an appearance similar to that of **1**.


1


2


3

Herein, we report on the varied responses of **1–3** to heat and light. Tricyclo[3.3.0.0^{2,6}]octa-3,7-diene (**4**), the smallest member of this series earlier synthesized by Meinwald[8a] and by Zimmerman,[9a] exhibits in its UV spectrum a bathochromic shift to 300 nm (contrast the λ_{max} for **6** at 250 nm)[8b] that has invited theoretical analysis.[2,10] The notable thermal lability of **4** (estimated $t_{1/2}$ of 10 min at room temperature)[9b] and its ready isomerization to semibullvalene (**5**) have precluded PE analysis.


4 5


6

Thermal and Photochemical Rearrangement of 1. During monitoring of the formation of **1** by analytical gas chromatography (GC), two peaks were noted in the (CH)$_{12}$ range, their ratio being markedly dependent on the injection port temperature. Under controlled conditions (C$_6$D$_6$, 102 °C, sealed NMR tube), **1** isomerized cleanly and quantitatively to **7**[11] (k = 1.8 × 10^{-4} s^{-1}; $t_{1/2}$ = 63 min). Homonuclear proton decoupling permitted specific assignment to be made to the ^{1}H NMR signals of **7** (see Experimental Section). Many similarities were seen between **7** and bicyclo[3.2.1]octa-2,6-diene, previously analyzed by Brown and Occolowitz.[12]

The stage was now set for use of deuterium labeling as a probe of mechanistic detail. Halogen–lithium exchange in the 3,9-dibromo derivative[4] followed by a D$_2$O quench gave **1**-d_2 with 87% deuterium incorporation. The D_{2d} symmetry of **1** causes C-3, -6, -9, and -12 to be equivalent. Consequently, **1**-d_2 can be considered to be quadruply labeled as shown in **8**. When **1**-d_2 in carbon tetrachloride solution was thermolyzed for 5 h at 110–115 °C in a sealed

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