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STERIC REPULSION AND INTRAMOLECULAR INTERACTION OF SUBSTITUENTS IN 4-SUBSTITUTED ADAMANTAN-2,6-DIONES[1]

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Abstract—By ^{13}C NMR measurements in presence of Yb(dpm)$_3$ all ^{13}C signals of the title compounds **2–6** were assigned. Ratios of "bound shifts" ($R^{\Delta\pi}$) can be correlated with Vögtle's n-values and reflect the spatial requirement of the substituent, unless the substituent participates significantly in complexation with Yb(dpm)$_3$. Effects of intramolecular substituent interactions of different types within one molecule are additive, i.e. the individual interactions mechanisms are acting more or less independently.

In continuation of our studies on the effects of intramolecular substituent interaction upon ^{13}C chemical shifts[2] we were interested in molecular systems in which several kinds of intramolecular interactions are present simultaneously, e.g. 4-substituted adamantan-2,6-diones **2–6**.

For the discussion of these effects, however, a safe signal assignment by an independent method first had to be completed. Thus, the ^{13}C NMR spectra of **2–8** were measured in the presence of the lanthanide shift reagent Yb(dpm)$_3$.

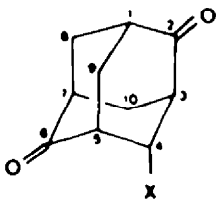
RESULTS

In Table 1 all ^{13}C chemical shifts of the diketones **1–6** are listed. The signals were assigned with the aid of ^1H "off-resonance" decoupled spectra and by measurements with incremental addition of Yb(dpm)$_3$. This particular reagent was chosen, because the substrate signal shifts are dominated by pseudo-contact contributions (perhaps except for the carbonyl signals).[4] Furthermore, the formation of LS$_3$-complexes (L: shift reagent, S: substrate) can be ignored.[5]

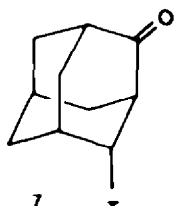
In order to exclude external influences on the measurements relative "bound shifts" (Δ^{π}) for **2–6** were determined (Table 2) which represent the slopes from the plots of lanthanide induced shifts (LIS) vs ratios of Yb(dpm)$_3$ to substrate, relative to the respective largest slope (C-2: 100). Since quantitative elucidation is often obscured by various difficulties,[5,6] we confined to semiquantitative LIS evaluations assuming that the larger the distance r between the Yb-ion and carbon i, the smaller is its "bound shift" $\Delta^{\pi}(i)$ (Fig. 1). This appears reasonable as long as $\theta < 40°$, a condition[7] which according to our experience is fulfilled in adamantane derivatives of this kind (*cf* Δ^{π}-values of **7** and **8** in Table 3).

Table 3 demonstrates that, if the iodo substituent is in an axial position (**8**), the absolute "bound shifts" are considerably smaller than if it is equatorial (**7**). This arises from steric repulsion within the L···S complex. On the other hand, the averaged position of the Yb-ion in the complex with **8** is still approximately in the extension of the C-2···O bond, since the Δ^{π}-values of C-1 and C-3 are similar to each other; the same is found for the pair C-5 and C-7, as well as for C-4/C-8/C-9/C-10. In the light of Chadwick's four-site binding model for ketones[8] this means that there is not one (or more) of these sites considerably favoured above others, rather the equilibrium binding constant[7,10] is reduced. Similar findings have been reported.[7,11]

It is plausible to transfer these arguments to the



X =	H	CH_3	$N(CH_3)_2$	Br	I	$COOCH_3$
	1	2	3	4	5	6



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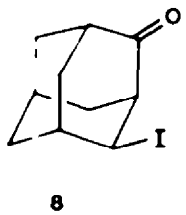

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Table 1. ^{13}C chemical shifts of 4-substituted adamantan-2,6-diones 1–6[a]

	1[b]	2	3	4	5	6
C-1	45.3	44.4	43.8	43.9	44.3	44.7
C-2	211.7	213.1	212.4	207.7	207.6	209.7
C-3	45.3	51.0	48.3	53.2	54.1	46.7
C-4	39.6	43.7	72.4	53.0	32.4	52.1
C-5	45.3	51.7	47.3	54.3	54.1	46.5
C-6	211.7	213.1	212.1	207.7	208.6	209.5
C-7	45.3	45.4	44.8	44.6	44.4	44.8
C-8	39.6	39.8	39.7	40.1	40.0[c]	40.4
C-9	39.6	38.9	35.3	37.3	39.3[c]	38.3
C-10	39.6	34.0	33.9	35.3	37.4	35.0
others	-	17.2	42.8	-	-	170.3/52.1

a In ppm downfield from internal TMS; $CDCl_3$ as solvent.

b The data of 1 have been published previously[3]. For consistency reasons, however, the present values were measured in this laboratory under the same experimental conditions.

c May be interchanged.

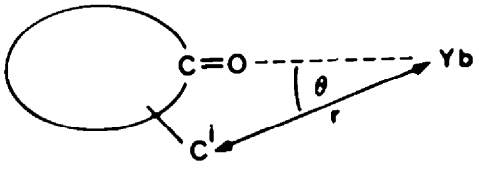

Fig. 1. Definition of distance r between Yb-ion and carbon i under consideration and angle θ between vector r and the assumed principal magnetic axis[7] (dashed line)

diketones 2–6 with their two carbonyl groups competing in complexation so that larger "bound shifts" for C-2 than for C-6 signals and analogous sequences for the carbon pairs C-1/C-7 and C-3/C-5 are expected. The substituents X = CH_3, Br and I do not participate noticeably in complexation and the same seems to be valid for X = $N(CH_3)_2$, since the methyl signals experience by far the smallest "bound shifts" (*cf.* $\Delta^{rel}(CH_3)$ in 2). This is easily explained by steric hindrance.[7] More complicated is the situation in the

Table 2. Relative "bound shifts" (Δ^{rel})[a] of 4-substituted adamantan-2,6-diones 2–6

	2	3	4	5	6
C-1	46.00	47.78	44.62	50.24	46.55
C-2	100.00	100.00	100.00	100.00	100.00
C-3	45.63	49.36	43.53	49.91	51.96
C-4	32.43	37.91	32.50	26.52	41.82
C-5	38.83	47.53	29.59	31.43	37.74
C-6	72.72	88.56	52.95	51.33	55.40
C-7	38.20	41.79	33.18	30.88	33.58
C-8	29.88	31.95	28.10	26.52	27.80
C-9	31.04	34.80	27.49	28.32	30.56
C-10	31.85	34.80	26.95	27.41	32.20
CH_3	18.70	15.58	-	-	17.48
COO	-	-	-	-	51.13

a Δ^{rel}-values are the slopes from plots of LIS vs. ratios of $Yb(dpm)_3$ to substrate, relative to the respective largest slope (C-2: 100).

Table 3. Absolute and relative "bound shifts" for 4-iodoadamantanones 7 and 8[a]

	7		8	
	abs.	rel.	abs.	rel.
C-1	16.98	50.45	10.42	39.60
C-2	33.66	100.00	26.31	100.00
C-3	16.69	49.58	10.73	40.78
C-4	8.20	24.36	4.72	17.94
C-5	6.30	18.72	4.04	15.36
C-6	4.73	14.05	3.09	11.74
C-7	6.70	19.90	3.64	13.84
C-8	8.79	26.11	4.72	17.94
C-9	8.46	25.13	4.72	17.94
C-10	8.55	25.40	5.64	21.44

a) See caption of Table 2; ^{13}C chemical shifts of these compounds have been published previously[9].

case of ester 6. Apparently, the ester carbonyl is a significant complexing site.

DISCUSSION

Steric effects of substituents X

As discussed in the preceding section, the different "bound shifts" of the two carbonyl signals in 2–6 are explained by steric repulsion of X reducing the binding constant for the $C^* = O$–Yb complexation. Therefore, it is interesting to compare these effects with parameters describing the size of X, i.e. their spatial requirement. In a series of papers Vögtle[12] published so-called n-values for a variety of substituents which excellently reflect their effective size, because these parameters are derived from dynamic NMR monitoring of conformational processes during which the substituents' "shapes" are scanned by a mobile alkane chain.

Thus, in Fig. 2 the ratios $R^{2/6} = \Delta^{rel}(C\text{-}2)/\Delta^{rel}(C\text{-}6)$, $R^{1/7} = \Delta^{rel}(C\text{-}1)/\Delta^{rel}(C\text{-}7)$ and $R^{3/5} = \Delta^{rel}(C\text{-}3/\Delta^{rel}(C\text{-}5)$

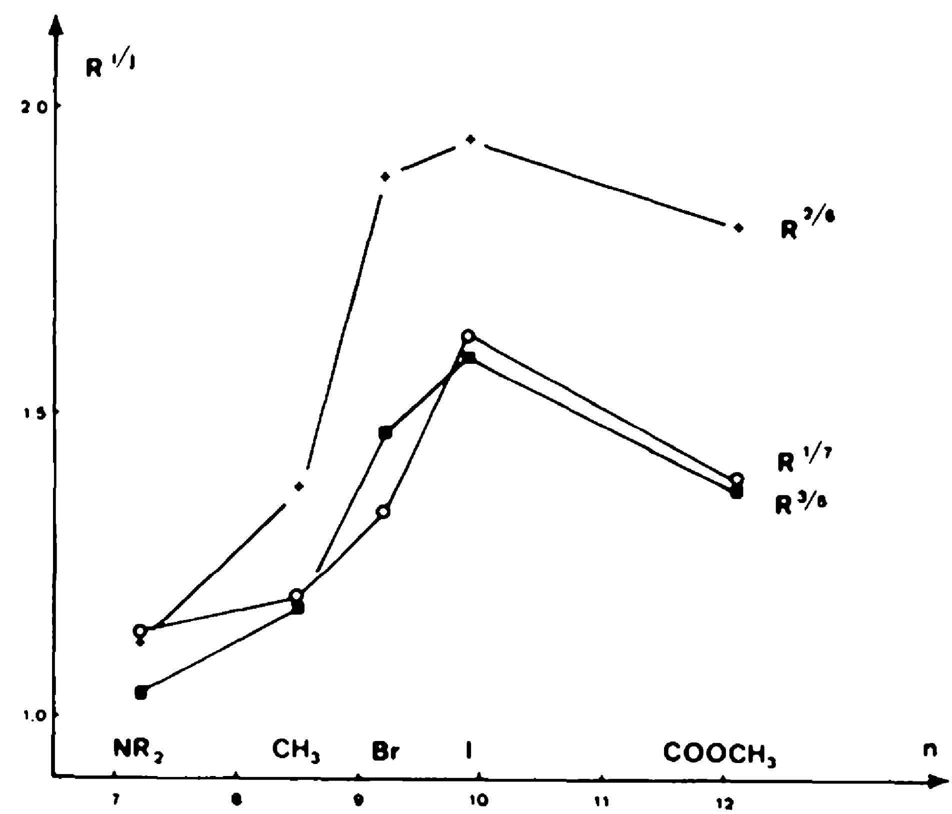

Fig. 2. Plot of ratios $R^{i/j} = \Delta^{rel}(C\text{-}i)/\Delta^{rel}(C\text{-}j)$ vs Vögtle's n-values[12] for substituents X in 2–6

characterizing the substituents' repulsive effects in 2–6, are plotted vs Vögtle's n-values.[12] Fairly good correlations are observed for X = CH_3, $N(CH_3)_2$, Br and I, although, unfortunately, there is no n-value reported for $N(CH_3)_2$ and that of NH_2 had to be used. Apparently, the steric repulsion of this substituent is caused predominantly by the nitrogen atom, the two methyl groups being turned off the Yb(dpm)$_3$-part of the L S complex This parallels the observation of similar A-values for the alkyl substituents in methyl-, ethyl- and isopropylcyclohexane.[13] The R^{vi} of 6 (X = $COOCH_3$), however, are too small to fit the correlation This can be explained by the complexing capability of this substituent (see above) which delivers additional contributions to Δ^{ax}(C-6), Δ^{ax}(C-7) and Δ^{ax}(C-5)

In conclusion, the R^{vi} represent good relative measures for substituents' spatial requirements as long as they do not participate significantly in lanthanide shift reagent complexation.

Intramolecular substituent interactions

In a series of publications[2] we reported on intramolecular substituent interactions of 1,3-disubstituted cyclohexane-typed compounds with various substituents in different configurations. These interactions are manifested in non-additivities (NA) of the individual substituent effects on the ^{13}C chemical shifts (SCS). SCS were obtained from corresponding monosubstituted derivatives It was shown that the NA are strongly dependent on the configuration, and a number of underlying interaction mechanisms could be derived.[2] In the compounds 2–6 three kinds of interactions acting simultaneously are conceivable, and the question arises whether they are independent, i.e. the NA are additive This appeared important to us, since one of the aims of our investigations in this field is to establish rules for reliable prediction of ^{13}C chemical shifts in multiply substituted compounds

The three different relative orientations of two substituents/groups in 2–6 are (a) Carbonyl group and X in an equatorially substituted cyclohexanone (C-2/3/4/5/9/1; as in 7), (b) Carbonyl group and X in an axially substituted cyclohexanone (C-6/5/4/3/10/7 as in 8), and (c) Two carbonyl groups in a 1,5-diketone (1).

Types (a) and (b) have been discussed in detail[2] for the given substituents among many others. The NA of SCS in 1 (type (c); − 3.4 ppm) was explained very recently[3] by a through-space π-electron interaction of the nearby and ideally aligned carbonyl groups. This, however, ignores that the π-electron systems are orthogonal in this molecule Therefore, another interpretation may be a through-space interaction of the two anti-parallel, aligned dipoles By that the bond polarities are decreased a little enhancing the electron density at the carbonyl carbons so that they become more shielded (upfield signal shift).

The chemical shifts of the carbons in 2–6 were calculated (δ_{calc}) as follows: Those of the appropriate 4^{ax}-substituted adamantanones[2] (for X = I, 7) were taken as basic values which already contain NA effects of interaction type (a). Comparison of the ^{13}C chemical shifts in 4^{ax}-substituted adamantanones[2] (for X = I, 8) and those in the corresponding 2-substituted adamantanes[2] afforded SCS of the carbonyl oxygen atoms which, on the other hand, include NA effects of interaction type (b). Those SCS were added to the basic values according to the position of the C-6 carbonyl in 2–6. Finally, the NA effects type (c) are enclosed in this summation.

Table 4. Difference of experimental and calculated ^{13}C chemical shifts ($\Delta\delta = \delta_{exp} - \delta_{calc}$, see text) for substituted carbon atoms in 2–6, in ppm

	2	3	4	5	6
C-2	[illegible]	[illegible]	2.6	2.3	−1.4
C-4	[illegible]	[illegible]	[illegible]	2.6	−2.1
C-6	0.2	0.2	1.8	1.5	−0.7

The δ_{calc} are subtracted from the experimental chemical shifts (δ_{exp}) to obtain $\Delta\delta$'s. These latter values are very small for all unsubstituted carbons. Only for some substituted ones modest deviations from zero are found (Table 4), especially for those compounds where individual NA effects are large (X = Br and I).[2]

The evidence of Table 4 is that different intramolecular substituent interactions are acting more or less independently and their individual NA effects can be regarded as additive, when chemical shifts in multiply substituted derivatives are to be predicted This, however, is only valid for such conformationally rigid molecules

EXPERIMENTAL

All ^{13}C NMR measurements were carried out at 22.63 MHz using a Bruker WH-90 spectrometer in approx 0.5 molar $CDCl_3$ solutions

Compounds 1[14], 3[15], 6[16], 7[9] and 8[9] were synthesized according to known procedures

4-Methyladamantan-2,6-dione (2)

4-Exomethyleneadamantan-2,6-dione[17] was dissolved in abs EtOH and hydrogenated at room temperature and under normal pressure over Pd/C After filtering and evaporation of the solvent dil HCl was added and the mixture was refluxed overnight to hydrolyze the acetals Extraction with methylene chloride and column chromatography purification (silica gel/petrol-acetone as eluent) afforded 2 in 90% yield IR($CHCl_3$) 1715 cm^{-1} NMR($CDCl_3$) 1.05 (d, 3H), 2.1–2.5 (complex, 10 H) MS(Intensity) 178 (100)(M$^+$), 163 (2), 150 (11), 132 (43), 117 (29)

4-Iodoadamantan-2,6-dione (5)

9-Oxobicyclo[3.3.1]non-6-en-3-endo-carboxylic acid[18] was refluxed in 57% HI for 4 hr After cooling, water was added, the mixture extracted with methylene chloride and the crude product purified by column chromatography (see above) Yields of 5 were 50%. IR($CHCl_3$) 1715 cm^{-1} NMR($CDCl_3$) 2.1–3.2 (complex, 10 H), 4.80 (m, 1 H) MS(Intensity) 163 (100)(M$^+$ − I), 135 (6), 107 (37), 89 (58)

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