Conformational Analysis Part 14: A Lanthanide-induced Shift N.M.R. Analysis of Indan-1-one and Norcamphor

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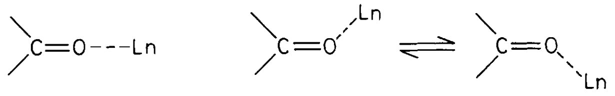
A model for the analysis of the lanthanide-induced shift (LIS) of molecules with asymmetric binding sites is presented and used to analyse the LIS of indan-1-one and norcamphor. The spatial environment of the carbonyl groups has been modelled using non-symmetry-related binding sites which can be varied independently to achieve the required agreement between the observed and calculated pseudo-contact shifts. The model proved very successful for indan-1-one with an essentially three-site complexation geometry reflecting the environment around the carbonyl group. The bond localisation in indan-1-one was investigated using this model and other theoretical and experimental methods. MNDO gives the opposite bond fixation to that predicted from both *ab initio* and n.m.r. coupling constants. The LIS excludes an idealised structure but gives good agreement for both calculated structures. A comparable LIS analysis of norcamphor illustrated again the sensitivity of the method to the correct substrate geometry. Of the three geometries obtained (MNDO, crystal structure of an analogue, and *ab initio*) the 3-21G *ab initio* structure gave significantly better agreement for both LIRAS3 and HARDER (four-site) than any other analysis. Both LIRAS3 and HARDER solutions are acceptable in this case, probably due to the asymmetric environment about the carbonyl group in norcamphor which is not completely reflected in either the HARDER or LIRAS3 models.

In previous parts of this series[1] we have shown that the LIS technique can, under certain conditions, be used quantitatively to determine the conformation and structure of carbonyl compounds in solution.[2–4] However, reliable results can only be obtained on removal of any diamagnetic shifts, using an over-determined data set, and with a chemically reasonable model for lanthanide-ion binding.

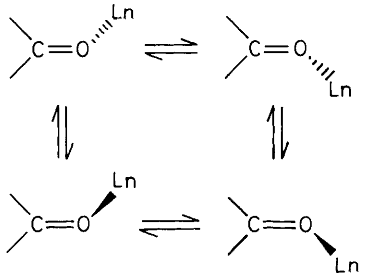
Using the LIS technique, together with the conditions stated above, the *trans*-decalin-2-one system has been shown to be a much better model for a conformationally locked cyclohexanone than the 4-t-butyl derivative due to distortion of the ring in the latter.[5] The conformational isomerism of *ortho*- and *meta*-substituted benzaldehydes has also been investigated with the LIS technique[4] yielding the following preferences for the O-*trans* conformer; *m*-methyl 44%, *m*-chloro 42%, *m*-methoxy 32%, *o*-methyl 59%, and *o*-chloro 100%.

In certain circumstances structural information can also be obtained. For 2,4,6-trimethylbenzaldehyde a reasonable solution could only be obtained on relaxation of the methyl C–C–C bond angles to 126° to relieve steric interactions.[6] Thus, the LIS technique can provide valuable structural, as well as conformational, information.

These studies and those by other workers[7–9] have encouraged the application of the technique to a wider range of compounds containing the carbonyl functional group. As a result several problems have been encountered when applying the technique to compounds which have different steric environments on either side of the carbonyl group. These problems are a consequence of the model used for lanthanide binding.



(*a*) One-site (*b*) Two-site



(*c*) Four-site

Figure 1. Modes of lanthanide-ion binding to carbonyl groups.

When a lanthanide binds reversibly to a carbonyl group on a substrate, three modes of binding are considered; one-site, two-site, and four-site (see Figure 1). In the one-site model the lanthanide binds to the carbonyl oxygen in a single preferred site usually, but not universally, with a C–O–La angle of *ca.* 180°. In the two-site model the lanthanide binds to one of the oxygen lone pairs from which the second binding site can be obtained by reflection of the first site in the mirror plane orthogonal to the carbonyl group. Finally, the four-site model may be considered as a reflection of the two-site model in the second mirror plane of the carbonyl group. These three binding modes are illustrated in Figure 1.

Although arguments for a one-site model have been given,[10] our work [11a] and that of others [11b,c] has favoured the use of two- and four-site models, depending on the molecule in question, with the four-site model usually preferred.[11a] Hence, we developed a computer program LIRAS3,[2] which implements the above scheme using two- or four-site models for lanthanide ion binding and this has proved very successful.[2–6]

Although LIRAS3 works well for symmetric compounds,[2–6]

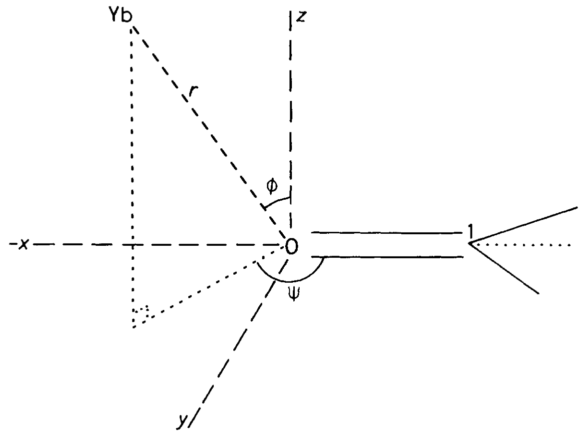


Figure 2. Co-ordination geometry for LIRAS3 and HARDER.

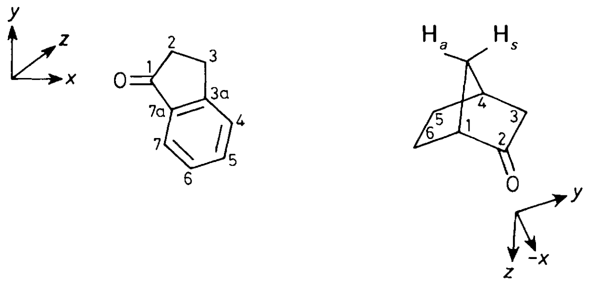


Figure 3. Numbering system and axes for indan-1-one and norcamphor.

Table 1. Observed shifts (δ/ppm), LIS values (ΔM/ppm), diamagnetic shifts (ΔD/ppm) and pseudo-contact shifts [($\Delta M - \Delta D$)/ppm] for indan-1-one.

Nucleus	δ^a	ΔM^b	ΔD^c	$\Delta M - \Delta D$
C=O	207.15	141.94	13.52	128.42
C-2	36.36	56.82	0.37	56.45
C-3	25.94	25.95	0.97	24.98
C-4	126.87	14.70	—	14.70
C-5	134.77	14.01	3.35	10.66
C-6	127.42	15.07	0.58	14.49
C-7	123.84	36.22	3.52	32.70
C-7*a*	137.28	53.79	−1.28	55.07
C-3*a*	155.33	30.75	4.26	26.49
2-H	2.67	40.12		
3-H	3.13	16.99		
4-H	7.47	10.57		
5-H	7.58	8.11		
6-H	7.35	8.83		
7-H	7.74	33.87		

[a] $[S]_0 = 1.0$ mol dm^{-3} in $CDCl_3$. [b] From four additions of $Yb(fod)_3$, $10^{+2}\rho = 3.40, 6.60, 9.70$, and 14.00. All correlation coefficients $\geqslant 0.999$. [c] From four additions of $La(fod)_3$, $10^2\rho = 4.30, 7.50, 11.60$, and 15.50.

Table 2. Observed shifts (δ/ppm), LIS values (ΔM/ppm), diamagnetic shifts (ΔD/ppm) and pseudo-contact shifts [($\Delta M - \Delta D$)/ppm] for norcamphor.

Nucleus	δ^a	ΔM^b	ΔD^c	$\Delta M - \Delta D$
C-1	49.73	59.31	0.45	58.86
C=O	217.61	159.83	14.52	145.31
C-3	45.19	59.47	—	59.47
C-4	35.30	29.08	—	29.08
C-5	27.19	22.11	−0.91	23.02
C-6	24.19	32.46	−0.30	32.76
C-7	37.57	30.15	—	30.15
1-H	2.59	45.84		45.84
3*n*-H	1.84	40.31		40.31
3*x*-H	2.06	39.65		
4-H	2.67	16.83		
5*n*-H	1.47	17.08		
5*x*-H	1.82	12.89		
6*n*-H	1.50	33.05		
6*x*-H	1.82	18.47		
7*s*-H	1.73	25.56		
7*a*-H	1.55	17.72		

[a] $[S]_0$ *ca.* 1.0 mol dm^{-3} in $CDCl_3$. [b] From four additions of $Yb(fod)_3$, $10^2\rho = 1.68, 2.67, 6.30$, and 8.28. All correlation coefficients $\geqslant 0.999$. [c] From one addition of $La(fod)_3$, $10^2\rho = 6.61$.

problems do arise when considering compounds which are highly asymmetric in the vicinity of their binding site.[12] It is for this reason that an extension of the LIRAS3 program has been developed to account for this asymmetry. The new program, called HARDER, will be described fully here using two illustrative examples. Other applications in conformational analysis have already been presented.[12,13]

The HARDER program can best be understood by re-examining the methodology used in LIRAS3. Figure 2 shows the co-ordination geometry for the lanthanide–substrate complex which uses the variables r, φ, and ψ to define the lanthanide-ion position. In the two-site model the lanthanide-ion position on the $+y$ side of the carbonyl group is reflected in the xz plane to obtain the lanthanide position on the $-y$ side. The population of these two sites can then be varied in the analysis. In the four-site model, reflection occurs in both the xz and xy planes producing four symmetry-related binding sites. However, only the populations of the different sites about the xz plane may be varied. This procedure results in five unknowns (r, φ, ψ, % population, and a normalisation factor) which can be used in the analysis. Therefore, r, φ, ψ, and the % population may be varied independently in order to fit the calculated to the observed lanthanide-induced shifts.[2]

HARDER differs from LIRAS3 in that the second lanthanide position (obtained by reflection in the xz plane for LIRAS3) may be varied independently of the first, giving a two-site model which can accommodate different steric interactions on either side of the carbonyl group. The four-site HARDER model may be achieved by reflection of these two independent sites in the xy plane producing four binding sites (two pairs of symmetry related binding sites). Again, the population between different sites about the xz plane may be varied but not that between sites about the xy plane. Hence, HARDER has eight unknowns: r, φ, ψ on the $+y$ side; r, φ, ψ on the $-y$ side; % population between the $+y$ and $-y$ sites; and a normalisation factor.

Therefore, HARDER can be used on compounds with asymmetric binding sites (*e.g.* indan-1-one) and will hopefully solve some of the problems associated with LIRAS3. It should be noted that, as there are now eight unknowns, we need at least eight shift values to solve explicitly, with approximately twice as many shift values (*i.e.* 16) being preferable to help ensure an over-determined solution.

Applications of HARDER to conformationally flexible molecules have shown that the model, when applied carefully, is useful in determining the conformational preference of molecules in solution. For example, in the LIS analysis of 3-(3,5-di-iodobenzoyl)-2-butylbenzofuran[12] the only satisfactory analysis consisted of a single conformation in which the phenyl group was coplanar with the carbonyl group and the benzofuran moiety twisted *ca.* 90° out of the plane of the carbonyl group. This contrasted with the 2,6-dibromo derivative (benzofuran coplanar and phenyl *ca.* 90°) and is supported by molecular-mechanics calculations. However, further investigations have

Table 3. MO geometries for indan-1-one.[a]

Bond	Form A	Form **B**	Form **C**	STO-3G[b]	3-21G[b]
C(1)–O(1)	1.221	1.220	1.221	1.218	1.209
C(1)–C(2)	1.542	1.541	1.542	1.554	1.534
C(2)–C(3)	1.549	1.552	1.550	1.551	1.554
C(3)–C(3a)	1.514	1.515	1.513	1.529	1.523
C(3a)–C(4)	1.397	1.397	1.406	1.387	1.382
C(4)–C(5)	1.419	1.397*	1.389*	1.388	1.385
C(5)–C(6)	1.401	1.397*	1.402*	1.391	1.391
C(6)–C(7)	1.414	1.397*	1.389*	1.386	1.381
C(7)–C(7a)	1.400	1.397*	1.405	1.388	1.381
C(7a)–C(1)	1.497	1.502	1.496	1.511	1.477
C(7a)–C(3a)	1.427	1.397*	1.425	1.386	1.389
C(2)–H(2)	1.110	1.109	1.110	1.090*	1.090*
C(3)–H(3)	1.111	1.111	1.111	1.090*	1.090*
C(4)–H(4)	1.090	1.092	1.092	1.080*	1.080*
C(5)–H(5)	1.090	1.092	1.092	1.080*	1.080*
C(6)–H(6)	1.090	1.092	1.092	1.080*	1.080*
C(7)–H(7)	1.090	1.092	1.092	1.080*	1.080*
O(1)–C(1)–C(7a)	127.0	127.0	127.1	127.2	126.6
C(2)–C(3)–C(3a)	106.0	105.3	105.3	105.1	104.2
C(4)–C(5)–C(6)	120.7	120.0*	120.8	120.9	121.2
C(5)–C(6)–C(7)	120.2	120.0*	120.5	120.2	119.9
C(6)–C(7)–C(7a)	119.6	120.0*	119.8	118.6	118.5
C(7)–C(7a)–C(1)	130.0	129.8	130.9	128.6	127.0
C(7)–C(7a)–C(3a)	120.0	120.0*	119.7	121.2	121.9
C(1)–C(7a)–C(3a)	110.0	110.2	109.4	110.2	111.1
C(3)–C(3a)–C(7a)	110.6	111.5	111.4	112.0	111.5
H(2)–C(2)–C(1)	111.3	111.1	111.3	110.0	109.1
H(3)–C(3)–C(2)	111.1	111.2	111.3	111.4	111.5
H(4)–C(4)–C(5)	119.4	119.6	120.1	120.3	120.4
H(5)–C(5)–C(6)	120.0	120.1	119.4	119.5	119.4
H(6)–C(6)–C(7)	119.5	119.9	120.0	120.0	120.3
H(7)–C(7)–C(7a)	121.1	120.6	120.3	120.5	119.9
H(2)–C(2)–C(3)–C(3a) (±)	120.3	120.6	120.6	119.8	119.1
H(3)–C(3)–C(3a)–C(7a) (±)	120.8	120.3	120.4	120.5	120.0

[a] Bond lengths in ångströms, all angles in degrees. [b] Optimised using the GAMESS program (see footnote p. 1380). [c] Values not optimised.

also shown limitations on the use of HARDER especially when there are only a few experimental shift values *i.e.* where the solution is under-determined.[13]

To compare HARDER with LIRAS3 we have analysed two conformationally rigid carbonyl compounds to ensure that the fit of calculated to experimentally induced shifts does not include other unknown factors such as conformational isomerism. The two molecules chosen were indan-1-one and norcamphor (see Figure 3). The results are encouraging and show the importance of choosing a chemically reasonable lanthanide-binding model and having an over-determined solution.

Results

Tables 1 and 2 show the observed LIS values (ΔM), the diamagnetic complexation shifts (ΔD), the unperturbed shifts (δ), and pseudo-contact shifts ($\Delta M - \Delta D$) for indan-1-one and norcamphor, respectively. The pseudo-contact shifts were then used (ignoring contact shifts[14]) in the LIS analysis. A good solution is considered to have an agreement factor ($\%R_x$) below 5% with all individual shift errors less than 1.0 ppm and resulting from a chemically reasonable co-ordination geometry *i.e.* r = 2.5–3.5 Å, φ = 20–160° (two-site) or 20–90° (four-site), and ψ = 120–180°.

The results for each molecule will be considered in turn.

Indan-1-*one*.—Indan-1-one has 18 atoms and 15 individual shift centres (carbon and proton, shown in Table 1), all of which have been used in the analysis and should produce a well-determined solution. Because of the conjugated nature of indan-1-one several of the shift centres have significant diamagnetic complexation shifts (ΔD for C=O, C-5, C-7, and C-3*a*) and illustrates the importance of obtaining the pure pseudo-contact shifts for the analysis.

Although indan-1-one is a crystalline solid we have been unable to find a crystal-structure determination in the literature. Spectroscopic evidence[15] has shown that the related compound cyclopent-2-enone exists in a planar conformation with the conjugation between the carbonyl group and the double bond presumably large enough to overcome the staggered preference of the two methylene groups. It is, therefore, safe to assume that indan-1-one will also be planar.

Using this assumption, and the molecular-orbital package MNDO,[16] the geometry of indan-1-one has been obtained by geometry optimisation of the planar form using the appropriate symmetry constraints (full geometry optimisation gave an essentially planar geometry). The resulting geometry, form A shown in Table 3, has been used in the LIS analysis by both LIRAS3 and HARDER.

The results of the LIS analysis are shown in Table 4. On examination of the steric interactions near the binding site, the co-ordination geometry should depend on the side of approach of the lanthanide ion. Lanthanide binding on the $+y$ side (see Figure 3) should favour a lanthanide position which lies between the methylene protons at C-2, *i.e.* in the plane of the molecule [$\varphi(+y)$ = 90°]. Binding on the $-y$ side, however, will occur out of the plane of the molecule to reduce steric interactions with the aromatic proton at C-7 [$\varphi(-y) \neq 90°$].

Table 4. LIS analyses for indan-1-one.[a]

	$\%R_x$	$r(-y)$	$\varphi(-y)$	$\psi(-y)$	$r(+y)$	$\varphi(+y)$	$\psi(+y)$	Pop$(+y)$
Form **A**								
LIRAS3	1.67	3.10	50	145	3.10	50	145	80%
HARDER	1.25	3.10	25	125	3.00	90	145	80%
Form **B**								
LIRAS3	3.56	3.00	90	135	3.00	90	135	80%
HARDER	1.68	2.80	50	100	3.05	55	150	95%
Form **C**								
LIRAS3	1.64	3.10	50	145	3.10	50	145	80%
HARDER	1.25	3.10	25	125	3.00	90	145	80%
STO-3G								
LIRAS3	1.83	3.10	55	140	3.10	55	140	80%
HARDER	1.49	3.10	30	110	3.05	75	145	85%
3-21G								
LIRAS3	2.14	3.10	60	135	3.10	60	135	80%
HARDER	1.41	2.95	40	110	3.00	65	145	90%

[a] r in ångströms, φ and ψ in degrees. Two-site and four-site models are equivalent.

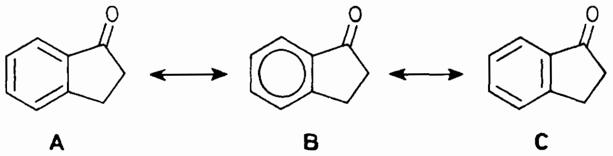


Figure 4. Conjugational schemes for indan-1-one.

Table 5. ^{1}H N.m.r. spectroscopic analysis for the aromatic protons of indan-1-one.[a]

	ppm	
$\delta_{4\text{-H}}$	7.486	
$\delta_{5\text{-H}}$	7.590	
$\delta_{6\text{-H}}$	7.374	
$\delta_{7\text{-H}}$	7.766	
	Hz	
$^3J_{4,5}$	7.72	$R_{\text{C(4)–C(5)}} = 1.394$ Å
$^4J_{4,6}$	1.00	
$^4J_{4,3}$	0.97	
$^5J_{4,7}$	0.78	
$^3J_{5,6}$	7.25	$R_{\text{C(5)–C(6)}} = 1.407$ Å
$^4J_{5,7}$	1.27	
$^5J_{5,3}$	−0.07	
$^3J_{6,7}$	7.72	$R_{\text{C(6)–C(7)}} = 1.394$ Å
$^6J_{6,3}$	0.79	
$^5J_{7,3}$	0.51	

These steric interactions are important because of the sheer bulk of the lanthanide ligands (fod). Clearly, LIRAS3 cannot model this type of situation explicitly whereas, HARDER has been designed specifically for this type of situation and should show considerable improvement in the analysis compared with LIRAS3.

The results for form **A** (Table 4) show that the HARDER analysis is a definite improvement over LIRAS3 for the planar MNDO geometry ($\%R_x = 1.25$ *vs.* 1.67). In the LIRAS3 analysis the calculated value of $\varphi = 50°$ indicates the absence of steric interactions between the lanthanide and the C-2 methylene protons and, as mentioned previously, would seem unreasonable. Indeed, the errors on individual shifts are often > 1.0 ppm (C-3*a*, C-7, 3-H, 4-H, and 5-H; not shown). In the HARDER analysis, however, the lanthanide ion positions on both sides of the carbonyl group are chemically very reasonable. Co-ordination on the $-y$ side occurs out of the plane of the molecule while the geometry on the $+y$ side locates the lanthanide in the plane of the molecule, as predicted. Values of r and ψ are also chemically reasonable for both sides leading to correspondingly small individual shift errors indicating the improvement over LIRAS3 (only C-3*a* $\geqslant$ 1.0 ppm).

Although the results for HARDER are superior to LIRAS3 this may be because of the better model of lanthanide co-ordination or merely the use of three extra parameters in the analysis. This point is very difficult to clarify but the agreement factor ($\%R_x$) does show a substantial improvement and we believe this could have been even greater if indan-1-one did not possess a plane of symmetry which aids in the LIRAS3 analysis *via* an averaging process. This situation does not occur in the analysis of norcamphor.

Before leaving the analysis of indan-1-one several other observations warrant further investigation. Close examination of Table 3 shows some interesting features of the MNDO structure for indan-1-one. MNDO optimisation of the planar form results in the geometry shown for form **A**, with bond-length alternation in the aromatic ring corresponding to the structure illustrated in Figure 4. By analogy with *cis* and *trans* acrolein, where the *trans* form is the preferred conformation,[17] a bond-length alternation corresponding to form **C** in Figure 4 would be expected, contrary to that predicted by MNDO. The crystal structure of the analogous compound acetophenone[18] does not show any observed bond alternation (*i.e.* form **B**) and so, to investigate further, we have analysed the ^{1}H n.m.r. spectrum of indan-1-one.

Gunther[19] has studied the effect of delocalisation on proton–proton coupling constants. A good correlation between coupling constants and bond length was observed for a series of aromatic and alkenic compounds with the analysis yielding the following expression;

$$^3J = -35.10R + 56.65$$

where, ^3J is the proton–proton coupling (*ortho* coupling) constant in Hz and R is the corresponding carbon–carbon bond length in ångströms.[19b] Using this relationship, together with the observed coupling constants, the bond lengths C(4)–C(5), C(5)–C(6), and C(6)–C(7) can be estimated and hence the pattern of bond alternation can be determined. This has been achieved using the four aromatic protons of indan-1-one. The calculated spectrum is shown in Figure 5 with the chemical shifts, coupling constants, and resulting bond lengths appearing in Table 5. Further details of the analysis can be found in the Experimental section.

The results support a bond alternation as shown in form **C**, in contrast with the MNDO results. Hence, there are three possible forms for indan-1-one represented by structures **A**–**C** in Figure 4. For further comparison, the STO-3G and 3-21G planar geometries have been obtained by geometry optimisation using the GAMESS package.* All the geometries are included in Table 3.

Form **B** represents the situation in which there is no conjugation between the aromatic ring and the carbonyl group and was obtained by MNDO optimisation of a planar indan-1-one restricting all the aromatic-ring bond lengths to equal that in benzene.[20] Form **C** was obtained by MNDO optimisation of a planar geometry with just the three bond lengths restrained to equal the n.m.r. spectroscopy-derived values. Although bond alternation in structure **C** is induced as shown in Figure 4 the bond length obtained for C(3a)–C(7a) is anomalous compared with the rest of the ring. However, the structure has still been included in the LIS analysis.

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* M. F. Guest, UMRCC Quantum Chemistry Project.

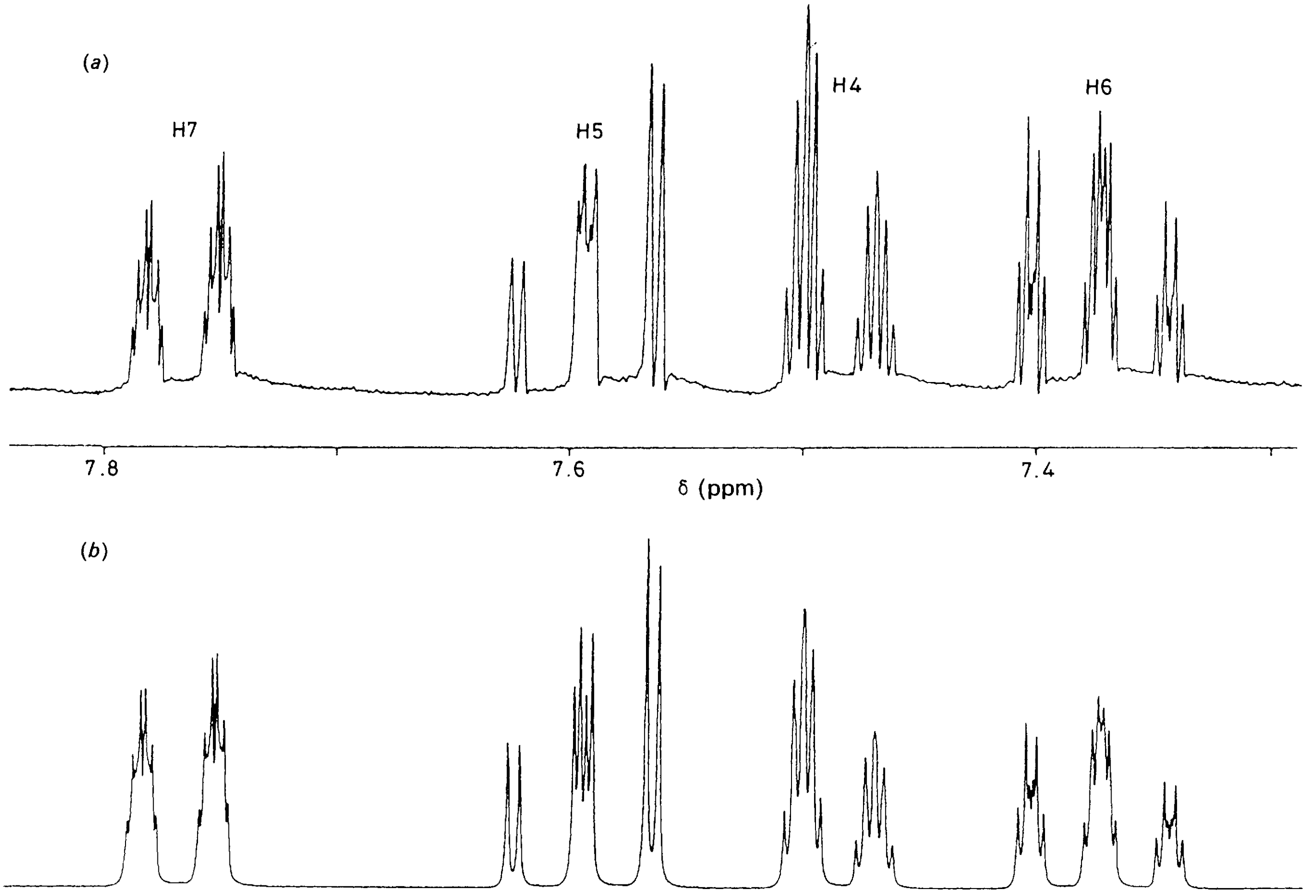

Figure 5. Observed (*a*) and calculated (*b*) ^{1}H n.m.r. spectrum of indan-1-one.

The *ab initio* geometries show less ring alternation but the benzene-ring bond lengths calculated are in good agreement with the n.m.r. spectroscopy predictions. The 3-21G basis set predicts a smaller carbonyl bond length than the other methods and may give a significantly different LIS analysis. The major differences between the various calculated structures arise for the C(1)–C(7a) and C(3a)–C(7a) bond lengths and the C(7)–C(7a)–C(1) bond angle.

It may be that the expected pattern of bond alternation is not apparent for the C(3a)–C(7a) bond because this is a ring-fusion bond. The lengthening of this ring-junction bond, analogous to that in decalinones,[21a] could be investigated by comparison with indane where there is no conjugation. Unfortunately no experimental structure of indane could be found in the literature and, as further investigations employing *ab initio* calculations are beyond the scope of this paper, the problem of bond alternation in indan-1-one (if there is any) will have to await a crystal-structure determination.

Could HARDER (or LIRAS3) differentiate between the various forms? The results of the analysis for all the structures are included in Table 4. Both LIRAS3 and HARDER cannot differentiate between forms **A** and **C** with the results being essentially identical. The results for form **B**, however, are considerably worse, with both methods giving poor solutions compared with forms **A** and **C**, and this is surprising because form **B** is intermediate between forms **A** and **C**. The HARDER co-ordination geometry for form **B** is also chemically unreasonable with a very low value of $\psi(-y)$ (100°). The analyses using *ab initio* geometries is intermediate between forms **A**(**C**) and **B**. The poorer agreement is also reflected in the low values of $\psi(-y)$ (110°) although this may be due to the high lanthanide population on the $+y$ side of 80–90%. The differences between the analyses using the various geometries are not easily translated into the differences between the respective geometries.

Table 6. Calculated lanthanide-induced shifts of indan-1-one.

Atom	Obs.	Calc.[a]	Error
C-1	128.4	128.6	0.2
C-2	56.5	56.3	−0.2
C-3	25.0	25.5	0.5
C-3a	26.5	27.6	1.1
C-4	14.7	14.4	−0.3
C-5	10.7	11.5	0.8
C-6	14.5	14.3	−0.2
C-7	32.7	32.5	−0.2
C-7a	55.1	54.6	−0.5
2-H	40.1	40.2	0.1
3-H	17.0	16.2	−0.8
4-H	10.6	9.8	−0.8
5-H	8.1	7.4	−0.7
6-H	8.8	8.8	0.0
7-H	33.9	33.7	−0.2

[a] Substrate geometry from Table 3 (Form **C**). Lanthanide co-ordination geometry as given for the HARDER analysis in Table 4 (Form **C**).

An illustrative example of the calculated *vs.* observed LISs is presented in Table 6 and shows the good agreement between observed and calculated values for the HARDER analysis of form **C**.

Norcamphor.—Norcamphor is a highly asymmetric compound yielding 17 carbon- and proton-shift values for analysis. The framework geometry was originally obtained by MNDO

Table 7. LIS analyses for norcamphor.[a]

	$\%R_x$	$r(-y)$	$\varphi(-y)$	$\psi(-y)$	$r(+y)$	$\varphi(+y)$	$\psi(+y)$	Pop$(+y)$
MNDO (2-site)								
LIRAS3	2.44	3.00	95	130	3.00	95	130	65%
HARDER	1.50	3.30	130	100	2.70	80	150	85%
HARDER	1.90	3.25	110	120	2.90	90	135	65%
MNDO (4-site)								
LIRAS3	2.08	2.90	65	140	2.90	65	140	75%
HARDER	1.80	3.00	90	135	2.90	60	140	70%
HARDER	2.29	3.00	65	135	2.90	90	135	65%
XRAY (2-site)								
LIRAS3	3.03	2.60	95	145	2.60	95	145	70%
HARDER	1.58	3.45	130	85	2.40	85	160	90%
HARDER	2.38	3.25	125	120	2.50	90	150	70%
XRAY (4-site)								
LIRAS3	1.83	2.70	60	150	2.70	60	150	80%
HARDER	1.42	3.35	90	105	2.65	60	155	90%
HARDER	1.84	2.85	50	165	2.65	90	135	40%
STO-3G (2-site)								
LIRAS3	2.45	3.00	95	130	3.00	95	130	65%
HARDER	1.45	2.60	125	180	3.00	50	140	40%
STO-3G (4-site)								
LIRAS3	1.77	3.00	65	135	3.00	65	135	70%
HARDER	1.49	2.80	90	100	3.05	50	125	45%
3-21G (2-site)								
LIRAS3	2.06	2.85	90	135	2.85	90	135	65%
HARDER	1.59	3.50	130	180	2.75	60	155	60%
3-21G (4-site)								
LIRAS3	1.40	2.85	65	140	2.85	65	140	70%
HARDER	1.25	2.70	90	155	2.90	55	130	45%

[a] r in ångströms, φ and ψ in degrees. The two sets of results for the HARDER analysis relate to the unrestricted analysis and the restricted analysis (see text for restrictions).

optimisation, and the proton positions added according to Abraham and Fisher.[21b] The LIS results for norcamphor are shown in Table 7.

In the analysis of the MNDO structure HARDER proved to be more successful than LIRAS3, $\%R_x = 1.50$ *vs.* 2.44 (two-site) and 1.80 *vs.* 2.08 (four-site). The smaller difference for the four-site model is probably due to the averaging procedure used in the LIRAS3 four-site model. The best solution, although giving an acceptable $\%R_x$ (1.50), has been achieved with $\psi(-y) = 100°$ which infers a 'side on' co-ordination of the lanthanide to the carbonyl group. We consider this situation to be conceptually unreasonable. Hence, the HARDER calculations have been repeated, restricting the solutions to cover a range of chemically reasonable co-ordination geometries. Examination of the MNDO geometry shows that the carbonyl group bisects the H(3*x*)–C(3)–H(3*n*) bond angle when viewed along the C(2)–C(3) bond. This observation would suggest lanthanide binding on the $+y$ side to be in the plane of the carbonyl group thereby minimising steric interactions. Using this assumption the restrictions imposed on the HARDER analysis are, $r = 2.50$–3.50 Å, $\psi = 120$–180°, and $\varphi(+y) = 90°$. The results for the second HARDER analysis are slightly worse than the first but are chemically more reasonable. The HARDER two-site model is superior to the LIRAS3 two-site model (1.90 *vs.* 2.44), even with the restrictions. However, some of the individual shift errors are of the order of 1.0–2.5 ppm and suggest a better co-ordination geometry or molecular geometry is needed. For the four-site case the restricted HARDER analysis is worse than the LIRAS3 analysis and, as LIRAS3 is a sub-unit of HARDER, the restriction of $\varphi(+y) = 90°$ must be doubtful in this particular case.

Using the MNDO geometry the analysis of norcamphor has not proved totally successful in terms of the agreement factor, the individual errors on shifts and the co-ordination geometry. So the use of different geometries for the norcamphor framework was investigated to see if the lack of agreement is due to an incorrect substrate geometry. The first was taken from the *X*-ray crystal data of the Pd–camphor oxime complex.[22] This assumes that the camphor framework is comparable to that of norcamphor and that the oxime functionality can be directly replaced by a carbonyl group. The other two geometries were obtained *via* geometry optimisation at the STO-3G basis set levels.

The geometries are shown in Table 8 and differ from the original MNDO geometry near the functional group *i.e.* bonds C-1–C-2, C-2–C-3 and bond angle C-1–C-2–C-3. As these differences are close to the co-ordination site, and therefore determine the co-ordinates of the rest of the molecule relative to the carbonyl group, it is possible that the analysis could be improved.

Using the geometry of the Pd–camphor oxime the LIS analysis results (Table 7, XRAY) show no improvement over the previous results. The $\%R_x$ does improve in some cases but at the expense of a realistic co-ordination geometry *e.g.* $\psi(-y) = 85°$ for the unrestricted HARDER analysis. The restricted HARDER analyses show no improvement over LIRAS3.

The *ab initio* geometries do show a significant improvement in the analyses and there is no longer the need to restrict the HARDER calculations. Only one co-ordination geometry is suspect and that is for the HARDER two-site analysis of the 3-21G geometry where $\psi(-y) = 180°$ *i.e.* a linear $C{=}O \cdots Ln$ complex. The best result is obtained for the four-site HARDER analysis of the 3-21G geometry giving both a good $\%R_x$ of 1.25 and a chemically reasonable co-ordination geometry (see Tables 7 and 9). However LIRAS3 also gives an acceptable solution for this case ($\%R_x = 1.40$), hence there is no real advantage in using HARDER over LIRAS3. This is undoubtedly due to the asymmetric environment around the carbonyl group in norcamphor which is not completely reflected in either the LIRAS3 or HARDER models.

However this analysis illustrates the usefulness of LIS technique in determining unknown substrate geometries. The lowest agreement factor for both the LIRAS3 and HARDER analyses without any restrictions is the 3-21G structure with a four-site co-ordination geometry, and this is very substantial evidence for the accuracy of the structure.

Conclusions

The extension of LIRAS3 to consider the spatial environment of many different carbonyl groups has proved very successful in the analysis of indan-1-one. The analysis of norcamphor was sensitive to the substrate geometry used with both LIRAS3 and HARDER giving good solutions for the 3-21G derived geometry. The new program, HARDER, should be used with care and the following factors should always be taken into consideration: (*i*) the analysis should involve as many shift centres as possible to help ensure an over-determined solution; (*ii*) the lanthanide co-ordination geometry should be (or should be restricted to be) chemically reasonable (see the text); and (*iii*) a good solution should consider the individual errors on calculated shifts as well as the absolute value of $\%R_x$. Using these guide lines it will be

Table 8. Geometries for norcamphor.[a]

	MNDO[b]	XRAY[c]	STO-3G[d]	3-21G[d]
C(2)–O(2)	1.217	1.220	1.214	1.207
C(1)–C(2)	1.555	1.500	1.550	1.521
C(2)–C(3)	1.550	1.513	1.555	1.537
C(3)–C(4)	1.558	1.541	1.548	1.543
C(4)–C(5)	1.562	1.537	1.552	1.549
C(4)–C(7)	1.563	1.555	1.546	1.552
C(5)–C(6)	1.559	1.541	1.560	1.570
C(6)–C(1)	1.561	1.565	1.554	1.560
C(1)–C(7)	1.561	1.571	1.543	1.546
C–H	1.090	1.090	1.090	1.090
C(1)–C(2)–C(3)	105.4	108.3	105.2	105.7
C(1)–C(2)–O(2)	128.1	128.4	127.7	127.8
C(2)–C(3)–C(4)	101.8	101.0	101.7	102.4
C(3)–C(4)–C(5)	109.3	106.5	108.4	107.7
C(4)–C(5)–C(6)	103.4	103.0	103.4	103.0
C(5)–C(6)–C(1)	103.3	104.9	103.2	103.4
C(7)–C(1)–C(2)	100.3	99.4	100.7	101.3
H(1)–C(1)–C(6)[C(7)]	116.1	116.1	114.6 (117.5)	115.0 (118.4)
H(3*x*)–C(3)–C(2)[C(4)]	110.8	110.8	110.3 (111.4)	109.2 (111.6)
H(3*n*)–C(3)–C(2)[C(4)]	112.0	112.0	111.9 (113.4)	111.1 (114.0)
H(4)–C(4)–C(5)[C(7)]	116.1	116.1	113.9 (116.0)	114.4 (116.1)
H(5*x*)–C(5)–C(4)[C(6)]	110.8	110.8	110.5 (110.9)	110.7 (110.7)
H(5*n*)–C(5)–C(4)[C(6)]	112.0	112.0	112.0 (112.3)	111.8 (112.2)
H(6*x*)–C(6)–C(1)[C(5)]	110.8	110.8	110.3 (111.1)	109.8 (111.0)
H(6*n*)–C(6)–C(1)[C(5)]	112.0	112.0	112.1 (112.4)	111.8 (112.6)
H(7*s*)–C(7)–C(1)[C(4)]	113.0	113.0	113.2 (113.2)	113.1 (112.9)
H(7*a*)–C(7)–C(1)[C(4)]	113.0	113.0	112.8 (112.9)	112.5 (112.8)
C(1)–C(2)–C(3)–C(4)	−1.5	1.7	2.3	2.1
C(2)–C(3)–C(4)–C(5)	−69.8	−73.3	−69.7	−70.1
C(3)–C(4)–C(5)–C(6)	71.1	69.3	−72.0	−70.0
C(4)–C(5)–C(6)–C(1)	0.5	3.7	0.0	−1.4
C(5)–C(6)–C(1)–C(2)	−69.9	−71.4	70.1	71.5
C(7)–C(1)–C(2)–C(2)	146.2	144.4	147.1	147.3
C(4)–C(3)–C(2)–O(2)	178.0	−178.9	177.7	177.9

[a] Bond lengths in ångströms, all angles in degrees. CH bond lengths and CCH bond angles taken from ref. 21(*b*). [b] MNDO optimised structure. [c] Crystal structure of palladium camphor oxime ($R = 0.025$) from ref. 22. Standard C=O bond length taken from ref. 23. [d] Optimised using the GAMESS program, footnote p. 1380.

Table 9. Calculated lanthanide-induced shifts for norcamphor.

Atom	Obs.	Calc.[a]	Error
C-1	58.9	58.8	−0.1
C-2	145.3	145.3	0.0
C-3	59.5	59.1	−0.4
C-4	29.1	28.9	−0.2
C-5	23.0	22.4	−0.6
C-6	32.8	32.3	−0.5
C-7	30.1	30.8	0.7
1-H	45.8	45.9	0.1
3*n*-H	40.3	40.1	−0.2
3*x*-H	39.7	40.3	0.6
4-H	16.8	16.4	−0.4
5*n*-H	17.1	17.2	0.1
5*x*-H	12.9	13.5	0.6
6*n*-H	33.0	32.3	−0.7
6*x*-H	18.5	17.7	−0.8
7*s*-H	25.6	26.9	1.3
7*a*-H	17.1	18.1	1.0

[a] Substrate geometry from Table 8 (3-21G). Lanthanide co-ordination geometry as given for the HARDER analysis in Table 7 (3-21G).

possible to extend the LIS technique to compounds previously unsuited to investigation.

Experimental

The ^{1}H and ^{13}C spectra were obtained on a Bruker WM-250 spectrometer at a probe temperature of 25 °C. All spectra were measured for solutions in $CDCl_3$, which had been stored over molecular sieves, with $SiMe_4$ as an internal standard.

Commercial lanthanide-shift reagents were dried *in vacuo* over P_2O_5 for 24 h prior to use, as were commercial samples of indan-1-one and norcamphor. Indan-1-one had previously been recrystallised from methanol–water and thoroughly dried.

The results obtained from the LIS experiments were obtained using Yb(fod)$_3$ (the incremental weighing method) and are shown in Tables 1 and 2. The proton assignments for indan-1-one have been determined by decoupling techniques with the carbon assignments.[24] For norcamphor, proton[25] and carbon[26] assignments were found in the literature.

The experimental plots were all obtained with a molar ratio $\rho = [L]/[S]$ (L = shift reagent, S = substrate) in the range 0.00–0.14. Except for 5*n*-H and 5*x*-H (norcamphor), where overlapping resonances confused the assignments, all shifts showed a good correlation and intercept, demonstrating the linearity of the plots. Analogous experiments using La(fod)$_3$ were also performed, observing only the ^{13}C nuclei, as protons have been shown not to display any significant shifts. For indan-1-one four additions of La(fod)$_3$ were made over the range $\rho = 0.00$–0.16 giving significant shifts for all the sp^2 hybridised carbons except C-4. On addition of La(fod)$_3$ to norcamphor only four carbons gave substantial shifts. The corresponding ΔD values have been subtracted from the ΔM values to give the pseudo-contact shifts ($\Delta M - \Delta D$).

All computational work was performed on a DEC VAX 11/780 using a simple LSQF procedure to obtain the ΔM and ΔD values and implementing both the LIRAS3 and HARDER programs (source code in FORTRAN).

The aromatic proton region of indan-1-one was analysed using a degassed sample of freshly recrystallised and dried compound dissolved in $CDCl_3$ with $SiMe_4$ as an internal standard. Spectral conditions were, 32 transients accumulated in 8K data points with a pulse width of 5.0 μs and a sweep width of 200 Hz, giving an acquisition time of 10.2 s. A Gaussian multiplication of the FID was then carried out using values of LB = −0.5 Hz and GB = 0.2 Hz. The FID was then zero-filled to 32K data points giving a digital resolution of 0.01 Hz per point. The spectrum was then analysed as an ABCDX$_2$ spin system. The final refinement of the parameters (Table 5) was carried out by the iterative computer program PANIC[27] to an RMS error of 0.015.

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References

1 R. J. Abraham and I. S. Haworth, *Magn. Reson. Chem.*, 1988, **26**, 252.

2 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 1485.

3 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron*, 1982, **38**, 3245.

4 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1037.

5 R. J. Abraham, H. A. Bergen, and D. J. Chadwick, *J. Chem. Res. (S)*, 1983, 118.

6 R. J. Abraham, H. A. Bergen, and D. J. Chadwick, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1161.

7 R. Benassi, D. Larossi, U. Folli, L. Scheratti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1981, 228.

8 R. Benassi, U. Folli, D. Larossi, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1983, 911.

9 F. Inagaki, S. Takahashi, M. Tasumi, and T. Miyazama, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1590.

10 (*a*) D. J. Raber, J. A. Peters, and M. S. Nieuwenhuizen, *J. Chem. Soc., Perkin Trans. 2*, 1986, 853; (*b*) D. J. Raber, C. M. Janks, M. D. Johnston, Jr., and N. K. Raber, *J. Am. Chem. Soc.*, 1980, **102**, 6591.

11 (*a*) R. J. Abraham, D. J. Chadwick, L. Griffiths, and F. Sancassan, *Tetrahedron Lett.*, 1979, **48**, 4691; (*b*) B. H. Lienard and A. J. Thomson, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1390; (*c*) R. E. Lenkinski and J. Reuben, *J. Am. Chem. Soc.*, 1976, **98**, 276.

12 R. J. Abraham, P. E. Smith, C. Deleuze, and V. Lo Gatto, *Magn. Reson. Chem.*, 1987, **25**, 147.

13 R. J. Abraham and M. S. Lucas, *J. Chem. Soc., Perkin Trans. 2*, 1988, 669.

14 R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron Lett.*, 1981, **22**, 2139.

15 T. H. Chao and J. Laane, *J. Mol. Spectrosc.*, 1973, **48**, 266.

16 M. J. S. Dewar and W. Theil, *J. Am. Chem. Soc.*, 1977, **99**, 4899.

17 R. Wagner, J. Fine, J. W. Simmons, and J. H. Goldstein, *J. Chem. Phys.*, 1957, **26**, 634.

18 Y. Tanimoto, H. Kobayashi, S. Nagakura, and Y. Saito, *Acta. Crystallogr., Sect. B*, 1973, **29**, 1822.

19 (*a*) H. Gunther, *Tetrahedron Lett.*, 1967, **31**, 2967; (*b*) J. B. Pawliczek and H. Gunther, *Tetrahedron*, 1970, **26**, 1755.

20 A. Langseth and B. P. Stoicheff, *Can. J. Phys.*, 1956, **34**, 350.

21 (*a*) R. J. Abraham, H. A. Bergen, and D. J. Chadwick, *Tetrahedron*, 1982, **38**, 3271; (*b*) R. J. Abraham and J. Fisher, *Magn. Reson. Chem.*, 1985, **23**, 856.

22 A. G. Constable, W. S. McDonald, B. Odell, and B. L. Shaw, *J. Chem. Soc., Dalton Trans.*, 1983, 2509.

23 J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, 1967, **89**, 4253.

24 D. W. Hughes, B. C. Nalliah, H. L. Holland, and D. B. MacClean, *Can. J. Chem.*, 1977, **55**, 3304.

25 J. L. Marshall and S. R. Walter, *J. Am. Chem. Soc.*, 1974, **96**, 6358.

26 G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.

27 PANIC: Bruker n.m.r. software. Version for the ASPECT 2000.

28 (*a*) T. H. Dunning and P. J. Hay, in 'Modern Theoretical Chemistry,' ed. M. F. Schaefer, Plenum, New York, 1977; (*b*) R. Ahlrichs and P. R. Taylor, *J. Chim. Phys.*, 1981, **78**, 315.

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