

A LANTHANIDE INDUCED SHIFT (LIS) INVESTIGATION OF THE CONFORMATION OF CYCLOHEXANONES IN SOLUTION

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Abstract—The solution conformations of cyclohexanone **1** and 4-*t*-butyl cyclohexanone **2** have been obtained by the use of the LIS given by Yb(fod)₃. A starting geometry for the substrates was obtained by molecular mechanics calculations. The use of a two-site model for lanthanide-substrate complexing, together with iteration on the ¹H and ¹³C induced shifts allowed the angle of pucker of the cyclohexanone rings to be determined. In contrast, a one-site model gave no acceptable solutions. The cyclohexanone ring is somewhat flatter at the carbonyl end than cyclohexane, the angle of pucker (α) being reduced from 51° to 49° i.e. the dihedral angle (ω_{12}) is reduced from 56 to 51°. In 4-*t*-butyl-cyclohexanone the angle of pucker at the carbonyl end is further reduced. The solution conformation of **1** agrees closely with that deduced by MM calculations; interestingly, the conformation of **2** is essentially identical with the geometry found in the crystal.

Despite the wealth of investigations into lanthanide induced shifts (LIS)¹ since Hinckley's discovery of these reagents,² quantitative conformational analysis using LIS, although an intriguing prospect,³ has still not been satisfactorily proven.⁴ Although in concept a straightforward and simple technique, in practice a number of problems arise which so far have prevented the full use of this method in conformational analysis.

The elucidation of the bound shift Δ of each nucleus, i.e. the difference between the shift of the complexed (LS) and free substrate (S), is straightforward if only one kind of complex is present in solution and it has a large stability constant. In this case, the plot of the observed chemical shift against ρ , the shift reagent/substrate ratio, is a straight line (at low ρ values) of slope equal to Δ , the bound shift, if the stoichiometry of the complex is 1:1. The bound shifts (Δ), sometimes corrected for the small diamagnetic shift^{5,6} are then usually directly related to the complex geometry by the McConnell-Robertson equation (1).⁷

$$\Delta = K \cdot (3 \cos^2 \theta - 1) / R^3 \quad (1)$$

Several difficulties in this apparently simple procedure arise. The bound shifts may be affected by the formation of more than one kind of complex, e.g. in the system 4-*t*-butyl cyclohexanone-Eu(fod)₃ both LS and LS₂ complexes are present.⁸ The use of equation (1) assumes that contact contributions and non-axial symmetry in the complex can be neglected. Equation (1) is also a rather soft function⁹ and deceptively good fits owing to the acci-

dental compensation of errors have been obtained.¹⁰ The use of broadening reagents in conjunction with the shift analysis, often cited, has now been shown to lead to considerable additional problems.¹¹ Finally, the substrate conformation so determined is that in the LS complex: this may differ from that of the free substrate.

However, previous investigations are now generally agreed on the following points:

(1) If the plots of δ_{obs} versus ρ for low values of ρ are straight lines, a predominance of one complex is present and in this case the *relative* slopes are good approximations to the relative bound shifts. This is true even when over the range of ρ studied the main complex is LS₂.⁸

(2) The use of relative slopes also reduces experimental errors, particularly those arising from the presence of scavenger impurities in the system.¹²

(3) In saturated compounds the contact shift is negligible for proton shifts but a major contribution for carbon shifts. Only with ytterbium shift reagents can the contact-contribution be neglected for all nuclei except adjacent atoms^{6,13} (e.g. the C and O in C=O).

(4) Effective axial symmetry, although questioned,¹⁴ is generally accepted¹⁵ and in this case the symmetry axis is assumed to be along the lanthanide-co-ordinating atom bond.^{9,15}

(5) The simultaneous use of proton and C-13 data results in a much greater degree of determination of the system geometry.^{4,17}

It is of interest to note that the major limitation in many previous investigations concerns point (5) above. If the LIS shifts of only one type of nucleus (commonly ¹H or ¹³C) are determined the resulting set of data will usually be insufficient to define *both* the lanthanide position *and* the substrate geometry.

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A further fundamental objection to many previous investigations is their assumption of a unique, but chemically unreal, lanthanide-substrate geometry. Some time ago Abraham *et al.*¹⁸ and Chadwick and Williams^{6,19} independently showed that a two-site model, when the donor atom of the substrate has available two lone-pairs, as in carbonyls and alcohols was both chemically more feasible and gave better agreement with experiment than a one-site model. Recent investigations on cyclic and acyclic ketones^{15,20} have supported this model.

On this basis we decided to initiate a detailed investigation into the conformations and energetics of alkylcyclohexanones. Cyclohexanones are very convenient substrates for a LIS investigation, as the lack of rotation about the C=O bond and the presence of a well-defined ring conformation restricts the possible complex geometries.

A further consideration was the availability of a generalised force-field program to provide an initial substrate geometry. The LIS ΔM values and the applicability of the two-site model can then be tested and used to refine the substrate molecular geometry. In this investigation the angle of buckle of the cyclohexanone ring was determined in this fashion for cyclohexanone **1** and 4-*tert*-butyl cyclohexanone **2**.

LIS shifts on **2** have been reported previously^{8,10,12,14,19,21} and investigations on the lanthanide-substrate equilibrium⁸ and on the position of the lanthanide in the complex are reported.^{10,14,19} **16,22** and alkylcyclohexanones²³ have been studied by LIS. However, the conformational applications of LIS in this class of compounds were restricted to the study of ring inversion and conformer populations in alkyl cyclohexanones (using the *t*-butyl cyclohexanones as models for the LIS shifts)¹² and a semiquantitative study of the conformation of 3- α -naphthyl-5,5-dimethylcyclohexanone²⁴ and 3-aryl-3,5-trimethyl cyclohexanones.^{25,26}

The trial geometry of cyclohexanone was kindly provided by Dr. J. Krane²⁷ who has developed the Boyd force-field²⁸ to include a carbonyl group. It will be shown (Table 4) that the force-field geometries of the cyclohexane ring in cyclohexanone and methylene cyclohexane are virtually identical. Therefore we have used the alkene force-field of White and Bovill²⁹ to calculate a geometry of 4-*t*-butyl-1-methylene cyclohexane to provide the initial geometry for **2**.

The LIS program used here, LIRAS (Lanthanide Induced Relaxation and Shifts), is based on the METASEARCH program⁶ in which the position of the lanthanide with respect to the substrate is varied incrementally (r , ϕ , ψ see Fig. 1). For each

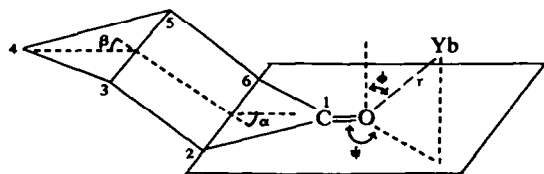


Fig. 1. Lanthanide-substrate geometry—definitions.

position of the lanthanide, the ΔM values are calculated from eqn (1), and the calculated and observed ΔM values compared using the crystallographic agreement factor R (eqn 2)

$$R = \sqrt{\left\{ \frac{\sum (\Delta_{\text{obs}} - \Delta_{\text{calc}})^2}{\sum \Delta_{\text{obs}}^2} \right\}} \quad (2)$$

The two-site model employed is one in which the two lanthanide positions are mirror images with respect to the plane of the carbonyl π orbitals, (they are not, however, constrained to be in the C.CO.C plane). The relative populations of these sites can be varied, but not, thus far, their relative geometries. Of course, for symmetrical molecules such as **1** and **2** this is not a restriction. The calculated shift for each nucleus is thus the weighted mean of the shifts for the two equilibrating LS complexes. Either the atomic co-ordinates or the "Z-matrix" of the substrate can be input and in the latter case the geometry of the substrate can be varied incrementally and the best solutions for each geometry output. Full details of the program will be given elsewhere.³⁰

Note that this analysis does not preclude the formation of some LS_2 complexes, and also, more importantly, even for symmetric molecules such as **1** and **2** (where the two-site populations are identical) the average over two sites is *not* equivalent to a one-site model (see later).

EXPERIMENTAL

The proton and ¹³C spectra were obtained on PE R-34 (220 MHz) and Varian XL-100 (25.2 MHz) spectrometers with probe temperatures *ca.* 30°C. All spectra were obtained in CDCl₃ which was stored over molecular sieves and passed through an alumina column immediately before use. Lanthanide shift reagents were used as purchased. Commercial samples of the ketones were purified by distillation *in vacuo* and recrystallisation **2** from *n*-pentane, respectively. All computations were performed on the University ICL 1906 S computer.

Two different methods have been reported to obtain ΔM values, the incremental dilution²⁶ and incremental weighing¹ procedures. In the former, incremental amounts of a stock solution of substrate are added to the lanthanide reagent, whilst in the latter incremental amounts of shift reagent are added to a solution of the substrate. The two methods gave significantly different

Table 1. Bound shifts (ΔM) and relative bound shifts (R) for **2** with incremental weighing and with Eu(fod)₃ and Yb(fod)₃

Nucleus	Eu(fod) ₃		Yb(fod) ₃	
	ΔM	R	ΔM	R
H _{2a}	13.0	100.0	42.7	100.0
H _{2b}	10.2	78.5	31.6	74.0
H _{3a}	5.1	39.2	19.2	45.0
H _{3b}	3.4	26.2	13.0	30.4
H _{4a}	4.2	32.3	14.8	34.7
Me	1.3	10.0	5.1	11.9
C ₁	32.0	246.2	123.0	288.1
C ₂	8.5	65.4	48.5	113.6
C ₃	8.0	61.5	22.5	52.7
C ₄	4.8	36.9	16.9	39.6
Cq	2.7	20.8	8.5	19.9
C(Me)	1.6	12.3	5.7	13.3

Table 2. Observed shifts (δ) and bound shifts (ΔM) for cyclohexanone-Yb(fod)₃^a

[L] × 10 ⁻² M	ρ (× 10 ⁻²) ^b	C ₁	C _{2,6}	C _{3,5}	C ₄	H _{2,6}	H _{3,5}	H ₄
0.00	0.00	211.57	41.94	27.04	25.02	2.336	1.868	1.731
2.39	1.89	213.90	42.85	27.48	25.33	3.035	2.169	1.956
7.36	5.83	218.14	44.57	28.26	25.94	4.354	2.733	2.376
10.51	8.33					5.139	3.062	2.614
12.33	9.77					5.614	3.274	2.782
ΔM^c		108.5	43.6	20.2	15.3	33.34	14.26	10.61
intercept		211.7	41.97	27.06	25.03	2.36	1.88	1.74
corr. coeff.		.9994	.9997	.9994	.9998	.9997	.9997	.9996

^a[S₀] = 1.2617 M^b $\rho = [L]/[S]$ ^ccarbon data normalised to H_{2,6} (3 points), ΔM 34.4

values of the ΔM values, though the relative bound shifts were in much closer agreement, as expected. As the incremental weighing method is more convenient for ¹³C experiments, and we wished to utilise both ¹H and ¹³C ΔM values, we use this method henceforth, measuring the proton and ¹³C spectra on the same solutions, or normalising them (see later).

The relative bound proton shifts for **2** are very similar for Eu(fod)₃ and Yb(fod)₃ but the relative bound ¹³C shifts are very different (Table 1). This is due to the significant contact contribution of the ¹³C shifts with Eu(fod)₃. For this reason we use henceforth only Yb(fod)₃.

The results of the LIS experiments with Yb(fod)₃ (incremental weighing method) on **1** and **2** are given in Tables 2 and 3. For cyclohexanone, the ¹³C bound shifts were well defined from three incremental additions of shift reagent, but two further additions proved necessary for the proton data. As the ΔM values for the complete set of proton data are slightly different from those obtained from the first three points (which are for the same solutions as the ¹³C data) the initial ¹³C ΔM values were normalised to the more accurate final proton data, using H_{2,6}. Both the correlation coefficients (>0.999) and the intercepts (which are identical to the unshifted spectrum) demonstrate the accurate linearity of these plots.

For **2**, the proton and ¹³C shifts were from different experiments, and the ¹³C bound shifts have again been normalised by determining the shift of H_{2,6} eq. from the solutions used for the ¹³C experiments (Table 3). Again the correlation coefficients and intercepts for the ¹³C data are very good, but although the former are acceptable for the proton data, the intercepts differ by more than experimental error from the δ_0 values of the proton spectrum, even after allowing for the accidental degeneracy of the spectrum at 220 MHz.

The ΔM values of Tables 2 and 3 can now be used to obtain information on the lanthanide-substrate geometries.

RESULTS AND DISCUSSION

The molecular mechanics geometry of **1** is given in Table 4 together with the calculated geometries of methylene cyclohexane **3** and 4-*t*-butylmethylene cyclohexane **4** and experimental geometries for **1** and **2** from several different techniques. The agreement between the ring geometries of **1** and **3** is within the differences obtained by different force-fields (cf data for **3** from the present force-field and that obtained by Anet³¹), thus providing support for our use of **4** as the trial geometry for **2**.

The electron diffraction data³² given is subject to

larger errors (± 0.01 Å in the bond lengths and $\pm 2.5^\circ$ in the bond angles) which means that the only parameters which differ significantly from the MM geometries are the C=O and C₁C₂ bonds. The value of 1.24 Å for the CO group does not agree with a number of other determinations of this bond length (1.215 ± .005). Gaultier *et al.*³³ obtained angles of buckle of 43 and 63° from the electron diffraction data, but these should be viewed with circumspection. The microwave investigation³⁴ of **1** also agrees with the MM geometry. In particular, the values of the ring carbon angles are in good agreement with the MM geometry.

The MM geometry of **4** compares reasonably well with the X-ray diffraction data^{33,35} for **2** at the non carbonyl end of the molecule, but the C₆C₁C₂ fragment is sharper and less buckled in the crystal. The dihedral angle ω_{23} in **2**, which is sensitive to the angle of buckle, differs in the crystal from the value obtained by NMR coupling constants.³⁶ This is not surprising as the C₆C₁C₂ fragment of the cyclohexanone ring is known to be more flexible than that e.g. in cyclohexane and could well change with solvent, or crystal packing forces. (It is of interest to note that the solvation energy of **1** does increase by a significant amount as the ring becomes flatter.)³⁷ It was this uncertainty which prompted the LIS study.

Our approach was to vary the C₆C₁C₂ angle of pucker, find the best lanthanide position for any given value and compare the agreement factor R (eqn 2) for each geometry. The best agreement (lowest value of R) should indicate the appropriate geometry. However in all cases, as the angle of buckle was increased, the O...Yb distance changed to compensate. In the absence of any indication of the appropriate O...Yb distance to use (values ranging from 2.8–3.2 Å have been obtained from LIS experiments, which may be compared with the ionic distance of 2.18 Å found in the crystal), the minimisation now becomes a flatter three dimensional rather than two dimensional function. The results obtained in this way are shown graphically in Figs. 2 and 3, which include for comparison the equivalent results using the one-site model.

In **1** the two-site model gives much better agreement factors than the one-site case (Fig. 2), even though there are the same number of unknown

Table 3. Observed shifts (δ) and bond shifts (ΔM) for 4-*t*-butyl cyclohexanone-Yb(fod)₃^a

[L] × 10 ⁻² M	ρ (× 10 ⁻²)	C ₁	C _{2,6}	C _{3,5}	C ₄	C _q	C _{Me}	H _{2,6eq}	H _{2,6ax}	H _{3,5eq}	H _{3,5ax}	H ₄	H(Me)
0.00	0.00	211.94	41.24	27.59	46.67	32.42	27.59	2.345	2.345	2.079	1.458	1.458	.899
4.67(2.23) ^b	4.92(4.38) ^b	219.45	44.17	28.94	47.68	32.91	27.91	4.437	3.878	2.735	2.411	2.227	1.163
9.55(4.23)	10.06(8.32)	224.99	46.38	29.98	48.46	33.32	28.19	6.317	5.277	3.303	3.234	2.889	1.387
(6.22)	(12.22)							7.986	6.519	3.816	4.012	3.446	1.581
(9.51)	(18.68)							10.288	8.219	4.499	5.033	4.230	1.842
ΔM^c		123.0	48.5	22.5	16.9	8.5	5.7	42.71	31.62	13.00	19.23	14.85	5.06
intercept		212.3	41.38	27.65	46.71	32.44	27.60	2.55	2.49	2.15	1.55	1.56	0.93
corr. coeff.		.995	.996	.996	.996	.998	.999	.998	.998	.997	.997	.996	.996

^a[S]₀ = 0.9494 M for ¹³C, 0.5091 for ¹H^bFor the proton data, see text.^cCarbon data normalised to H_{2,6} (ΔM 45.0) see text.

Table 4. Comparative geometries of cyclohexanone and related compounds



Compound	Bond lengths (Å)				Bond Angles ^a				Torsional Angles ^b		Angle of Pucker ^c		Technique and Reference	
	C=X	C ₁₂	C ₂₃	C ₃₄	C ₁	C ₂	C ₃	C ₄	ω ₁₂	ω ₂₃	ω ₃₄	α		β
1 R=H, X=O	1.222	1.506	1.537	1.539	116.4	110.3	110.8	111.3	-52.5	53.0	-57.0	47	51	MM, ²⁷
	1.24	1.54	1.54	1.54	117	109.5	109.5	109.5				43	63	ED, ³²
	1.222 ^d	1.507 ^d	1.526	—	117.2 ^d	109.4	109.5	110.3						
3 R=H, X=CH ₂	1.338	1.510	1.528	1.529	116.1	110.2	111.0	111.9	-52.4	52.7	-56.7			MM, this work
					115	111	111	111	-54	54	-56			
2 R=tBu, X=O	1.214	1.489	1.533	1.517	115.5	112.1	112.5	109.0	-47.4	52.1	-56.6	43.0	50.5	X-ray, ^{33,35}
4 R=tBu, X=CH ₂	1.338	1.508	1.528	1.539	115.0	110.1	112.0	109.6	-52	53.8	-56.7			MM, this work
					115.0	110.1	112.0	109.6	-52	53.8	-56.7			

^aThe internal angle, i.e. C₁ is C₅C₁C₂ etc.

^bThe C.C.C. angle, i.e. ω₁₂ is for C₆C₁C₂C₃ etc.

^cThe angle between planes C₂C₃C₅C₆ and C₆C₁C₂ (α), and C₃C₄C₅ (β).

^dassumed values.

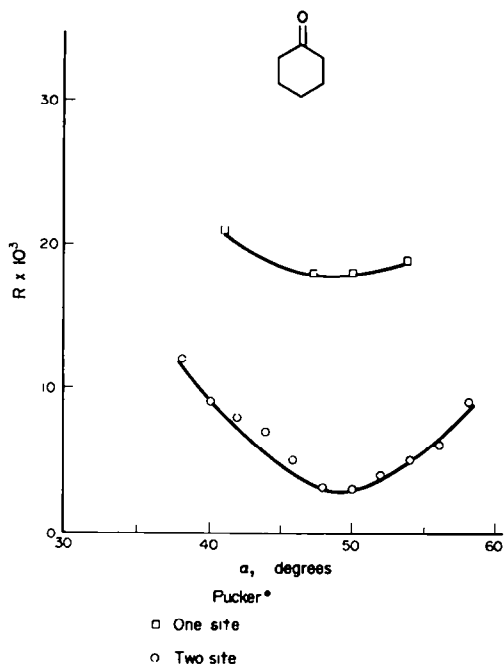


Fig. 2. The agreement factor $R(\times 10^3)$ versus the angle of pucker (α) for cyclohexanone, \square one-site model, \circ the two-site model.

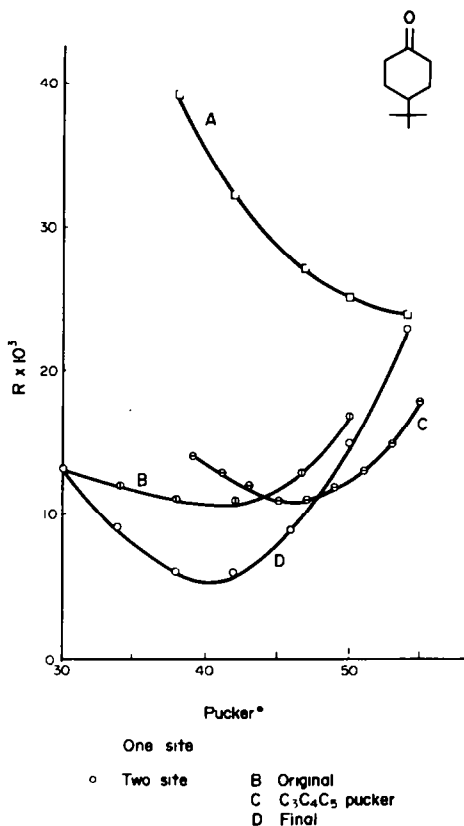


Fig. 3. The agreement factor $R(\times 10^3)$ versus the angles of pucker of the ring for 4-*t*-butyl cyclohexanone. A) one-site model versus α ; B) two-site model versus α , original geometry, C) and D) two-site model versus β and α respectively.

parameters to be determined in both cases. (The values of r , φ and ψ , see Fig. 1). In the one-site model the best solution is found along the $C=O$ axis. This is not surprising, but is *not* a consequence of the molecular symmetry as in the LIRAS program the calculated shifts for chemically equivalent nuclei (e.g. C_2 and C_6) are averaged before comparison with the observed data. In contrast the two-site model gives chemically reasonable values of these parameters. The values of r , φ and ψ obtained are 3.2–3.3 Å, 90 and 125° respectively. The values of φ and ψ in particular are indeed reasonable values for the orientation of the oxygen lone-pairs, in complete contrast to the position found in the one-site model.

For 1 the best agreement is found for both models for an angle of pucker of *ca.* 49°. The definition is quite good, but it must be emphasised that this is not a particularly well-determined system. Due to the molecular flipping and symmetry there are only six ΔM values. (The carbonyl carbon being excluded due to the contact contribution). One of these is used as a reference, giving only 5 equations to determine the lanthanide position (3 unknowns) and the substrate geometry. For this reason we did not consider it either necessary or justified to refine the $C_3C_4C_5$ angle of pucker in this case.

In 2 the solutions are better-determined as there are now nine ΔM values (four C and five H) to use. Again the $C=O$ is excluded, and we have also excluded the *t*-butyl methyl carbons and hydrogens. Their ΔM values are small (Table 3) and averaging processes would decrease their dependence on the molecular geometry.

The results (Fig. 3) are of some interest. The one-site model (Fig. 3A) shows no convergence at all, the agreement became progressively better with increasing angles of pucker (α) until unreasonable geometries are reached. The two site model initially gave ambiguous results (Fig. 3B) in that there was only a broad ill-defined minimum. Detailed inspection of the results showed that this was due to a poor fit of the three atoms at C_4 (i.e. C_4 , C_4-H and C_4-C) for all values of α . As it is these atoms which are most affected by the angle of buckle of the C_4 moiety (β) and also the bond angles at C_4 are highly strained, due to the *t*-butyl group, it is possible that the MM calculations may not reproduce this angle precisely. Thus in this case a double iteration was performed, varying both α and β . The R values converged smoothly and quickly to a well-defined minimum in both parameters (Fig. 3C and D), though obviously the definition is much better w.r.t. α as in this case all the ΔM values are affected, whereas changing β only affects the three C_4 atoms (and to a lesser extent $H_{3,5}$ eq and ax).

The curves show very clearly that in this system the observed ΔM values when used with eqn (1) and the two-site model are capable of providing a unique and well defined substrate geometry.

Furthermore the definition is such as to demonstrate small inaccuracies in the trial substrate geometry. This is most encouraging and suggests if substantiated further, that this technique can indeed provide reliable substrate geometries.

The co-ordinates of the Lanthanide for the best substrate geometry are 3.0 Å and 100 and 140° respectively (τ , ϕ , ψ).

The final geometry obtained from the LIS analysis has angles of pucker of ca. 40° (α) and 47° (β). If we assume a 0.1 error in the ΔM values then this gives errors in the agreement factor (R) of 2.0×10^{-3} for **1** and 1.5×10^{-3} for **2**. Inspection of Figs. 2 and 3 shows that this leads to uncertainties in the final values of α and β of ca $\pm 4^\circ$.

It is of interest to note (Table 4) that the geometries obtained by this investigation are, within experimental error, identical to the crystal geometry for **2**, and identical to the force-field geometry for **1**. However the difference in the angle of pucker of the carbonyl end of the molecule in **1** and **2** does appear to be a real effect, and one which could not have been deduced from the previous investigations.

CONCLUSIONS

The results of this LIS study on the conformations of **1** and **2** show considerable promise for the application of this technique to structural investigations. The geometries which have been obtained by an objective approach compare well with those found by other techniques and also illustrate small differences in the substrate geometry.

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