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13a, 77153-67-4; 13b, 77153-68-5; 14a, 77153-69-6; 15a, 77153-70-9; 15b, 77153-71-0; 16, 77153-72-1; 17, 5025-38-7; 19, 77209-99-5; 22, 64465-53-8; 23, 321-28-8; 24, 50868-72-9; 26, 77153-73-2; 27, 399-55-3; *p*-toluidine, 106-49-0; 4-butylaniline, 104-13-2; 4-isopropylaniline, 99-88-7; *m*-anisidine, 536-90-3; 2-methoxy-5-phenylaniline, 39811-17-1; 2-(methanesulfonyloxy)aniline, 77153-74-3; 4-aminoestrone 3-methyl ether, 13010-21-4; 4-fluorotoluene, 352-32-9; 4-fluorocumene, 403-39-4; 4-butylfluorobenzene, 701-30-4; 3-fluoroanisole, 456-49-5; piperidine, 110-89-4; 2-methoxyaniline, 90-04-0; 2-methoxy-5-methylaniline, 120-71-8.

Structure Elucidation with Lanthanide-Induced Shifts. 10. Generation of Atomic Coordinates: Empirical Force Field Calculations vs. Other Methods¹

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Structure analysis by methods such as lanthanide-induced shifts requires a mathematical description of a molecular structure. The validity of the final results depends upon the particular model used to generate atomic coordinates for the proposed structure. We have evaluated several different models which have been employed by workers in the field of lanthanide shift reagents. Three of the models are based on X-ray crystallographic data, one utilizes standard bond lengths and bond angles, and a last model uses empirical force field calculations. The results clearly show that empirical force field calculations provide the most reliable model for molecular structure. The dangers of using other less accurate structural models are also demonstrated, since incorrect structures can fortuitously result in excellent statistical agreement with experimental data.

In the last 10 years lanthanide shift reagents (LSR's) have proved to be a valuable development in the use of NMR spectroscopy for organic structure determination.² While LSR's can be used qualitatively to simplify and interpret spectral patterns, more recent work has been directed at a quantitative comparison of experimental lanthanide-induced shifts (LIS) with values predicted via the pseudocontact equation³ (eq 1 and Figure 1). The

$$\text{LIS} = k(3 \cos^2 \theta - 1)/r^3 \quad (1)$$

predicted LIS for some proposed structure are compared with the experimental LIS, and a statistical comparison (usually with the crystallographic agreement factor)⁴ is used to assess the validity of the proposed structure. We have found considerable success in applying this technique to the analysis of both nitriles⁵ and ketones.^{1,6} The pre-

diction of induced shifts with eq 1 requires a mathematical description of the complex in terms of interatomic distances and angles. In this paper we present an evaluation of various models which have been used to calculate these geometric parameters. Our results demonstrate that calculation of substrate geometry by using empirical force field calculations affords the most accurate and reliable method available.

Caution must be exercised in the rigorous analysis of structures with LIS, since substantial errors may arise in both the determination of experimental LIS and in the calculation of predicted LIS. The difficulties in determining experimental LIS have been discussed at length,^{7,8} and the importance of using bound shifts corresponding to the 1:1 complex⁷ has also been emphasized.^{5a,9} Questions regarding the validity of eq 1 for calculating predicted LIS have been evaluated elsewhere.^{2,5a} A major problem still remains in the application of eq 1, however, and that is the determination of atomic coordinates for a proposed structure. Hinckley¹⁰ has shown that errors in these co-

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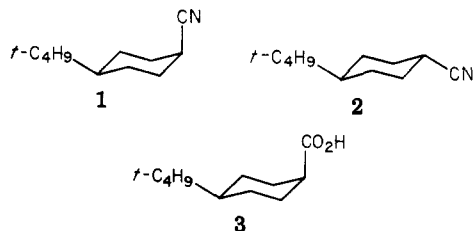
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ordinates can have a dramatic effect on the structure evaluation process, but the general problem of how to obtain accurate coordinates has not been adequately addressed. The geometric relationship between the substrate moiety and the lanthanide ion of the LSR complex has generally been evaluated by a fitting process between experimental and calculated LIS (although we have demonstrated that a good approximation for one of the parameters—the bond length—can be obtained from related X-ray crystallographic structures^{5a,6}). Nevertheless, the problem remains as to how the coordinates of the substrate moiety can best be obtained.

Workers in the field of shift reagents have almost invariably resorted to the approximation that the structure of the substrate moiety in the complex is unchanged from that of the free substrate, and within that basic assumption a variety of procedures have been used. Some workers have utilized coordinates derived from X-ray crystal structures (of either the same or of related compounds)¹¹ while others have used either standard geometry parameters^{5b-d,12} or even such crude methods as measurement from Dreiding models.¹³ A very few have calculated the structure of the substrate by methods such as empirical force field calculations,^{1,5a,d,6,14} although even here subsequent modification of the calculated structure has sometimes been employed in order to improve the fit with experimental LIS.^{14b,d} It is our intention in this work to demonstrate the reliability of such structure calculations as well as the necessity for using them when an attempt is made to carry out rigorous structure evaluation with lanthanide induced shifts.

Results and Discussion

We have investigated the LIS structure fits obtained with five different models for calculating the coordinates of *cis*- and *trans*-4-*tert*-butylcyclohexanecarbonitriles (1 and 2). These compounds were selected because of the



availability of an X-ray crystal structure of the closely related carboxylic acid (3). The coordinates of the *cis*-

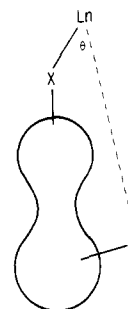


Figure 1. Idealized geometric features of a lanthanide-substrate complex.

Table I. Experimental and Bound Shifts for 1 and 2^a

proton ^b	exptl	X-ray	EXTND	SKEL	SGM	MMI
<i>cis</i> -4- <i>tert</i> -Butylcyclohexanecarbonitrile (1)						
<i>cis</i> -2	8.59	8.44	8.33	8.60	8.27	8.35
<i>trans</i> -2	5.93	5.78	5.59	5.57	5.61	5.56
<i>cis</i> -3	9.66	8.20	8.21	8.31	10.85	9.21
<i>trans</i> -3	4.46	4.24	4.05	4.05	4.38	4.22
<i>trans</i> -4	3.99	3.89	3.78	3.68	3.96	3.87
<i>t</i> -Bu	1.46	1.56	1.49	1.53	1.47	1.39
<i>trans</i> -4- <i>tert</i> -Butylcyclohexanecarbonitrile (2)						
<i>cis</i> -2	8.41	8.39	8.27	8.29	8.67	8.39
<i>trans</i> -2	8.15	8.05	7.92	8.00	8.20	8.18
<i>cis</i> -3	3.29	3.26	3.16	3.22	3.41	3.36
<i>trans</i> -3	3.94	4.04	4.01	4.04	3.97	4.05
<i>cis</i> -4	3.63	3.40	3.36	3.33	3.87	3.65
<i>t</i> -Bu	1.45	1.51	1.51	1.55	1.76	1.61

^a Experimental bound shifts are those for the 1:1 complex; LIS for each of the models were calculated with eq 1. The detailed procedure is described in the Experimental Section. All shifts are reported in parts per million.

^b The LIS of the proton on C-1 includes a substantial contact shift contribution⁵ and was therefore excluded from the calculations.

nitrile (1) were obtained for each of the models by the following procedures. (i) **X-ray**. The coordinates of the X-ray structure¹⁵ of *cis*-4-*tert*-butylcyclohexanecarboxylic acid (3) were used. The coordinates of the nitrile carbon of 1 were taken to be identical with those of the carbonyl carbon of the acid, and the nitrogen was placed on a linear extension of the C-C (carbonyl) bond at a distance of 1.16 Å.¹⁶ (ii) **EXTND**. Since X-ray structures are known¹⁷ to afford short C-H bond lengths, this model employed the X-ray data but had all C-H bond lengths extended to 1.095 Å. (iii) **SKEL**. Since the locations of hydrogen atoms are not well determined by X-ray crystallography, only the X-ray coordinates for the carbon skeleton were employed. The hydrogen coordinates were generated by using standardized bond lengths and angles,^{18,19} and the coordinates for the cyano group correspond to those of the X-ray model. (iv) **SGM**. In this standard geometry model the coordinates of all atoms were obtained from standard bond lengths and angles¹⁶ by geometrical calculation.²⁰ (v) **MMI**. The coordinates for all atoms were obtained by empirical force field calculations with a full geometry op-

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(20) A computer program which transformed an internal coordinate system (with standard bond lengths and angles) into a Cartesian coordinate system was employed. A variety of programs of this type are available from QCPE.

Table II. LIS Structure Fits for 1 and 2^a

	X-ray	EXTND	SKEL	SGM	MMI
<i>cis</i> -4- <i>tert</i> -Butylcyclohexanecarbonitrile (1)					
agreement factor	0.072	0.061	0.068	0.075	0.013
C-N-Eu angle, deg	175	176	175	175	174
torsional angle, ^b deg	180	180	180	180	180
scaling correction ^c	0.93	0.92	0.93	1.03	0.96
<i>trans</i> -4- <i>tert</i> -Butylcyclohexanecarbonitrile (2)					
agreement factor	0.019	0.022	0.026	0.044	0.025
C-N-Eu angle, deg	170	170	173	163	176
torsional angle, ^b deg	0	0	0	180	180
scaling correction ^c	1.00	0.98	0.99	1.03	1.01

^a For a detailed description of the comparison between calculated and experimental LIS see the Experimental Section. ^b The europium was restricted to the symmetry plane of the molecule, and the torsional angle was therefore either 180° (europium bent toward the hydrogen on C-1) or 0° (europium bent away from the hydrogen on C-1). ^c To correct for small systematic errors in the experimental shifts (see Experimental Section).

timization by using Allinger's MMI program.^{19,21} The same five models were used with the trans compound 2. The X-ray coordinates derived for the *cis* compound 1 were used to generate the corresponding coordinates for *trans*-4-*tert*-butylcyclohexanecarbonitrile (2) by interchanging the substituents on C-1. (The angular orientations of the equatorial and axial substituents were held constant.) The EXTND and SKEL models were then derived from the molecule constructed in this manner. The SGM and MMI coordinates were obtained as described above for 1.

The coordinates for 1 and 2 from each of the five models were used to calculate the predicted LIS for each set of protons in the molecule, and these are presented in Table I together with the experimental, bound shifts for the 1:1 complexes with Eu(fod)₃ in CCl₄. The statistical comparisons between experimental and predicted LIS are summarized in Table II. For the *cis*-nitrile 1 the agreement factor obtained with the MMI model is substantially superior (smaller by a factor of three) than that from any of the other models. In fact it is the only agreement factor below 0.03. Further examination of Table II shows that this trend does not extend to the trans isomer 2. While the agreement factor for the MMI model is again below 0.03, so are the results for several of the other models. Indeed, the only model which yields an agreement factor greater than 0.03 is SGM. The other four models all yield agreement factors which are quite similar and fall within the range of 0.02–0.03.

Clearly these results demonstrate that reliable structure fits are obtained by using coordinates from full geometry optimizations with empirical force field calculations. Similarly, the data suggest that SGM coordinates are not satisfactory. This conclusion is in agreement with our earlier work⁵ in which we found that satisfactory agreement factors could be obtained with the SGM model only when the molecule had no sterically bulky substituents. On the other hand "good" agreement factors can sometimes be obtained with the other models as shown by the results

Table III. Steric Energies of Structural Models for 1 and 2^a

	X-ray	EXTND	SKEL	SGM	MMI
1	65.84	20.96	22.46	36.24	15.29
2	85.13	20.71	21.90	35.34	14.81

^a From empirical force field calculations with no geometry optimization (see Experimental Section). All energies are in kilocalories/mole.

in Table II for *trans*-4-*tert*-butylcyclohexanecarbonitrile. Indeed, the X-ray model affords the lowest agreement factor for 2 despite the fact that all C-H bond lengths are consistently too short. This means that a determination of the best structure proposal (or in this case of the best model) cannot be made on the basis of agreement factor alone. A similar conclusion has been reached by Hofer²² in terms of finding the best location of the lanthanide ion relative to the organic moiety in the complex.

Since the data for 2 show that the agreement factor alone is not always capable of distinguishing between structure proposals, we have used a second method to evaluate the coordinates obtained for each of the five models with both 1 and 2. The total steric energy of each set of coordinates was calculated by empirical force field calculations (without any geometry optimization). The results of these calculations are summarized in Table III. Table III shows that the MMI model affords the structure of lowest energy (a necessary consequence of the geometry optimization procedure) and that all four of the other models yield consistently higher steric energies. That the calculated energies for the X-ray model are extremely high is not surprising. The C-H bond lengths determined by this method are too short because they reflect centers of electron densities rather than locations of nuclei,¹⁷ and this discrepancy with the optimal bond length of the force field must result in a large C-H compression energy. Indeed, extension of all C-H bond lengths in the EXTND model results in a very substantial decrease in steric energy. The energy of the SKEL model is slightly larger than that of EXTND in both cases. Finally the SGM energies are quite large, as might be expected for a model which ignores steric interactions.

Figure 2 presents a comparison of steric energy for each of the five structure models, with the corresponding agreement factor determined for the LIS results. If the point for the X-ray model is disregarded (as it should be because of its necessarily high steric energy), a remarkable trend is observed. Despite the fact that these two variables are only indirectly related, there is a clear tendency for the agreement factor and the steric energy to increase together. This must be regarded as further support for MMI as the best of the five models. The ideal model would have both the agreement factor and relative steric energy approaching zero, and any substantial deviation of a point from the origin must reflect flaws in the structural model. That both EXTND and SKEL for the trans isomer 2 exhibit agreement factors which are comparable to that for MMI appears therefore to be only a coincidence. Both models afford substantially higher steric energies than MMI, and the agreement factors are probably not significantly different²³ for any of these three models. In any event the comparison reinforces the conclusion²² that incorrect structure proposals can sometimes afford excellent agreement factors. Consequently, it is dangerous to base a structural hypothesis on a minimization of the agreement

(21) Reference 17, pp 1–82.

(22) See ref 2a, pp 130–131, 158.

(23) Reference 2a, p 129.

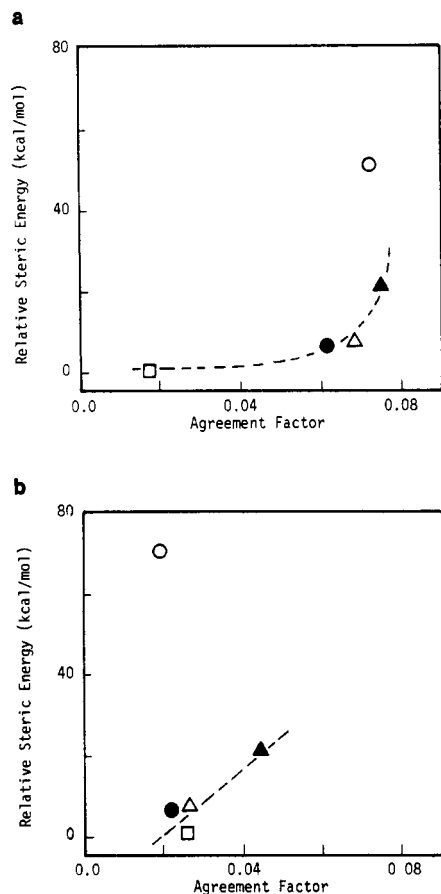


Figure 2. Plots of relative steric energy vs. agreement factor for (a) *cis*-4-*tert*-butylcyclohexanecarbonitrile and (b) *trans*-4-*tert*-butylcyclohexanecarbonitrile (O, X-ray; ●, EXTND; △, SKEL; ▲, SGM; □, MMI).

factor without additional evidence in favor of the particular structural model which is employed.

Conclusions

We believe that the specific examples analyzed here provide strong support for our earlier recommendations^{5,6} that empirical force field calculations be used to obtain atomic coordinates for LIS structure correlations. The derivation of coordinates from X-ray structures of related compounds is inadequate, even if the C-H bond lengths are adjusted to correct internuclear distances. Even if X-ray coordinates were available for the precise compound being evaluated, these coordinates might not be adequate. Solid-state structures can sometimes be substantially distorted by crystal packing forces,²⁴ and compounds sometimes crystallize in different conformations than those which predominate in solution.²⁵ Structures obtained by empirical force field calculations on the other hand reflect an energy minimum, and while they may exhibit differences from the X-ray structures,²⁶ they should reflect the structure of the molecules in solution. The ready availability of the computer programs employing Allinger's MMI¹⁹ and MM2²⁷ force fields, the speed with which these calculations can be carried out for even moderately large molecules,²¹ the structural accuracy of the calculations,^{21,28}

and the applicability of these force fields to functional compounds^{21,28} all argue strongly for the calculation of coordinates by this method. We have previously demonstrated that reliable and accurate LIS structure calculations can be carried out by using geometries obtained from empirical force field calculations,^{1,5,6} and we propose that the well-defined and reproducible geometries obtained with such calculations be adopted as the standard for structural correlations such as those carried out by using lanthanide-induced shifts.

Experimental Section

Reagents. Eu(fod)₃ is commercially available (Aldrich, Resolve-Al EuFOD, 16,093-8) and was sublimed (15 °C, 0.05 torr) and stored under vacuum desiccator over P₂O₅ prior to use. CCl₄ was dried by storing over 4A molecular sieves.

Nuclear magnetic resonance spectra were obtained by using Varian EM-360 (25 °C) and A-60 (37 °C) spectrometers. All spectra were recorded at either 600- (EM-360) or 500-Hz (A-60) sweep widths. Chemical shifts were measured relative to internal Me₄Si, and sweep widths were calibrated with an external audio oscillator. When the widths of spectra exceeded the sweep widths, offset spectra were recorded, and peak positions were measured relative to a Me₄Si audio side band.

Experimental LIS. Shift reagent runs utilized the incremental dilution method^{7a} in which a solution in CCl₄ containing both shift reagent (0.6 M) and the substrate (0.2 M) is successively diluted with a 0.2 M solution of the substrate in the same solvent. Thus the concentration of the substrate remains constant at 0.2 M, while the concentration of the shift reagent decreases with each dilution. The precise concentrations of shift reagent and substrate were determined gravimetrically for each sample by weighing the sample tube after each dilution, and spectra were recorded for a total of ca. 25 different concentrations of shift reagent.

Bound shifts and equilibrium constants were calculated via nonlinear regression analysis of the NMR data as described by Shapiro and Johnston.^{7a}

Predicted LIS. The predicted LIS were calculated with eq 1 by using $k = 976.6$ and a europium-nitrogen bond length of 2.5 Å.^{5a} The LIS of the hydrogen on C-1 (i.e., the hydrogen α to the cyano group) includes substantial contact shift⁵ and was therefore excluded from all calculations. Symmetry-equivalent protons were grouped into sets. The LIS was calculated with eq 1 for each individual proton in a set, and the average value was used as the predicted LIS for each hydrogen in the set. The symmetry of the LSR-substrate complex was restricted to the symmetry plane of the substrate as defined by C(4)-C(1)-C(N), and the LIS were then calculated for various C-N-Eu angles at intervals of 1° with a C(4)-C(1)-C(N)-Eu torsional angle of both 0° and 180°. The europium-substrate geometries reported in this work are those which afforded the lowest agreement factors (see below).

Comparison of Experimental LIS with Predicted LIS. Statistical evaluation of the fit between experimental and predicted LIS was carried out by using the crystallographic agreement factor.⁴ The shift of each hydrogen in the substrate molecule (with the exception of that on C-1) was included in the summation. (This is equivalent to assigning each set of symmetry-equivalent protons a weight equal to the number of protons in the set.) Refinement^{5a} of the initial fit was then carried out in order to minimize small systematic errors in the determination of experimental bound shifts.^{5b} All experimental shifts were modified by a small scaling factor according to the following equation: scaled experimental shift = Q (experimental shift), where Q was determined by finding the value leading to a minimum in the agreement factor. In general, the scaling factor, Q , is nearly unity for a "correct" structural hypothesis. For all of the structure fits reported here (including those based on inaccurate coordinates) Q is within the range 1.00 \pm 0.08.

Preparation of *cis*- and *trans*-4-*tert*-butylcyclohexanecarbonitriles (1 and 2). Commercially available 4-*tert*-butylbenzoic acid (Aldrich, No. 15,035-5) was hydrogenated with Pt in acetic acid in a Parr apparatus to yield a mixture of 4-*tert*-bu-

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tylcyclohexanecarboxylic acid. A mixture of *cis*²⁹ and *trans*²⁹ nitriles was prepared from the acid by successive conversion to the acid chloride (PCl₅) and the amide (aqueous NH₃) followed by dehydration (POCl₃). The isomers were separated by preparative GLC (30% Carbowax 20M).

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Registry No. 1, 15619-19-9; 2, 15619-18-8; 4-*tert*-butylbenzoic acid, 98-73-7.

Chlorination of Aliphatic Ketones in Methanol

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The chlorination of aliphatic ketones in methanol has been examined. The product distributions in methanol differ substantially from those obtained by chlorination in carbon tetrachloride. The reaction in methanol favors addition of chlorine to the least substituted carbon α to the carbonyl group. The effect is especially pronounced if an α carbon bearing two substituents is present. The distribution of products is determined by the relative stability of the enol ethers formed from the ketone under the reaction conditions.

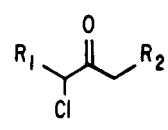
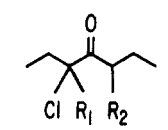
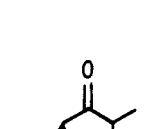
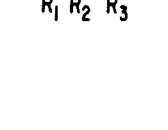
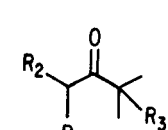
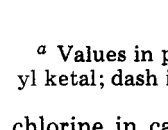
The monobromination of various ketones in the presence of methanol has been reported to give substantially different product distributions vs. bromination in other solvents.^{1,2} Exclusive α,α' -halogenation has been observed when cyclic ketones or their ketals are brominated in methanol.³ It was of interest to determine if the effect of methanol on the orientation of halogenation in these systems extended to the halogenation of aliphatic ketones. In addition to exploring the effects of the ketone structure and solvent on the regioselectivity of halogenation, the type of halogen used in this reaction is also an important variable. While both α -bromo and α -chloro ketones are reported to undergo acid-catalyzed rearrangement, α -bromo ketone equilibration has been more readily observed.^{4,5}

Results

Methanol solutions of acetone, 2-butanone, 3-methyl-2-butanone, or 4-heptanone were allowed to react with 1 or 2 equiv of chlorine at 20–50 °C. Chlorine is bubbled into the reaction mixture. After a short induction period, the yellow solution becomes colorless and the temperature increases. When addition of 1 equiv of chlorine is complete, the solution turns yellow and cooling of the reaction is necessary. The reaction products at this point are HCl and a mixture of monochloro ketones and their dimethyl ketals. Addition of a second equivalent of chlorine at room temperature leads to further chlorination. The final products are mixtures of dichloro ketones and their ketals (Table I). At room temperature further chlorination, even with excess chlorine present, is slow.

For the purpose of comparison, the same set of ketones listed above was allowed to react with 1 or 2 equiv of

Table I. Ketone Chlorination Products^a

		$R_1=C1$	$R_2=H$	$R_2=C1$	$R_1=H$
	MeOH	-	(40)	-	(60)
	CCl ₄	67		33	
		$R_1=C1$	$R_2=H$	$R_2=C1$	$R_1=H$
	MeOH	7	(-)	44	(49)
	CCl ₄	41		59	
		$R_2R_3=H$	$R_1=C1$	$R_1R_2=H$	$R_3=C1$
	MeOH	25	(30)	32	(13)
	CCl ₄	22		78	
		$R_1R_2=C1$	$R_3=H$	$R_2R_3=C1$	$R_1=H$
	MeOH	16	(3)	22	(59)
	CCl ₄	13		87	
		$R_1R_2=H$	$R_3=C1$	$R_2R_3=H$	$R_1=C1$
	MeOH	8	(-)	92	(-)
	CCl ₄	53		47	
		$R_1R_2=C1$	$R_3=H$	$R_2R_3=C1$	$R_1=H$
	MeOH	46	(31)	10	(13)
	CCl ₄	12		88	

^a Values in parentheses indicate corresponding dimethyl ketal; dash indicates product not observed.

chlorine in carbon tetrachloride. The results are also summarized in Table I.

The reaction mixtures were examined by using gas chromatography. Compounds were identified by mass spectroscopy and coinjection with authentic samples. The isolated yields of chlorination products were good

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