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Molecular Mechanics Calculations on Template-Directed Steroid Chlorinations: Are Transition States Rigidified by the Geometric Trajectory Requirements for Effective Energy Transfer?

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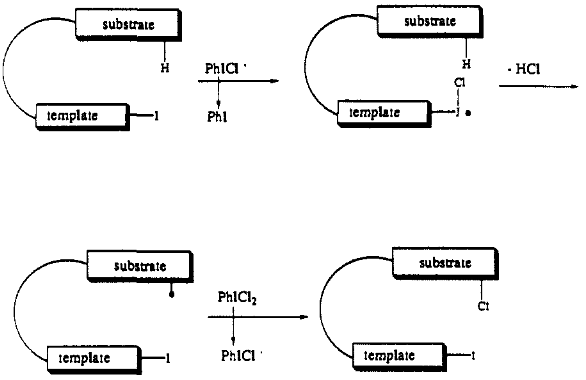
Abstract: Molecular mechanics calculations have been performed on the transition states for hydrogen abstraction by chlorine atoms that are attached to the iodines of various iodoaryl templates, esterified at C-3α of cholestanol. The calculations successfully account for the experimental observations in cases in which the template selectively directs chlorination to C-9, to C-14, or to C-17; they also agree with the findings in one case in which C-9 and C-14 are chlorinated equally. They account for the observed C-17 chlorination with a template esterified at C-5α and for a selective reaction in the coprostanol series, but do not yet successfully reproduce experimental findings with a silyl ether template. Best results require the use of relatively stiff bending force constants in the transition state, so that the reaction angle is held close to 180°. It is suggested that the need for a stiff transition state may in part reflect the trajectory needed for effective energy transfer. Molecular mechanics calculations also explain the experimental finding that the nominally free C-17 to C-20 single bond in cholestanol derivatives is conformationally locked, so the hydrogen at C-20 points to the β-face of the steroid.

Introduction

We have described a number of examples of the template-directed chlorination of steroids.[2] In our early work, an aryl iodide template was used to direct the chlorination of steroid tertiary carbons by the radical relay mechanism, in which a Cl• is transferred from a solution reagent to the iodine atom of the template and then relayed to a geometrically accessible hydrogen atom.[3] The product steroid radical then accepts a chlorine atom from the solution chlorinating agent, such as $PhICl_2$ or SO_2Cl_2, and the chain continues (eq 1).



(1)

The early work focused on aryl iodide esters of 3α-cholestanol, although in later work we have used other steroids.[2] We have also used templates with sulfur atoms,[4] pyridine nitrogens,[5,6] or pyridine *N*-oxide oxygen atoms[6] as chlorine-binding sites. In appropriate cases, we have also been able to chlorinate flexible chain substrates with fairly good selectivity[7] and even to achieve catalytic functionalizations with templates that are merely coordinated to the substrate, not linked as covalent esters.[8]

In all this work we were guided by CPK models that showed the likely hydrogen atom for radical relay attack. However, such models are of course not useful for quantitative predictions. Thus, we decided to see whether molecular mechanics calculations could account for our results, in particular our ability to select between hydrogens that are rather close in space. If a successful procedure could be devised, it seemed likely to be of great predictive use and might even give us insight into the factors determining our experimentally observed selectivities.

The challenge is formidable. Our molecules are very large and contain heavy atoms. Furthermore, we need to calculate relative energies for transition states of unknown geometries and with unknown force constants in reactions of metastable ArICl• species that also have unknown geometries and force constants. Thus, we set a simple initial goal. We wanted to devise procedures to account for our observations with the four steroid esters **1**–**4** (Chart I). Experimentally,[3] reaction intermediate **1** leads selectively to chlorination at C-9 after abstraction of the C-9 hydrogen, intermediate **2** leads to chlorination at C-14, and intermediate **3** attacks the hydrogen at C-17, while intermediate **4** leads to chlorination at both C-9 and C-14 with a 1/1 ratio. While the mixed selectivity of this last case means that it is not of synthetic use, it is particularly challenging to reproduce this 1/1 ratio in a calculation.

For the calculations, we used Allinger's MM2 force field,[9] as incorporated in Still's program MACROMODEL.[10] We have found that we can indeed account for our findings with an appropriate parameterization of this program. Interestingly, the best fit to our data requires that the transition state be relatively stiff; entropy terms must also be included.

There have been a number of related studies previously. In 1955, Ingold and co-workers published a series of calculations on S_N2 reactions.[11] They carried out calculations by hand using an empirical force field and very simple assumptions, but achieved quite good agreement with experimental activation energies. In 1963, Wiberg published a study of the reaction of methane with Cl•, clearly relevant to our calculations.[12] He held the C, H, and Cl atoms collinear, which corresponds to the use of extremely high bending force constants in the activated complex, and varied their separation to drive the system through the activated complex. The calculations were in reasonable accord with the experimentally

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[1] National Science Foundation predoctoral fellow, 1985–1988. This work is taken from the Ph.D. Thesis of P.W., Columbia University, 1989, which may be consulted for further details.

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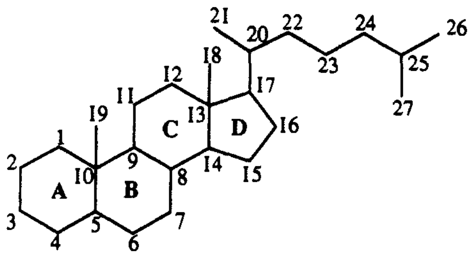
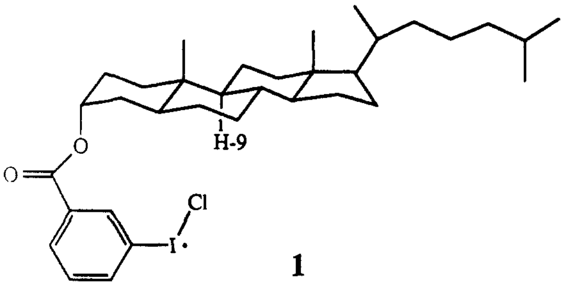
Chart I



numbering system for steroid derivatives:
α-face, below the plane of the paper;
β-face, above the plane of the paper



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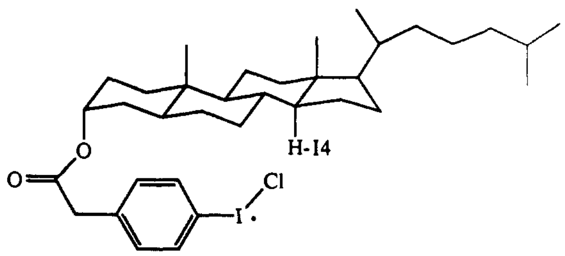

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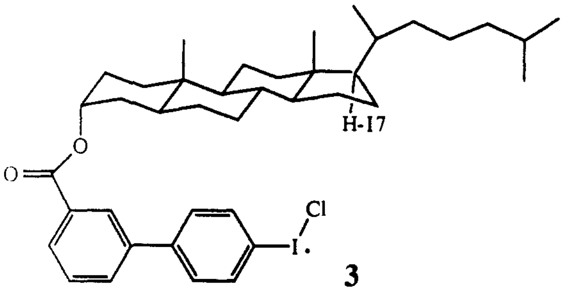

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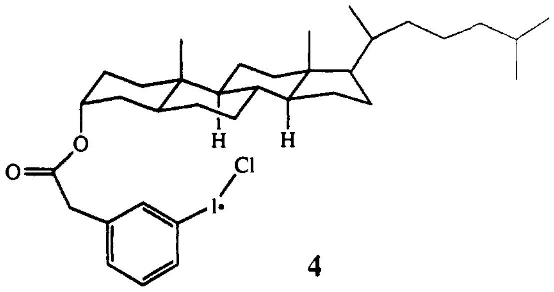

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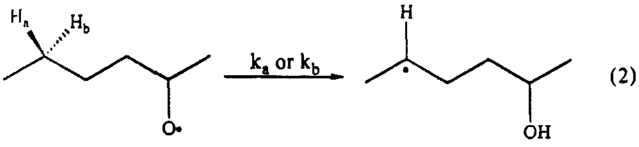
determined isotope effects at different temperatures.

Houk has done a number of studies combining ab initio methods, to derive parameters, with molecular mechanics methods using those parameters. He has used these procedures to calculate stereoselectivities of additions to olefins and carbonyl groups[13] and also the relative rate of lactonization of various hydroxyacids.[14] He found good correlations when, for the longer bonds in the transition states, force constants were used that were from 25% to 100% of the normal values for full single bonds. Beckwith has used a similar approach to model the relative activation energy barriers for endo and exo closure of ω-alkenyl radicals and similar systems.[15]

In a study[16] similar to ours with respect to the chemistry involved, Green, Allinger, et al., have used molecular mechanics to model γ-hydrogen transfer to a 2-hexyloxy radical, as in the Barton reaction (eq 2). They calculated the stereoselectivity of



(2)

this reaction with respect to the two diastereotopic hydrogens, and also the isotope effects. Parameters were varied; the best correlations with experimental findings required a linear transition state [O- -H- -C].

The study perhaps most relevant to ours is that of Dorigo and Houk.[17] They examined the flexibility of the transition state for hydrogen abstraction from methane by OH•. Ab initio methods were used to calculate appropriate parameters, and the results were extended to hydrogen abstractions by alkoxy radicals. In particular, they considered the Barton reaction (hydrogen abstraction over a six-membered ring by an alkoxy radical) in some steroids. They concluded that the bending force constants in such reactions should be relatively weak, consistent with previous arguments[18] that the partial bonds in transition states should be more easily bent than are normal chemical bonds. They also showed that for best agreement between calculation and experiment entropy must be included.

Methods

We performed molecular mechanics minimizations using version V2.5 of Still's MACROMODEL and BATCHMIN molecular mechanics programs[19] and Allinger's MM2 force field.[9] Minimizations were performed by first using the block-diagonal Newton Raphson method, to a root mean square of the first derivative of <0.1, followed by the full-matrix Newton Raphson method to a root mean square of the first derivative of <0.01.

Substructures were used for the templates. Charges for template atoms were calculated by doing a quantum mechanical geometry optimization of the iodine–chlorine complexes of methyl esters of the template acids whose cholestanyl esters are intermediates **1–4** with Dewar's AM1 semiempirical Hamiltonian.[20] (For the MM2 substructures, two hydrogens were deleted from the methyl group of the ester, creating a

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Table I. Stretch and Bend Constants for Local Transition-State Parameters (mdyn/Å for Stretches, mdyn/rad^2 for Bends)

calcn	I–Cl	Cl–H	H–C	C–I–Cl	I–Cl–H	Cl–H–C
"normal" value	2.0	4.84	4.6	0.36	0.36	0.36
1	1.5	1.21	3.45	0.27	0.068	0.068
2	1.0	2.42	2.3	0.18	0.09	0.09
3	0.50	3.63	1.15	0.09	0.068	0.068
4	0.25	0.605	0.575	0.045	0.0225	0.0225
5	2.0	4.84	4.6	0.36	0.18	0.18
6	4.0	9.68	9.2	0.72	0.36	0.36

methine that became C-3 of the steroid. Overall charge neutrality was maintained by adding the charges of the two deleted hydrogens to the carbon.) Since the charges calculated by this method are undoubtedly less accurate than those obtained by more rigorous ab initio methods, we checked the effect of these charges on our calculated energies. Setting the charges to 0 led to a real but small energy difference, so the AM1 results are probably good enough for our purposes.

We divided geometric parameters into three classes: (a) those that are not part of the local transition state; (b) those that are related to the positions of the atoms in the hydrogen abstraction reaction, but whose values should be unimportant in determining the relative activation energies for attack at different hydrogens; and (c) those that are part of the local transition state and whose values should help determine the differences in relative activation energies. The first set consists of most of the stretches, bends, and torsions in the steroid skeleton itself; the geometry of this part of the molecule was optimized with normal MM2 force constants.[9] The unimportant parameters involve torsions about the I–Cl, Cl–H, and H–C bonds, whose force constants were set to 0 so the angles could take up any value. In some calculations, we also set the bending constants to 0 for the C–I–Cl, I–Cl–H, or Cl–H–C angles to see the effect of assuming a very loose transition state.

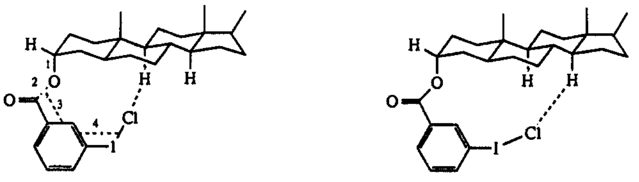
We mainly varied the parameters of the I–Cl, Cl–H, and H–C stretches and of the C–I–Cl, I–Cl–H, and Cl–H–C bends. These involve the bonds that are directly changing in the reactions. Calculations were usually done with a transition state assumed to be "halfway", in which the I–Cl, Cl–H, and H–C bonds all have a bond order of 0.5. We also looked at transition states 25% and 75% along the path, assuming that the I–Cl and H–C bond orders are the same (i.e., that reaction is concerted). Bond lengths were set to slightly lengthened values by using a modified version of Pauling's bond length/order relationship,[21] while stretching and bending force constants were obtained by multiplying a "normal" value by the bond orders. For other calculations, force constants were varied over a range from 6% to 200% of normal single-bond values; they are listed in Table I.

The normal bond length and stretching constant for H–Cl (1.27 Å, 4.84 mdyn/Å) are from the literature,[22] while the normal H–C parameters (1.02 Å, 4.6 mdyn/Å) are from MM2.[9] The I–Cl bond length was taken as 2.45 Å, as in the crystal structure of $PhICl_2$,[23] and the I–Cl stretching force constant was taken as 2.0 mdyn/Å.[24] The I–Cl–H and Cl–H–C ideal angles were set at their theoretical values of 180°, and the C–I–Cl angle was set at the 90° angle seen in the crystal structure of $PhICl_2$.[23] We chose a normal value of 0.36 mdyn/rad^2 for each of these bending force constants, typical for C–C–H and other bending constants[9] and similar to the choice made by Green, Allinger, et al., for the C–H–O bending force constant.[16]

The systems are so rigid that we could determine four to eight reasonable starting geometries for each transition state by inspection of CPK models. These collapsed to two unique minima for all transition states except that for attack at the C-17 H in system **3**, in which three minima were calculated. In the tables of results, we list only the data for one lowest energy geometry in each case, since the degeneracies are so small and similar that configurational entropy plays a minor role. In controls, we arbitrarily rotated some angles and found reminimization to one of our original conformations. As a sample, one pair of calculated geometries for attack at C-9 and at C-14 for compound **1** is listed in Table II.

We examined the individual contributions of each geometric parameter to the overall geometry of the transition state and to the resulting strain energy. The strain energy was in fact spread over the whole molecule, not just localized to our special transition-state parameters.

Table II. Geometries for Attack at C-9 and C-14 with System **1**



	C-9		C-14	
Dihedral Angles (Degrees)				
1 (H–C–O–C)	49.4	–50.2	65.8	–54.3
2 (C–O–C–C)	158.7	–159.2	154.5	–154.1
3	–0.1	0.2	5.1	4.1
4	–36.3	37.6	–59.7	61.4
Angles (Degrees)				
C–I–Cl	90.4	90.1	93.0	92.3
I–Cl–H	175.8	175.8	175.8	174.2
Cl–H–C	179.2	178.9	175.6	176.6
H (kJ/mol)	192.52	191.80	201.46	198.64

Table III. Energy Differences (kJ/mol) from Variation in Transition-State Position and Force Constants[a]

calcn	**1**	**2**		**3**	**4**	f
		$\Delta H°$				
1[b]	3.6	13.4	9.4	8.7	5.4	0.77
2[c]	4.2	13.3	9.3	9.1	5.7	0.75
3[d]	3.3	12.2	7.7	6.3	5.8	0.70
4[c]	5.2	10.2	1.2	6.3	5.2	0.46
5[c]	5.7	14.2	9.8	10.2	4.8	0.83
6[c]	6.8	14.7	9.9	11.2	2.9	0.91
		$\Delta G°$				
1	4.2	11.0	9.1	8.4	0.5	0.88
2	4.7	10.4	9.2	8.7	0.6	0.90
3	3.6	9.7	7.7	6.2	2.1	0.81
4	4.2	12.7	4.2	7.0	7.5	0.53
5	6.5	11.0	10.0	9.5	1.7	0.96
6	8.0	11.8	10.2	10.3	1.0	1.00
exptl	≥7.0	≥7.0	≥7.0	≥7.0	≤2.0	

[a] The values from Table I. [b] A transition state with the Cl 25% transferred from I to H. [c] A transition state with the same assumptions about the relationship between bond orders and force constants as in case *a*, but with the Cl 50% transferred from I to H. [d] A transition state with the same assumptions about the relationship between bond orders and force constants as in case *a*, but with the Cl 75% transferred from I to H.

Solvation calculations were done with routines implemented in version V2.0 of MACROMODEL.[19] They had little effect on the calculated selectivities, so the solvation results are not included. However, the entropy calculations did make a difference; they were performed with a standard normal-mode analysis, implemented in version V2.5 of MACROMODEL.[19] Only rotational and vibrational entropy and vibrational heat capacity terms were included in the calculation of total energies, since translational terms and rotational heat capacities are not dependent on conformation. The results are listed in Table III.

For system **1**, we calculated the difference in transition-state energy between chlorination at the observed[3] C-9 and chlorination at the unobserved C-14. For system **2**, we compared attack at the observed[3] C-14 with that at the unobserved C-9 and C-17, so two columns of data are listed for **2** in Table III. For system **3**, we compared the observed[3] C-17 with the unobserved C-14. Experimentally, the unobserved chlorinations should have been seen by NMR if as much as 5% were present, so we assumed that the preference for the observed positions was at least 7 kJ/mol. Thus, a successful calculation should predict at least a 7 kJ/mol difference between the transition state energies for the observed and the unobserved positions.

For the (*m*-iodophenyl)acetate system **4**, equal amounts of C-9 and C-14 products were observed,[3] so the transition states should have the same energy. We arbitrarily deemed a calculation successful for this case if the energy difference for the two transition states was less than 2 kJ/mol for the lowest energy conformations.

Generally, we tested a parameter set with five separate comparisons, one each for systems **1**, **2**, and **4** and two for system **3**. In some cases,

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we did only the two comparisons for systems **1** and **4**, but when a parameter set was successful for system **1**, it virtually always worked for systems **2** and **3** also.

We devised a function f to rate agreement with experiment. In the definition of this function (eq 3), N is the number of comparisons done

$$f = \frac{1}{N}\sum_{i=1}^{N}\left[1 - \left(\frac{x_i}{10}\right)^{1/2}\right] \quad (3)$$

(2 or 5) and x_i is the number of kilojoules by which the calculation is short of the 7 or 2 kJ/mol targets. The function f is a perfect 1.0 if the first four comparisons give differences all greater than 7 kJ/mol in favor of attack at the correct position and the fifth comparison gives a difference <2 kJ/mol. The use of the square root accentuates small differences in x_i and leads to a larger spread in the values of f.

Results and Discussion

After energy minimization, we found that the bond lengths deviated little from our initial values, typically by only hundredths of an angstrom. This was true even when relatively weak stretching constants were used. Angles deviated by 5–20° from the initial values, with much larger deviations in a few cases in which bending constraints were removed.

We utilized the entropy calculations described in Methods performed after minimizing the enthalpy of the structures. The $\Delta H°$ and $\Delta S°$ were converted to $\Delta G°$ at 273 K (where most of the chlorinations are run). In Table III, we list the results of these calculations. The first three entries, calculations 1–3, involve the initial parameters described above and a variation of the transition-state position from early to middle to late. There was not a large variation, but the best agreement with experiment was seen with a symmetrical transition state (i.e., with an H–Cl bond order of 0.5), so we used this 0.5 bond order for the later calculations. Calculations 4–6 involve variation in the force constants from our initial assumptions of calculation 2 to decrease them by a factor of 4 (calculation 4), or increase them by factors of 2 and 4 (calculations 5 and 6, respectively).

Calculation 6 is completely successful by our $f = 1.0$ criterion if entropy is included. Our best results are obtained with the stiff force constants of calculation 6, in which bending constants are set equal either to an assumed "normal" value for full bonding (I- -Cl- -H, Cl- -H- -C) or to twice the normal value (C- -I- -Cl). The observation that relatively stiff bending force constants are needed to fit the experimental results is not really surprising. Since our reactions involve selection between hydrogens that are 1,3-diaxial on a cyclohexane ring and only 2.3 Å apart, allowing more flexibility in the angles permits the chlorine to range over a wide area and attack more than one hydrogen. In fact, when we set some of the bending force constants to 0, to allow a completely unrestricted angle, the f value decreased sharply.

Can the Angular Requirements for Chemical Reaction Be More Strict Than Is Generally Believed? It is striking that we need to invoke the stiffness of the parameters in calculation 6 for the partial bonds of a transition state. The calculated bond lengths are little affected, so the stiff stretching constants of calculation 6 are probably irrelevant. However, the stiff bending force constants do lead to significantly less bond bending in the calculated minimum-energy structures. This requirement of stiff bending force constants is in contrast to the conclusions of Dorigo and Houk[17] that bending force constants for hydrogen abstraction by oxygen radicals should be relatively weak.

Our parameters may simply be required mathematically to make up for other deficiencies in what is after all only an approximate calculation. They probably instead indicate that there really is a relatively strict angular requirement for reaction. If so, this is in conflict with the ab initio predictions of Dorigo and Houk[17] or the general arguments that the partial bonds of transition states should bend easily.[18] We propose a possible reason that there could be a relatively strict angular requirement for reaction.

Is an Additional Angular Restriction Needed for Effective Energy Transfer on Collision? The energy needed to cross the transition state is derived as the kinetic energy of the moving chlorine atom (complex) is transformed into the energy needed to compress the H- -Cl incipient bond and to excite the H–C bond so that it can break. Such energy transfer will occur most readily with a linear collision, against the stiff compression potential of the C–H bond. This forces the H and Cl together and compresses the H–C bond into a higher vibrational state so that it can more easily break. A nonlinear collision, like an off-line hammer blow on a nail, will transfer the energy much less efficiently.

Such angular factors in energy transfer have been seen for the conversion of kinetic energy to vibrational energy.[25] Furthermore, reaction of Cl$^\bullet$ with cyclohexane in the gas phase produces H–Cl that is vibrationally excited but not rotationally excited, indicating that the collision in this case is essentially linear.[26]

Our normal view of transition-state theory is that collision automatically supplies the energy needed to cross the barrier and that any angular requirements are incorporated in the best geometry for the activated complex. The addition of energy-transfer trajectory arguments, like that given above, would imply that the preexponential factor in transition-state theory reflects in part the efficiency of energy transfer to the modes needed for crossing the barrier. In a molecular mechanics calculation, where such factors are not included, this angular requirement for energy transfer would simply show up as a stiffer set of bending force constants than otherwise expected. In other words, a flexible transition state with an additional angular requirement for efficient energy transfer can be approximated simply by a stiffer transition state.

Thus, transition states could well have more restricted angular requirements than normal molecules have. Koshland has suggested such an increased angular requirement, but with other arguments.[27] If there is indeed a stricter angular requirement for chemical reactions than is generally assumed, because trajectory considerations for energy transfer must also be included, this could have wide implications for the understanding of highly efficient reactions such as those catalyzed by enzymes.

It has been argued that the most probable angle for hydrogen abstraction is not the 180° of the energy minimum, but an angle closer to 150° because of the presumed flexibility of transition states and the greater number of trajectories corresponding to a larger cone angle.[17] Using the parameters of calculation 6, we checked the result of assuming instead that either the Cl–H–C or the I–Cl–H angle had the most probable value of 150°, not the 180° of a linear transition state. In both cases, the f value decreased sharply. Thus, in our case no such bending is permitted.

This is probably not a calculational artifact, but reflects the alignment needed to approach parallel to two axial C–H bonds and select between them. If the C–I–Cl angle is set at 150°, the Cl can range over a lateral distance of 2.7 Å; an H- -Cl- -I angle of 150° permits the Cl to range over 1.5 Å along the steroid face. In either case, it would then be extraordinary for the systems to select between two hydrogens only 2.3 Å apart.

We also varied the assumed bond lengths in the transition state (Table IV). There was little sensitivity to the individual I–Cl, Cl–H, and H–C lengths as long as the total separation of the iodine from the carbon was near the 5.37 Å of our original assumptions, or even shorter. With longer I- -C distances the f value decreased.

Since calculation 6 was successful, we tested these parameters against three other experimental results: the observed selectivities in chlorination of compounds **5**–**7**. The AB cis-fused coprostanol derivative **5** is selectively chlorinated[3] at C-14, in preference to C-9 or C-17. Using the parameters of calculation 6, we calculate that attack at C-14 should be favored over that at C-9 by 20.8 kJ/mol (ΔH = 19.8 kJ/mol) and over that at C-17 by 8.5 kJ/mol (ΔH = 11.2 kJ/mol). For system **6**, we calculated that the observed[28] C-17 attack should be favored over the unobserved C-14 attack by 18.9 kJ/mol (ΔH = 21.3 kJ/mol). Both calculations are consistent with experimental observations.

System **7** is a problem, since it incorporates a silicon atom for which new parameters are needed. With a variety of approaches,

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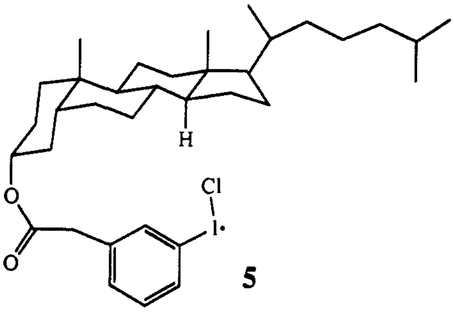

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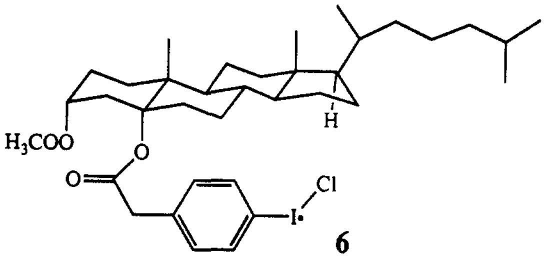

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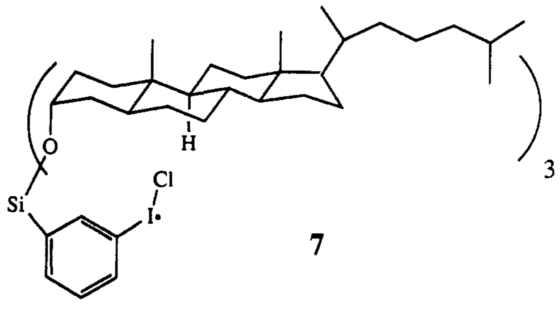

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Table IV

A. Bond Lengths for Calculations in Part B (Å)

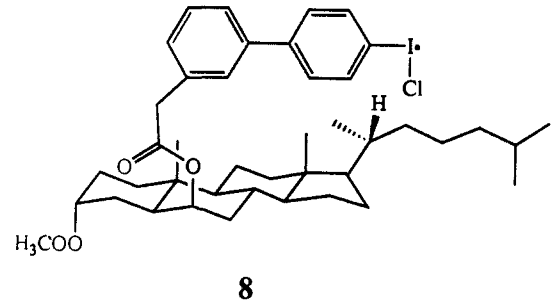
calcn	I–Cl	Cl–H	H–C	total
7	2.45	3.00	1.02	6.47
8	2.75	1.27	1.37	5.39
9	2.45	1.91	1.02	5.38
6	2.66	1.48	1.23	5.37
10	2.65	1.17	1.27	5.09
11	2.45	1.27	1.02	4.74

B. Energy Differences (kJ/mol) from Variation of Bond Lengths

calcn	1	4	*f*
	$\Delta H°$		
7	−2.2	4.1	0.29
8	7.2	3.3	0.82
9	5.4	2.2	0.73
6	6.8	2.9	0.78
10	7.7	3.5	0.81
11	7.9	2.4	0.90
	$\Delta G°$		
7	−0.4	3.3	0.39
8	8.2	1.2	1.00
9	6.7	0.5	0.92
6	8.0	1.0	1.00
10	8.7	0.8	1.00
11	8.8	−0.5	1.00
exptl	≥7.0	≤2.0	

we were not able to account for the observed[29] attack at C-9, but instead calculated a preference for C-14. This may indicate some fundamental problem in the procedures, but further work will be required to see whether the problem is simply related to the silicon parameters.

Some of our experimental results do not involve just choices between two tertiary hydrogens, and in these cases different calculations are required. As an example, we have observed[30] that the template in **8** or **9** can direct chlorination to C-20 in the steroid side chain but that templates mounted on the steroid α-face do not attack C-20. Although the side chain is attached by a single bond and is nominally free to rotate, we found that X-ray crystal structures[31] of steroids essentially always have this bond fixed so that the C-20 hydrogen points to the β-face, as it must for chlorination in **8** or **9**.



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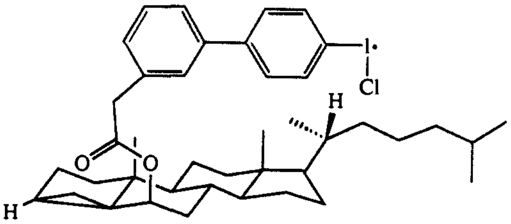

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We have now calculated this apparent conformational preference. A full Monte Carlo conformational search[32] on the side chain conformation of 3α-cholestanyl acetate within the standard MACROMODEL program gave 170 conformations within 25 kJ/mol of the lowest energy conformation. The lowest energy conformations in which the C-20 hydrogen was not pointing up on the β-face were numbers 22 and 23, approximately 9 kJ/mol above the ground state. A Boltzmann distribution over all 170 conformations indicated that the C-20 hydrogen should point to the β-face 99.5% of the time at 273 K. This is in complete accord with our chlorination results and with the X-ray data.

Conclusions

1. Molecular mechanics calculations using the MACROMODEL program can account for the observed selectivities in template-directed steroid chlorination within a group of steroid esters carrying iodoaryl template groups.

2. Best results were obtained with a linear C--H--Cl--I transition state and a total iodine–carbon separation of ≤5.37 Å. However, they were less sensitive to the precise values of the C--H, H--Cl, and Cl--I distances that contributed to this overall separation.

3. Success requires bending force constants no weaker than those of normal single bonds, or even a little stiffer, at the atoms directly involved in the transition state. It also requires the inclusion of entropies, not just enthalpies.

4. The apparent strict angular requirement in order for the calculations to agree with experiment may reflect the need for an almost linear collision, rather than a glancing blow, to achieve energy transfer into the modes needed for reaction. Such a geometric trajectory effect could mean that chemical reactions generally have a stricter angular requirement than has been believed.

5. Our calculations succeed for two other cases not involved

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in the original optimization of procedures, but not yet for a silyl ether derivative.

6. Molecular mechanics calculations also account for the experimental finding that the nominally free rotation of the side chain C-17 to C-20 bond is in fact restricted so that the C-20 hydrogen is pointing to the β-face of the steroid.

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Pressure Effects on the Dynamic Quenching by Oxygen of Singlet and Triplet States of Anthracene Derivatives in Solution

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Abstract: The mechanism for the quenching by oxygen of the singlet and triplet states of several anthracene derivatives in methylcyclohexane (MCH) under pressures of up to 700 MPa was investigated. The value for the rate constant of fluorescence quenching, k_q^S, at 0.1 MPa is found to vary from (3.2 ± 1.1) × 10^9 M^{-1} s^{-1} for 9,10-dicyanoanthracene (DCNA) to (2.88 ± 0.27) × 10^{10} M^{-1} s^{-1} for 9-methylanthracene (MEA), whereas values for the rate constant of the triplet-state quenching process, k_q^T, at 0.1 MPa are similar for each of the anthracenes, being in the range (3.0–3.8) × 10^9 M^{-1} s^{-1}. The values for k_q^S and k_q^T decrease with increasing pressure, mainly as a result of the increase in viscosity of the solvent that accompanies the pressure increase. A linear relation between ln k_q^S and ln η is found for anthracene (A) and MEA, with slopes of −0.57 ± 0.04 and −0.64 ± 0.02, respectively. However, plots of this relation show a distinct downward curvature for 9,10-dichloroanthracene (DCLA) and DCNA. It is also found that ln k_q^T does not vary linearly with ln η for any of the derivatives examined. The activation volumes of k_q^S for A and MEA are estimated to be in the range 12–14 cm^3 mol^{-1}. These values are about 2 times larger than those determined for k_q^T, but are only half of the value reported for the activation volume of the viscosity of MCH. The ratio of k_q^T to k_q^S for MEA and DCLA at 0.1 MPa is reasonably close to the predicted value of 1/9 and increases with pressure, reaching a value of approximately 4/9 for DCLA at 700 MPa. These results suggest that, in addition to $^1(AO_2)^*$, encounter complexes of the form $^3(AO_2)^*$ or $^5(AO_2)^*$, for which the total spin angular momentum is not conserved, may come to play an important role in the quenching of the triplet state as the pressure is increased. Dynamic aspects of the fluorescence quenching are also discussed in terms of the transient decay feature characterized by the $t^{1/2}$ function predicted by the Smoluchowski model.

Introduction

Molecular oxygen is an efficient quencher of the electronically excited states of many organic molecules. In most cases, the quenching by oxygen is so efficient that the reaction rate is believed to be diffusion-limited. However, quenching rate constants reported in the literature vary from compound to compound, for example, 3.3 × 10^{10} M^{-1} s^{-1} for *p*-methoxybiphenyl and 4.4 × 10^9 M^{-1} s^{-1} for fluoranthene.[1] Despite this wide range of magnitudes, it is often claimed that a quenching reaction is diffusion-controlled if the rate constant exceeds a value of approximately 10^{10} M^{-1} s^{-1}, or sometimes even a value smaller than this. This also appears to be the case for quenchers other than oxygen. It is important that a clear distinction is made between fully diffusion-controlled reactions and those that are nearly diffusion-controlled, since in the latter case the quenching efficiency is less than unity. When the probability is less than 1, the quenching reaction is not infinitely fast and encounter complexes with rather long lifetimes may become involved in the reaction. Consequently, a detailed investigation into the quenching mechanism, especially the structure and stability of such encounter complexes, is required.[2,3]

In a recent comprehensive review, Saltiel and Atwater discussed in detail the mechanism by which molecular oxygen quenches electronically excited states in solution.[1] According to their proposed mechanism (in which a charge-separated state is not included[4]), it is concluded that the maximum value of the rate constant for quenching of the singlet states of organic compounds is approximately 2.8 × 10^{10} M^{-1} s^{-1}. This is almost 9 times larger than that estimated for the triplet states due to the favorable spin statistical factor for the former, assuming that the total spin angular momentum is conserved upon quenching. For aromatic compounds whose electronic states are of $\pi\pi^*$ nature, the rate constants for quenching of the singlet states always appear to be larger than those for the corresponding triplet states.[1] However, the ratios of these values have not been examined extensively for

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