

Conformational Transmission. A Quantitative Approach to the Rates of Benzylidene Formation in Steroidal 3-Ketones^{1,2}

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Abstract: The steric energies of a series of 3-keto steroids have been calculated by force-field methods, together with the energies of the corresponding Δ^2 steroids. The energy differences are expected to be reflected in the rates of chemical reactions which approximate that geometric change, and in particular, 2-benzylidene formation. The available experimental rate constants on the latter reaction have been attributed to conformational transmission, and they span a range of 10^2 . For the available data (19 compounds), the calculated energy differences are proportional to the logs of the rate constants, with a correlation coefficient of 0.83, and relative values for ΔG^\ddagger are calculated with a standard deviation of ± 0.28 kcal/mol. It is concluded that molecular mechanics calculations offer a potential quantitative understanding and predictive capacity for the role of conformational transmission in chemical reactions.

The term "conformational transmission," in which steric strain due to a structural moiety is transmitted to remote parts of the same molecule, was introduced by Barton^{3,4} and has been repeatedly invoked in discussions of long-range structural effects.^{5,6} Barton found that the rate of benzylidene formation upon treatment of a steroidal or pentacyclic triterpene 3-ketone with benzaldehyde in ethanolic KOH varied, depending on the pattern of substitution. Of particular interest was the observation that the effect on the rate seemed to depend mainly on the geometry associated with the differing structural moieties rather than on polar (electrostatic and inductive) properties. For example, both a 7-keto function and a 7-methylene group result in a rate enhancement compared to the parent structure. Thus the suggestion was made that the observed variations in the reaction rate were due to the differential effects of the transmitted conformational strain on the parent ketone and the reaction transition state.

In 1963 Whalley and Robinson⁷ put forward a semi-quantitative analysis of some of Barton's data in which they attempted to assess the effects of transmitted conformational strain on the ketone and the transition state in order to see if the observations could be accounted for in this way. Qualitatively, the sense of the

variations in reaction rate due to the introduction of sp^2 centers in ring B was shown to be in keeping with the sense of the distortion transmitted to ring A of the ketone. The $C_3-C_4-C_5-C_6$ torsional angle in a cyclohexene ring system is opened up considerably from that in a cyclohexanone structure.^{6,8,9} Thus the facility of the reaction under consideration, assuming the transition state to have considerable C_2-C_3 double bond character, could be expected to correlate with the degree of opening or closing of the $C_1-C_{10}-C_5-C_4$ torsional angle, that is, with the degree of puckering of ring A. Subsequently, Baker and Hudec made the same qualitative analysis of Barton's data¹⁰ and reported an nmr study¹¹ which suggested that ring A of steroidal 3-ketones was in fact distorted by remote trigonal centers in the sense predicted.^{7,9,10}

The availability of rapid, reasonably accurate, and inexpensive force-field calculational methods has made possible the quantitative estimation of conformations and energies on a systematic basis, and suggests that a quantitative approach to problems of conformational transmission is now possible. Ingold¹² showed that steric effects in the SN_2 reaction, and by implication other reactions, could be dealt with in at least a semi-quantitative way if the necessary data and calculational capability were available. Schleyer¹³ has shown in an impressive series of calculations that solvolysis rates over a broad series of compounds can be understood and predicted by the force-field approach, notwithstanding the really threatening obstacles of internal return, solvation energies, nonclassical structures, etc., which plague studies of carbonium ions. The refinement of force-field methods, and the availability of further experimental data,¹⁴ have prompted us to re-investigate this problem to see how much of the observed variation in the rates can in fact really be ac-

(1) This is paper C in the series "Conformational Analysis." For paper XCIX, see N. L. Allinger, G. A. Lane, and G. L. Wang, *J. Org. Chem.*, **39**, 704 (1974).

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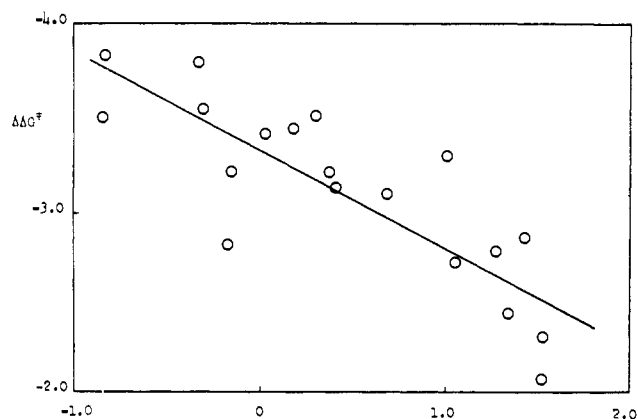


Figure 1. Regression of experimental ΔG^\ddagger (relative) against calculated Δ (steric energy).

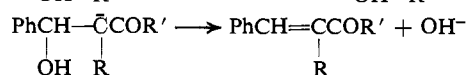
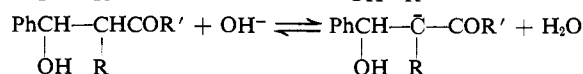
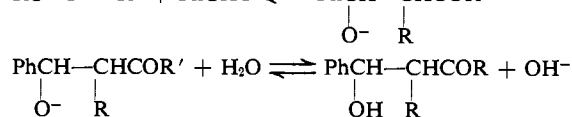
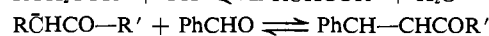
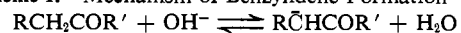
counted for as arising from conformational transmission. In the present case the total spread in rate constants is less than 10^2 , so the problems are different from the carbonium ion work¹³ where a spread of 10^{18} was available. To be useful in the present case, the predictions of ΔG^\ddagger must be accurate to within ~ 0.5 kcal/mol or a factor of 3 in rate (25°). Because these calculations are based on the average geometry of a vibrationless model, there is no assurance that the desired accuracy is possible. The assumptions inherent in the calculations include: (1) that zero point energies, and statistical mechanical contributions to energy from the population of vibrationally excited levels, will cancel out when appropriately chosen differences between compounds (or between compounds and transition states) are compared; (2) that solvation energies will similarly cancel; and, (3) that the transition-state energy can somehow be assessed. Whether or not these assumptions will in fact hold up can only be ascertained empirically. It is encouraging that previous calculations of this general type have approached or reached this degree of accuracy.¹⁵

The analysis of rate data in terms of calculated energies poses particular problems, since the structures and energies of transition states are not well understood, and approximations are involved concerning the transmission factor and the governing role of the rate-determining step. The condensation of benzaldehyde with ketones in ethanolic base has been shown to involve a series of preequilibria, and a rate-determining loss of OH^- from the aldol carbanion.¹⁶ As the detailed kinetics have not been investigated in each case in Scheme I, the possibility of variations in the substitution pattern and in the transmitted conformational strain inducing changes in the relative rates of the steps, or even a change in mechanism, cannot be ruled out. Similarly, differential solvation effects and variations in the entropy of activation cannot be excluded. Finally, we are not presently equipped to calculate the energy of the carbanionic species immediately prior to the transition state, to which the transition state would be expected to show considerable resemblance. Thus, the particular case chosen for investigation experimentally suffers from great difficulties from a theoretical

(15) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971), and references cited therein.

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Scheme I. Mechanism of Benzylidene Formation



point of view. Nonetheless, to be useful, conformational analysis must deal with real problems, not with just those that are theoretically convenient.

With these provisos in mind, the problem may be stated in a simpler manner, and a concomitantly less definitive answer obtained. If the crucial stage of the reaction pathway from the ketone to the transition state is assumed to be the introduction of an sp^2 center at C-2 coplanar to that at C-3,¹⁷ then comparison of the steric energies of the various substituted ketones and the corresponding 2-olefins should provide a measure of the effect of transmitted conformational strain. We have thus calculated the steric energy differences between a series of 3-keto steroidal structures and the corresponding Δ^2 olefins (Table I) in order to see to

Table I. Correlation of Calculated Steric Energy (ΔE) with Free Energy of Activation (ΔG^\ddagger , kcal/mol)

Compd ^a	Calcd ΔE Olefin- Ketone	$-\Delta G^\ddagger$		
		Obsd ^b	Calcd ^c	Devn
1b ¹⁴	1.344	2.415	2.617	-0.202
2b ¹⁴	1.056	2.695	2.767	-0.072
3b ¹⁴	1.533	2.078	2.519	-0.441
4b,4d, ¹⁴ b-f, 5 ⁴	0.403	3.091	3.106	-0.015
6b ¹⁴	0.030	3.389	3.300	0.088
7b ¹⁴	1.425	2.822	2.575	0.246
8b ^{4,14}	-0.836	3.833	3.751	0.082
9a,b,d ¹⁴	1.524	2.288	2.524	-0.236
10b, ⁴ c ¹⁴	1.006	3.280	2.793	0.486
11b, ⁴ c ¹⁴	1.288	2.742	2.646	0.095
12 ⁴	-0.151	3.196	3.395	-0.198
13 ⁴	-0.312	3.515	3.478	0.036
14b ¹⁴	0.685	3.070	2.960	0.109
15b ^{4,14}	0.301	3.492	3.159	0.332
16 ⁴	0.374	3.188	3.121	0.066
17b ^{4,14}	-0.333	3.794	3.489	0.305
18b-d ⁴	-0.168	2.786	3.404	-0.617
19 ⁴	0.179	3.430	3.223	0.207
20b ⁴	-0.855	3.485	3.760	-0.275
			Std. dev.	0.285

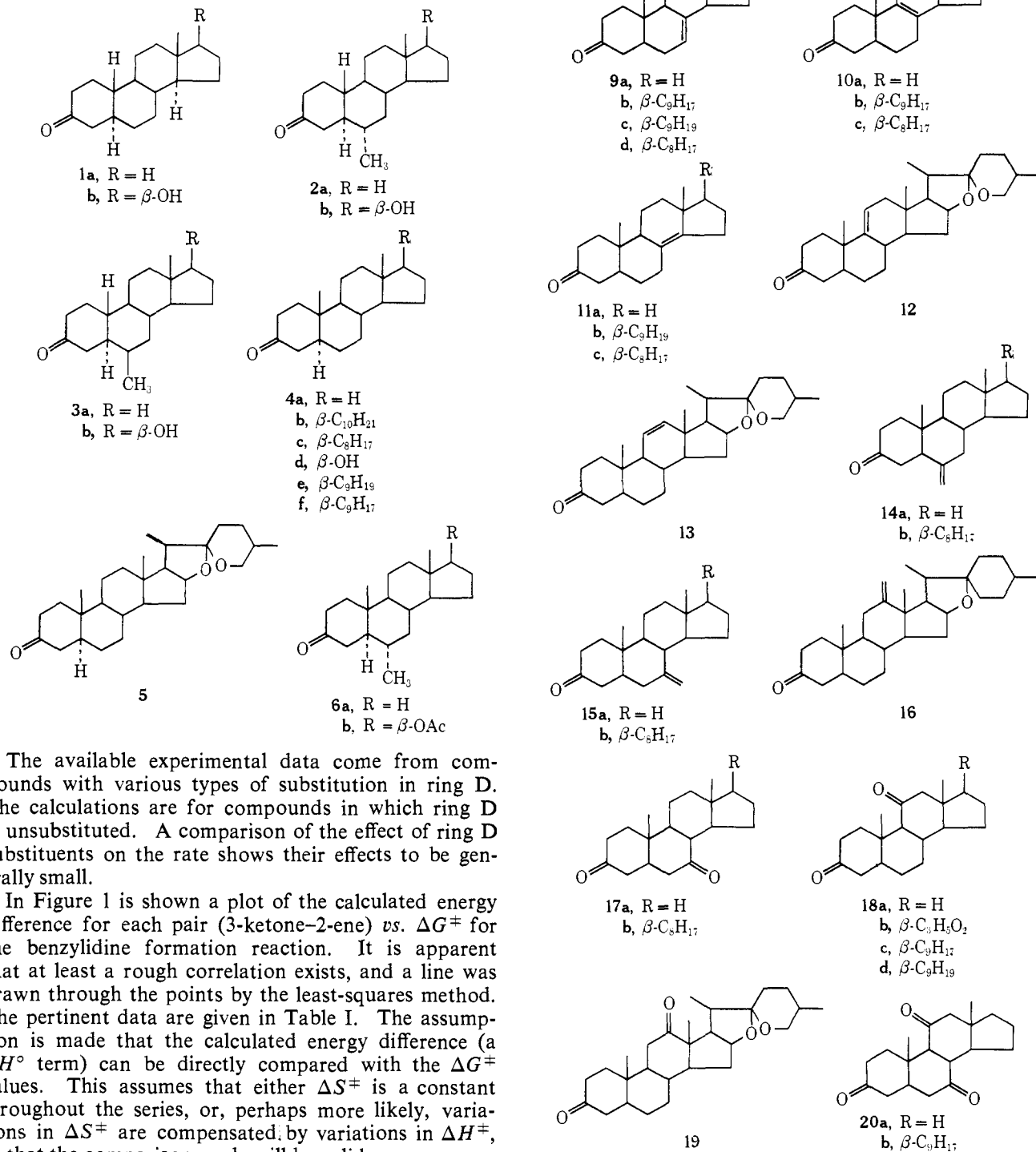
^a The rates were measured on compounds assigned reference numbers. The calculations were carried out on the ring D unsubstituted compounds. F test, 36.894; correlation coefficient, 0.827; slope, -0.519 ± 0.086 ; intercept, 3.136 ± 0.076 . ^b $-\Delta G^\ddagger = RT \cdot \ln k_{\text{rel}}(\text{obsd})$. ^c Calculated value of $-\Delta G^\ddagger$ from linear regression expression $-\Delta G^\ddagger = -0.519\Delta E + 3.316$.

what extent the observed variations in the rates of benzylidene formation could be accounted for by this model.

The study has been restricted to compounds unsubstituted at C-4. The model used here would not

(17) H. E. Zimmerman in "Molecular Rearrangements," P. deMayo, Ed., Vol. I, Wiley-Interscience, New York, N. Y., 1963, pp 345-406.

necessarily be expected to account very well for the effects of A-ring substituents which might be intimately involved in the transition state. The ring A unsubstituted compounds, on the other hand, are expected to provide a clear quantitative test of conformational transmission *via* ring strain effects. We have also omitted compounds containing a few special moieties such as alcohol groups and conjugated dienes which for technical reasons our calculational methods are not presently equipped to handle. The 3-ketones studied are shown. In each case the corresponding Δ^2 compound was also studied.



The available experimental data come from compounds with various types of substitution in ring D. The calculations are for compounds in which ring D is unsubstituted. A comparison of the effect of ring D substituents on the rate shows their effects to be generally small.

In Figure 1 is shown a plot of the calculated energy difference for each pair (3-ketone-2-ene) *vs.* ΔG^\ddagger for the benzylidene formation reaction. It is apparent that at least a rough correlation exists, and a line was drawn through the points by the least-squares method. The pertinent data are given in Table I. The assumption is made that the calculated energy difference (a ΔH° term) can be directly compared with the ΔG^\ddagger values. This assumes that either ΔS^\ddagger is a constant throughout the series, or, perhaps more likely, variations in ΔS^\ddagger are compensated by variations in ΔH^\ddagger , so that the comparison made will be valid.

The variance arising from experimental errors in the original rate data, and the variance between the rate data for differently substituted ring D compounds, are

estimated to account for a standard deviation of about 0.05 kcal in ΔG^\ddagger as against an observed standard deviation of 0.28 about the regression. If the model ac-

counted exactly for all of the variations in the rate, the slope should approach -1.0 and the correlation coefficient should approach 1.0 . The observed correlation coefficient is 0.83 . The value of the F test between the variance about the regression and the variance due to the regression indicates that the probability of obtaining such a correlation due to randomly distributed data is less than 1% .

Consideration of the discrepancies between the calculated and observed values for ΔG^\ddagger reveals only one case deviating by greater than 0.5 kcal in ΔH^\ddagger , and the standard deviation of 0.28 kcal corresponds to a standard deviation in the rate constants of a factor of 1.6 . Interestingly, the largest error occurs with the 11-keto compounds (**18**), for which the assumption of negligible polar effects might be expected to be least justified. The deviation in the 3,7,11-trione (**20**) is smaller, due perhaps to the cancelling effect of the deviation due to the 7-ketone.

The low value of the slope of the regression line (-0.52) indicates that the model tends to overestimate the changes in the activation energy, and the discrepancy cannot be accounted for by the scatter of the data. This may reflect the lesser double bond character of the Δ^2 enolate as compared to the Δ^2 olefin, which would be expected.

We have also considered the extent to which the qualitative analyses earlier developed^{7,9,10} have been borne out by the calculations. The calculated $C_1-C_{10}-C_5-C_4$ torsional angle (ω) for the steroidal ketone is listed in Table II along with the appropriate steric

Table II. Bridgehead Torsional Angles and Δ (Steric Energy, kcal/mol)

Ketone structure ^a	$C_1-C_{10}-C_5-C_4$ angle	Δ (steric energy)	Deviation
9a	48.6	1.52	-0.311
14a	49.4	0.69	0.392
2a	49.6	1.06	-0.006
11a	52.6	1.29	-0.167
1a	52.0	1.34	-0.537
3a	52.1	1.53	-0.880
6a	52.1	0.03	0.427
10a	52.3	1.01	0.299
7a	52.8	1.43	-0.211
17a	53.3	-0.33	0.715
4a	53.6	0.40	-0.019
19a	53.7	0.18	0.303
16	53.8	0.37	0.055
15a	54.0	0.30	0.336
20a	54.1	-0.86	0.318
12	56.1	-0.15	-0.170
18a	56.4	-0.17	-0.614
13	57.6	-0.31	-0.016
8a	59.7	-0.84	0.089
		Std. dev.	0.413

^a Calculated angles and energy from ring D unsubstituted compounds.

energy. In general, an increase in the dihedral angle is accompanied by an increase in the rate (as previously discussed) and a correspondingly more negative calculated steric energy difference. The quantitative agreement is only fair, however. The least-squares line of a plot of ω against Δ (steric energy) shows a lot of scatter, the correlation coefficient is only 0.58 , and the maximum and standard deviations in ΔG^\ddagger are

0.88 and 0.41 kcal/mol, respectively. The relatively poor agreement results from the fact that while the rates are related to the magnitude of ω , not only is this relation not necessarily linear, but the rates are affected by other things in addition. In particular, the effect of 6-methyl substituents is not related to the magnitude of the $C_1-C_{10}-C_5-C_4$ torsional angle, and the correlation is also poor for the 7-keto compounds (**17** and **20**), and the 11-keto compound (**18**). To illustrate the types of effects allowed for by the force-field calculation, but not taken account of by a simple analysis of torsional angle effects, we will discuss the 6-methyl compounds (**2**, **3**, **6**, and **7**).

With these structures, direct interactions with the ring A protons become important. Thus in the 6 β -methyl-3-ketones (**3** and **7**) the interactions between the 6-methyl group and the 4 β proton (0.31 kcal (**3**) and 0.37 kcal (**7**))¹⁸ become more severe in the Δ^2 olefin (0.35 and 0.59 kcal, respectively),¹⁹ whereas in the 6 α -methyl-3-ketones (**2** and **6**), the 6 α -methyl-4 α -hydrogen interactions (0.50 kcal (**2**) and 0.38 kcal (**6**))¹⁹ are relieved in the olefin (0.42 and 0.33 kcal, respectively). The introduction of a Δ^2 double bond makes ring A more flexible and results in a clockwise rotation about the C_4-C_3 bond, which relieves the 4 α -hydrogen-6 α -methyl interaction. The 6 β -methyl group, is, however, splayed out from ring B due to the interactions across the ring. To relieve the 6 β -methyl-4 β -hydrogen interaction by rotation past the methyl group would require a greater rotation than is possible, and in fact the introduction of the Δ^2 double bond forces the 4 β hydrogen close to the 6 β -methyl group. Thus the rate of reaction of the 6 α -methyl compounds is faster than that of the parent structure while the reaction rate for the 6 β -methyl compounds is slower. These effects are not reflected in the torsional angle ω .

Conclusions

Barton^{3,4} concluded earlier that conformational transmission did occur and could be measured, in particular in the condensation which he studied, but by implication, in general. We concur, and further conclude that we can calculate in a quantitative way the magnitude and direction of the effect, on the basis of a simple model for the reaction in the particular case at hand, and by implication, in general if an adequate model for the transition state is available or can be deduced. We further point out that there were no adjustable parameters chosen in the present work so as to lead to these results. The parameterization of the force field was carried out to fit the structures and energies of simple compounds, and is used here without change. Clearly, the assumptions made here are very simple ones, which are subject to improvement, and the case at hand is not a particularly favorable one for such a study. Considering this work, together with that of Schleyer¹³ on carbonium ions, we believe it is safe to conclude that force-field methods will in general be found to be applicable to studies of reaction rates, subject to assumptions about the transition states and the usual limitations of force-field methods.

(18) The energies quoted are for the interactions after the molecule has relaxed, and much of the energy has been dissipated into other degrees of freedom.

(19) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).

Appendix

The calculations described herein were carried out with a force field used previously¹ which differs slightly from that described earlier,¹⁹ specifically by the replacement of the absolute value in the stretch-bend interaction by a signed quantity, and the addition of a cubic stretching term, followed by a general reoptimization of parameters. These changes lead to only trivial changes in the geometries and energies of molecules such as those discussed here, so the numerous numerical details will not be elaborated. In addition, a refinement in our energy minimization scheme has been made which utilizes second derivatives including

cross products of the type $(\partial^2/\partial x \partial y)$ in locating the energy minimum. There are enough second derivatives that, proceeding as described earlier, it is not necessary to move the atom and recalculate derivatives to get enough equations to solve for the unknowns. The overall scheme is approximately twice as fast as that described earlier, and to minimize the energy of a typical steroid like those studied here takes about 5 min of CPU time on the IBM 360/65, and somewhat less on the 360/67. Because of the experimental difficulties involved in studies of transient species of all kinds, including transition states, we suggest that this is a method of potentially great power for such studies.

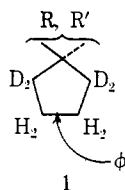
Nmr Spectroscopy of Cyclopentane Derivatives. III. Methylcyclopentane¹

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Abstract: A complete iterative nmr spectra analysis has been accomplished for two specifically deuterated methylcyclopentane derivatives, **7** and **11**, at three temperatures over a range of 117°. The magnitudes of the resulting vicinal interproton coupling constants have subsequently been related to a restricted pseudorotation model involving ten half-chair and ten envelope conformations and were found to be consistent with a conformational preference for those states (a, b, \bar{b} , c, \bar{c} , d, and \bar{d}) in which the methyl substituent is equatorially bonded.

In the previous paper in this series, nmr parameters were reported for a series of specifically deuterated mono- and 1,1-disubstituted cyclopentanes (**1**).² The derived values obtained for the average ring torsional angle, ϕ , about the 3,4-carbon-carbon bond are consis-



tent with a pseudorotation model having potential maxima and minima at $\phi \approx 50$ and 0° , respectively. While this previous work sheds light on the conformational mobility of the substituted cyclopentane ring, it affords no information regarding possible axial-equatorial bonding preference for the substituents.

A methyl group axially substituted on a cyclohexane ring experiences substantial 1,3-diaxial steric interactions when viewed in a space-filling model. For a cyclopentane ring, however, an axial methyl appears to experience no comparable steric hindrance. A comparison of these 1,3-diaxial interactions in the two ring systems is illustrated in Figure 1. On this steric basis alone, the energy difference between axial and equatorial methylcyclopentane (**3a** \rightleftharpoons **3b**) is likely to be substantially lower than in the corresponding methylcyclo-

hexane equilibrium (**2a** \rightleftharpoons **2b**). Pitzer and Donath estimate the energy difference for **3a** \rightleftharpoons **3b** to be about 0.54 kcal/mol,³ a value substantially lower than that of 1.7 kcal/mol for **2a** \rightleftharpoons **2b**.⁴

The actual methylcyclopentane conformational equilibrium is not limited solely to the two envelope forms **3a** and **3b** but includes to some extent all ring conformations encountered in the course of pseudorotation. The absence of any steep potential wells is reflected in the gradual change in conformational energy for the six possible half-chair conformers of methylcyclopentane recently calculated by Allinger and coworkers.⁵

Results

In order to assess the extent of axial-equatorial bonding preference, two specifically deuterated methylcyclopentane derivatives, **7** and **11**, were synthesized (Scheme I) for nmr analysis. The deuterium-decoupled 100-MHz pmr spectra were obtained for **7** and **11** at three temperatures over a range of 117° (Figures 2-5) and their corresponding solution parameters obtained iteratively using LAOCOON 3.⁶ The results are tabulated in Tables I and II, and the stereochemical assignments are shown in Figure 6. The details of the analysis and the

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(2) R. L. Lipnick, *J. Mol. Struct.*, in press.