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A quantum chemical AM1 study of some isomeric prostaglandin allylic acetates

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Abstract

The heats of formation of some synthetically meaningful prostaglandin allylic acetates were calculated by applying the AM1 quantum chemical method. The energy differences of isomeric pairs were used to estimate the thermodynamic equilibria. Good or satisfactory agreement with experiment was found in seven of the eight cases investigated. Although further computations are necessary to confirm the results obtained in this study, AM1 does seem to be a suitable method for roughly predicting the relative stabilities of isomeric natural products or their derivatives.

Introduction

Of all semiempirical quantum chemical methods AM1 [1] appears to have the most successful applications. It is superior to MNDO [2] in calculations on many organic compounds. However, it has been claimed that PM3 [3] shows a better agreement [4] with experiment than both the former approaches. Nevertheless, there is not enough computational evidence for this statement. Therefore AM1 is the method of choice in the laboratories of organic chemists because many of the calculated compounds are available for comparison. Furthermore, experimenters are rather more interested in rough and fast predictions than in accurate but late ab initio information.

In connection with some experimental work in synthetic chemistry we were interested in testing AM1 predictions of the relative stabilities of some isomeric pairs. The compounds investigated in the present study and the corresponding equations are presented in Scheme 1. There are few publications dealing with these or related problems. To our knowledge only Houk and co-workers [5] have published any results of systematic investigations into stereoselectivity using ab initio and molecular mechanistic methods.

The palladium-catalysed rearrangement of allylic acetates [6] has become an efficient route for the construction of the (3*S*)-3-hydroxyoct-1(*E*)-en-1-yl side-chain of prostaglandins and prostaglandin derivatives [7–10]. This rearrangement is stereoselective. For example, the 1′α-allylic acetate **1a** (Scheme 1) and also the 1′β-allylic acetate **3b** give the 3′α-allylic acetate **2a**. In contrast to Houk and co-workers [5], we assume that for all rearrangements considered, equilibria were achieved (reactions were ended after 24–30 h when the ratio of the isomers remained unchanged). It was found [9,10] that the ratios of the compounds **1/2**, **3/2** and **6/5** in equilibrium are different (Table 1). Therefore we were interested in calculating these ratios with AM1 to see the correspondence of calculation to experiment and to predict the ratio of the

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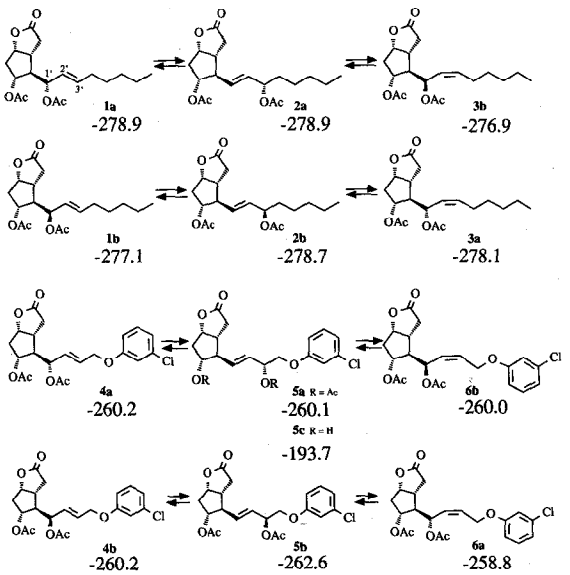

Scheme 1. Calculated energies (kcal mol^{-1}) of compounds.

compounds **4/5** for the rearrangements **4a** → **5a** and **4b** → **5b**, never done before.

Method

Computations

All computations were performed using the MNDO 89 (IBM version) package of computer programs [11]. In all cases presented here the DFP [12] optimization procedure was applied. Because all systems considered exhibit the C_1 point group, full optimizations are necessary. Because the present program only permits optimizing a system with up to 100 degrees of freedom, during the first estimations a number of geometric parameters were kept frozen (H–C bond lengths, the absolutely planar structure of the 3-chlorophenyl group, some angles). After successful optimization, a restart was performed with the geometry found, thereby partly changing some constants and variables. This procedure was continued, until the resulting heat of formation did not become lower.

Owing to the size of the molecules considered, the frequencies of the stationary points were not calculated. We have not included entropy corrections in the calculated energies because they are expected to be very small ($\Delta\Delta G \approx \Delta\Delta H$). Theoretical equilibria were calculated using eqn. (1):

$$k = \exp(\Delta\Delta H/RT) \quad (1)$$

Experiment

Equilibria of rearrangements of allylic acetates have been found by experiment [9,10]. For example, a mixture of defined amounts of acetates **6a** and **6b** has been rearranged to acetates **5b** and **5a**, and the change in composition of the mixture of acetates **5a**, **5b**, **6a** and **6b** were analysed (the acetates **4a** and **4b** were not found in the mixture).

TABLE 1

Calculated and experimental ratios of allyl acetates **1–6** in the investigated rearrangements ($x \rightarrow y$) and the corresponding differences in the heats of formation (kcal mol^{-1})

No.	x	y	Calc.		Exp.	
			$x-y$	x/y	x/y	$x-y$
1	**1a**	**2a**	0.0	50/50	36/64[a]	+0.3
2	**1b**	**2b**	+1.6	6/94	36/64[a]	+0.3
3	**3b**	**2a**	+2.0	3/97	20/80[b]	+0.8
4	**3a**	**2b**	+0.6	27/73	20/80[b]	+0.8
5	**4a**	**5a**	−0.1	54/46	–	–
6	**4b**	**5b**	+2.4	2/98	–	–
7	**6b**	**5a**	+0.1	46/54	5/95[a]	+1.7
8	**6a**	**5b**	+3.8	0.2/99.8	5/95[a]	+1.7

[a]Ref. 10(b).
[b]Ref. 9.

Results and discussion

To check whether the geometries defined in calculations are indeed in agreement with real structures, an X-ray analysis [13] was carried out for allylic alcohol (**5c**) (not all allyl acetates are solid at room temperature). Experimental and calculated geometries are in good agreement (Fig. 1).

The geometrics of the prostaglandin derivatives considered were optimized using AM1 in a manner described in the previous section (Method). The heats of formation obtained are shown in Scheme 1 below the corresponding compounds. They were

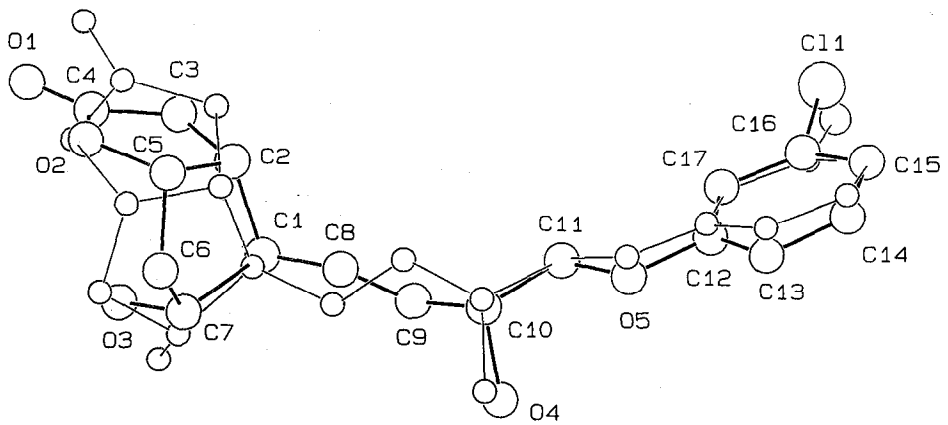

Fig. 1. Superposition of the molecule **5c** determined by an X-ray analysis (thick lines) and the AM1 molecule (thin lines).

used to calculate differences from which the theoretical ratios (eqn. (1)) were obtained. A comparison of theoretical and experimental results is given in Table 1.

Taking into account the fact that in calculations on neutral molecules, AM1 produces agreement with experiment with an average error of a few kilocalories per mole [1], it must be emphasized that the equilibria found correspond fairly well to experimental values. Theoretical predictions by AM1 for Nos. 5 and 6 (Table 1) are different. For the pairs of molecules Nos. 2, 4 and 8, fairly good agreement with experiment was obtained, whereas for cases Nos. 1, 3 and 7 the correspondence was poorer. Consequently, it can be concluded that the direction of equilibrium No. 6 was predicted correctly, but that the prediction fails for No. 5.

How reliable are the ratios of isomers estimated by AM1? In Table 1, in addition to the theoretical differences in heats of formation, the experimental values afforded from product distributions are also presented. Both series of results lie in a fairly narrow region. The highest value obtained from calculations is 3.8 kcal mol^{-1}, whereas only 1.7 kcal mol^{-1} was found experimentally. Clearly, it is seen from eqn. (1) that small changes in energy differences lead to substantial changes in the distribution of compounds. It is known from thermochemistry that heats of formation are usually measured with an accuracy of ± 1 kcal mol^{-1}. Thus it is very hard to calculate ratios for isomeric compounds under equilibrium conditions. However, the level of ab initio calculations applied in ref. 5 permits the calculation of reaction energies with an accuracy of only a few kilocalories per mole. Despite this, good agreement with experiment was achieved. Consequently, when applying both semiempirical and ab initio methods for estimating energy differences of isomeric compounds of almost the same stability, the errors in the procedures used cancel. Whether in our case this is a coincidence or a systematic phenomenon, can only be answered when further investigations are made.

Conclusions

It was shown with some examples of isomeric prostaglandin allylic acetates that results of AM1 calculations correspond satisfactorily or even well to experimental values obtained for equilibria. Although the agreement is only qualitative and in one case a failure was observed, the semiempirical approach used seems to be a good tool for investigating the relative stabilities of large isomeric molecules.

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