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Computers In Chemistry

A Computer Program to Calculate the Percent Total Deuteration in an Exchange Reaction

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The acid-catalyzed hydrogen–deuterium exchange reaction in aliphatic ketones was modeled as a purely random process. Using a computer program, a statistically random hydrogen–deuterium exchange was simulated for a particular molecule, 2-indanone. For this molecule, there are two α carbons, each providing two potential sites for exchange. The program determined the relative amounts for each of the partially deuterated species, including the total percent deuteration. A comparison with mass spectral data showed good agreement with this model.

A computer modeling program was written in Visual Basic based on simple, statistically random hydrogen–deuterium exchange….

Introduction

The deuteration reaction in aliphatic ketones has been well studied and is understood to be a series of hydrogen–deuterium exchanges via an acid-catalyzed enolization mechanism [1, 2]. A computer modeling program was written in Visual Basic

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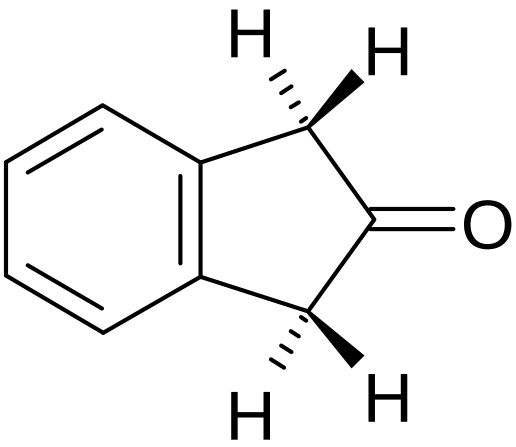

FIGURE 1. 2-INDANONE. THE FOUR HYDROGENS ON THE α CARBONS MAY BE EXCHANGED WITH DEUTERIUM. THESE CONSTITUTE THE FOUR DEUTERATION SITES IN THE COMPUTER PROGRAM.

based on simple, statistically random hydrogen–deuterium exchange to calculate the species concentrations in deuterated 2-indanone, which is shown in Figure 1. The symmetrical 2-indanone affords four hydrogen atoms at the α position for potential deuterium–hydrogen exchange. The calculation agreed extremely well with the mass spectral data.

Experimental

Sample preparation

The 2-indanone used was the result of a synthetic project by students in organic chemistry. Indene was hydroxylated using formic acid to yield the formate of 1,2-indanediol. Addition of sulfuric acid, followed by steam distillation, caused the formate to undergo an acid-catalyzed elimination and rearrangement, resulting in 2-indanone in about 70% yield [3].

Deuterated 2-indanone was prepared by either of two methods. In the first procedure, 3 g of the ketone was dissolved in 10 mL of acetone-d_6 followed by the addition of 10 mL D_2O. Additional acetone-d_6, but not more than 3 mL, was added to maintain a clear solution. Then, 0.5 mL of CF_3CO_2D was added and the mixture was stirred under dry nitrogen at room temperature for 3–4 days. The solvents were removed either by vacuum distillation, or by neutralization with sodium carbonate, extraction with ether, followed by rotary evaporation of the ether.

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After two exchange procedures, the deuterium incorporation at the α position was in the range of 96% [4]. A second and simpler procedure involved the refluxing of 2-indanone in D_2O under an atmosphere of dry nitrogen, using about 3 g of indanone in 5 mL of D_2O. After about 3–6 hours, the solution was allowed to cool, whereupon the crystals of 2-indanone that formed could be collected by suction filtration. After about six exchange procedures, 98% deuteration was obtained. Eight additional exchange procedures were needed to achieve 99% deuteration. With either procedure, because the exchange reaction is relatively slow, samples can be extracted during the reaction process and analyzed by NMR to determine the extent of deuteration. The products of both procedures were purified by multiple vacuum sublimation. To avoid decomposition, the product must be stored cold and kept under dry nitrogen. For this study, 10 samples with different levels of deuteration were prepared and the mass spectrometry performed. The parent peak offered a good reference to the extent of deuteration.

The mass spectrometer used a double-focusing magnetic sector with an electron ionization source. The masses were calibrated against a perfluorokerosene standard. Several scans were averaged from a section of the acquisition in which the total ion current remained relatively steady. Precision in the signal strength was within 5%.

A simple formula was used to correct the mass spectral data to account for the presence of ^{13}C, assuming a 1.11% natural abundance:

$$n' = \left[1/(1 - 0.0111 \cdot \mathrm{C})\right] n - 0.0999(n-1) - 0.00998(n-2)$$

Here, n, $(n–1)$, and $(n–2)$ are the mass spectral intensities of the n, $(n–1)$, and $(n–2)$ peaks, respectively, C is the number of carbon atoms in the molecule, and n' is the corrected intensity of the nth peak. Using 2-indanone as an example, the intensity of the first peak in the series of parent or fragmentation peaks needs to be multiplied by the coefficient of the first term, 1.111 (C = 9), because this first peak is smaller than what it *should* be by 11.1%. Note that this amount of intensity is given over to the $(n+1)$ peak. The same holds true when the intensity of the next peak in the series is corrected, but now, the intensity of 9 carbon atoms times the 1.11% natural abundance (9.99%) must be subtracted, because this intensity comes from the $(n–1)$ peak. To correct for the intensity of the third peak, the same two corrections as previously mentioned hold, but in addition, the contribution from the $(n–2)$ peak must be

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subtracted. This intensity amounts to 9.99% of 9.99% (0.998%). Additional corrections are discounted because of their magnitude.

The Computer Program

The computer model contained a user-definable number of indanone molecules, which was usually set at 8000. Each molecule was modeled as a four-element array, with each element corresponding to one of the four hydrogen–deuterium sites on the α carbons. If the site was a hydrogen atom, it was given the value of zero; if a deuterium atom, the value of one. In the Visual Basic program, (see Appendix), the product of the maximum number of molecules and the maximum number of sites, both user definable, cannot exceed 32,000 if this program is to be used without extensive modification.

The exchange occurred first by a random choice of a site. Whether or not the chosen site was hydrogen or deuterium depended upon the reaction bath's probability of deuteration, which was defined by the user as the "desired total percent deuteration." For example, if the bath's deuteration percentage was 50%, there was a 50% probability that the chosen site would be exchanged with a deuterium, in which the current element value was replaced with a one. For a low bath-deuteration percentage, such as 25%, there was a 75% chance of reprotonation in which the element value was replaced with a zero.

The reaction occurred by performing hundreds of exchanges with each of the thousands of molecules. In the end, each molecule was assigned a value equal to the sum of the values in its array representing the molecule's number of deuterium atoms. A completely nondeuterated molecule, for example, with each array element containing a zero, gave a sum of zero, corresponding to zero deuterium atoms. A trideuterated molecule, containing three ones and one zero in its array, gave a sum of three corresponding to the three deuterium atoms. By counting the number of molecules with 0, 1, 2, 3, and 4 deuterium atoms, the relative abundances of the d_0, d_1, d_2, d_3, and d_4-2-indanone species contained in the sample was calculated. The overall percent deuteration was calculated by dividing the total number of deuterated sites by the total number of sites.

By repeating the whole process many times and averaging the end results, a good approximation of the relative concentrations of each deuterated species in the actual

```
Iter#:  0016  %Deut:  41.43  Old %Deut:  41.40  Diff:  0.025  Desired Deut  042%
 00  Deuts: XXXXXXX                                                   11.29%
 01  Deuts: XXXXXXXXXXXXXXXXXXXX                                      33.89%
 02  Deuts: XXXXXXXXXXXXXXXXXXXX                                      35.11%
 03  Deuts: XXXXXXXXXX                                                17.25%
 04  Deuts: X                                                         02.46%

                                 Sample Molecules
      DPDP                       PPPP                 DPPP
      PDDP                       PPPD                 DPDP
      DDPP                       DDPP                 PPPD
      PPDD                       PPDP                 DPPP
      DPPP                       DDPD                 DPDD
      PPDP                       PPDP                 PDDD
      PPDP                       PPPP                 DPDP
      PDDP                       PDPP                 DPPP
      DDDD                       PPPP                 DPPP
      DPDP                       PPDD                 PPPD
      DDDD                       DPPP                 DDPP
      PPPD                       DPPP                 PDPD
Convergence within 0.100% Tolerance
Winth a final  %  deuteration of 41.4%.
Press a Key to Resume…
```

FIGURE 2. PRINT-OUT OF THE SCREEN DISPLAY DURING THE RUNNING OF THE MODEL PROGRAM.

sample may be made. Because the reaction bath's deuterium concentration was significantly greater stoichiometrically than the concentration of hydrogens to be exchanged, in this model, the deuterium content of the bath was held constant. The screen display is shown in Figure 2. The number of iterations, along with the desired percent deuteration are indicated. The percent abundances of each of the five molecular species are given. Then, as a visual display of the exchange process, three columns of representative molecules are shown, for which D = deuteron and P = proton. The test for convergence was when the difference in the total percent deuteration of three successive iterations was less than 0.1%. When convergence was reached, the program halted and displayed the final total percent deuteration. If convergence was not reached before the variable maximum iteration was reached, the calculation was terminated, the user alerted to this fact, and asked if additional iterations were desired. A typical calculation took less than two minutes on a 486-66

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TABLE 1. A comparison of the model (±1%) and the mass spectral (MS) data (±5%) for some representative 2-indanone samples containing a range of percent total deuteration. The columns d_0–d_4 are the percent composition of the nondeuterated, partially deuterated, and completely α-deuterated 2-indanone.

% Deuteration		d_0	d_1	d_2	d_3	d_4
27%	Model	29%	42%	23%	6%	0%
	MS	27%	44%	24%	5%	0%
42%	Model	11%	33%	35%	17%	4%
	MS	10%	31%	40%	18%	1%
79%	Model	0%	3%	17%	42%	38%
	MS	0%	3%	17%	42%	38%

MHz PC. The results of trial runs using identical initial parameters deviated by no more than 1%.

Results

Table 1 compares the random model and the mass spectral data for three samples with a wide range of total percent deuteration. When removed samples are less deuterated than the bath, thermodynamic equilibrium has not been attained. Hence, perfect agreement may not be possible due to the slow rate of the exchange reaction. However, the agreement between the model and experiment were found to be quite good, especially on the higher percentages of total deuteration.

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