

with dimethoxyethane (2 × 150 mL) and pentane (150 mL) followed by drying in vacuo (45 min). A brick-red solid (50.6 g, 92%) was obtained.

**2-Amino Alcohol Synthesis.** A dry 250-mL flask was charged with  $\text{NbCl}_3(\text{DME})$  (2.0 g, 6.9 mmol) and tetrahydrofuran<sup>11</sup> (ca. 80 mL). A tetrahydrofuran solution (4 mL) of the imine<sup>16</sup> (6.9 mmol) was then added dropwise (via syringe) over 30 s to the stirred mixture. When the solution became a homogeneous dark green (or yellow-green) color (ca. 1 min), the aldehyde or ketone (4.6 mmol) in tetrahydrofuran (ca. 2 mL) was added dropwise over 30 s. After stirring for 30 min the reaction was poured into a separatory funnel and treated with potassium hydroxide (10% w/v, 75 mL) and extracted with ether (2 × 150 mL). The combined ether layers were dried briefly over  $\text{MgSO}_4$  and filtered. The ether was removed in vacuo yielding the crude product as an oil which was purified by flash chromatography<sup>17</sup> (silica gel, 230–400 mesh, hexane/ethyl acetate).

**Acknowledgment.** S.F.P. is grateful to the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735). E.J.R. thanks the National Cancer Institute (DHHS) for a PHS Award (F32 CA08058-01).

**Supplementary Material Available:** Full NMR, IR, and mass spectral data and C, H, and N analysis information for all amino alcohols (10 pages). Ordering information is given on any current masthead page.

(15) Alternatively standard Schlenk filtration can be employed.

(16) All imines were prepared by combining the appropriate aldehyde, amine, and excess  $\text{MgSO}_4$  in dichloromethane and stirring overnight. The imines were purified either by recrystallization or Kugelrohr distillation.

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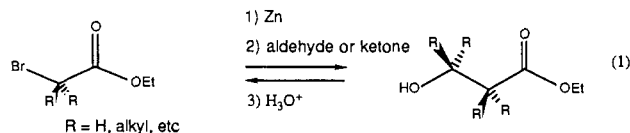
## The Reformatsky Reaction

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Received March 19, 1987

While the Reformatsky reaction<sup>2</sup> (see eq 1) is celebrating the centennial of its discovery this year, the mechanism is still a matter of controversy. Early mechanistic suggestions<sup>3</sup> have centered



around the rearrangement of adducts **1** and **2** of the two possible monomeric forms of the Reformatsky reagent (RR) with the majority of the chemical evidence favoring the enolate form **2**. However, recent X-ray evidence has shown that the RR is dimeric in THF,<sup>4</sup> throwing doubt on the suggestion that the monomeric forms participate at all. Here we report a detailed theoretical study of the reaction, with use of the MNDO method<sup>5</sup> as implemented by the AMPAC program.<sup>7</sup> MNDO has been recently

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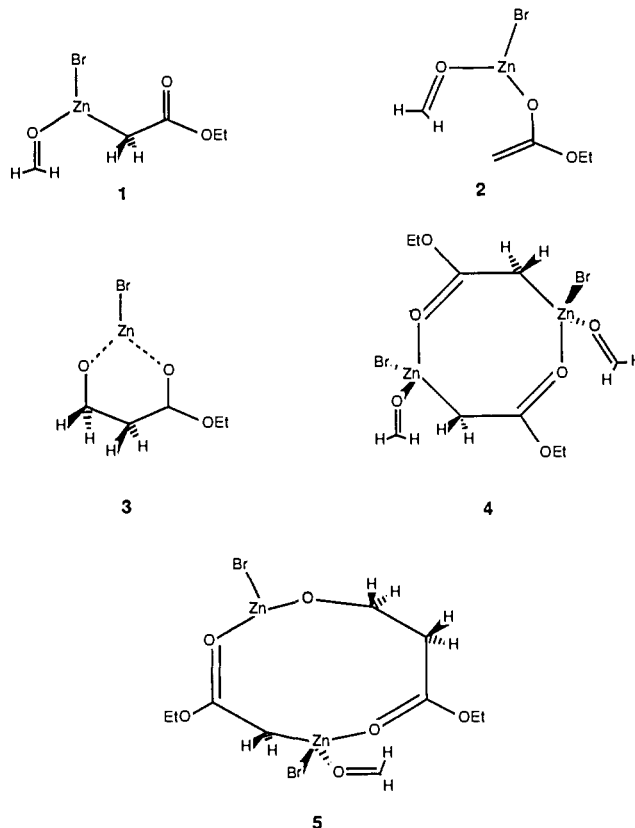
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parametrized to handle organozinc compounds.<sup>8</sup> The aldehyde and ether component of the RR was modelled by formaldehyde and dimethyl ether, respectively.

We first needed to know what MNDO predicts for the coordination number around zinc. We find, on the basis of purely energetic considerations, that MNDO favors the coordination around zinc to be three. This seems to be at variance with most of the available experimental evidence, which indicates that the usual coordination number for zinc in solution is four.<sup>8</sup> This discrepancy is not surprising because MNDO tends to overestimate repulsions between neutral atoms.<sup>9</sup> It should be noted here that we have also carried out extensive MNDO calculations on the mechanism of the Reformatsky reaction where the zinc is tetra-coordinated (i.e., with dimethyl ether as well as formaldehyde), and the results do not differ significantly from those we present below.

Chart I gives the reaction profile for the rearrangement of **1** and **2** to **3**. Our calculations predict **1** to be more stable than **2** by about 7.8 kcal/mol, **1** and **2** interconverting by a 1,3-shift with an  $E_a$  of 26.5 kcal/mol. We next located the transition states (TSs) for the formation of **3** from either **1** or **2**. **1** can rearrange to give **3**, by a 1,4-shift, with an  $E_a$  of 55 kcal/mol, while the formation of **3** from **2** only requires 15.45 kcal/mol.

The differences in the  $E_a$ s are easily understood in terms of the aromaticity or antiaromaticity of the respective TSs.<sup>10</sup> The TS for the 1,4-shift contains four delocalized electrons and is therefore antiaromatic.<sup>10</sup> The TS for conversion of **2** to **3** contains six delocalized electrons and is therefore aromatic. The latter reaction involves a [3,3]-sigmatropic shift, analogous to a Cope or Claisen rearrangement. We therefore would like to classify this rearrangement as a metallo [3,3]-sigmatropic shift (or metalloclaisen). Previous authors<sup>11</sup> have pointed out that the Reformatsky reaction

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Chart I

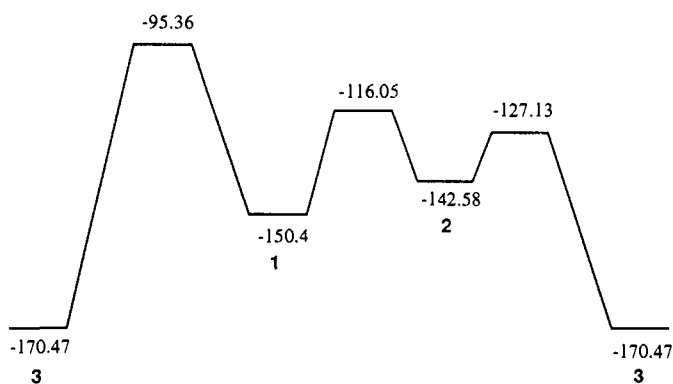
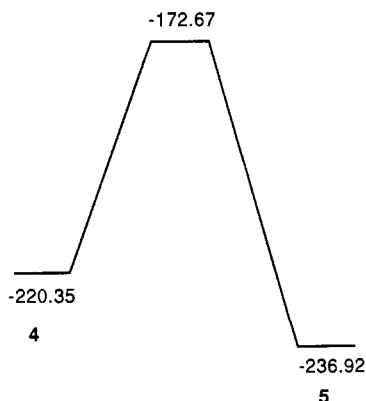


Chart II



can proceed by a pericyclic mechanism, without, however, identifying it as a [3,3]-sigmatropic process. It should be noted here that TSs of this type have been invoked in the case of the aldol reaction.<sup>12</sup> The TS for the metaloclaissen reaction adopts a chair conformation as one would expect by analogy with the Cope or Claisen rearrangements.<sup>13</sup>

The minimum energy reaction path for the formation of product in the case of the monomeric species is (see Chart I) first the conversion of **1** to **2** which then in the next step gives **3**. The rate-determining step for this reaction is predicted to be not the formation of the final product **3** but the formation of **2**. Therefore, the  $E_a$ , which for the moment neglects the involvement of dimer, is predicted to be 26.5 kcal/mol.

We next carried out calculations for the dimeric form of the RR. Our calculations predict dimerization to be exothermic by about 5 kcal/mol; implying that the RR should exist as a dimer in solution or in the crystal. This agrees with the experimental evidence that the RR is indeed a dimer in the solid state.<sup>4</sup> The authors responsible for the crystal structure of the RR pointed out that there are two possible pathways by which the RR can react to form product.<sup>4</sup> The first is a 1,3-sigmatropic shift of methylene carbon to carbonyl carbon while the second involves attachment of the carbonyl carbon to the transannular methylene (six-centered TS). These authors favored the latter reaction path. We have studied both pathways. While we found a TS for the 1,3-sigmatropic reaction, no TS could be located for the alternative reaction path. We found that this latter pathway broke apart the dimer at a great energetic cost, while the former led smoothly to product **5**. The reaction profile for the dimer is given in Chart II.

The  $E_a$  for product formation in the case of the dimer is 47.7 kcal/mol, and in order for us to compare this figure with that of the monomer reaction we have to include the heat of dimerization ( $\Delta H_{\text{dim}}$ ) of the monomer. For the  $\Delta H_{\text{dim}}$  of **1** we arrive at a value of 5.3 kcal/mol, hence the  $E_a$  for the conversion of **4** into **3** is 31.8

kcal/mol. However, since we underestimate the stability of four-coordinate zinc we feel that this  $E_a$  probably represents a lower limit to the actual  $E_a$ . Regardless, we feel that the Reformatsky reaction occurs via the monomeric form of the RR, because unless our  $\Delta H_{\text{dim}}$  is underestimated by over 15.8 kcal/mol the dimeric form of the RR cannot be competitive with the monomeric form.

**Acknowledgment.** This work was supported by the Air Force Office of Scientific Research (Contract no. AFOSR 86-0022), the Robert A. Welch Foundation (Grant no. F-126), and the National Science Foundation (Contract CHE 87-12022). Part of it was conducted by using the supercomputing resources of the Center of Theory and Simulation in Science and Engineering at Cornell University, which receives funding in part from the NSF, New York, and IBM corporation. K.M.M. thanks Professor Roald Hoffmann for his support and guidance during his stay at Cornell.

### Direct Experimental Evidence for Cleavage of Both Exo- and Endocyclic C-O Bonds in the Acid-Catalyzed Reaction of Alkyl $\beta$ -Tetrahydropyranyl Acetals

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Received April 27, 1987

The mechanistic and stereoelectronic aspects of acetal hydrolysis have attracted a great deal of attention from both organic chemists and biochemists in recent years.<sup>1-3</sup> The continuing interest is due largely to the biological importance of the reaction. A significant objective has been to understand the mode of action of lysozyme.<sup>4,5</sup> Model studies related to the lysozyme problem

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