

# **ORGANIC SYNTHESIS AT HIGH PRESSURES**

Edited by

**Kiyoshi Matsumoto  
R. Morrin Acheson**

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# PREFACE

Although one of the earliest chemists to use high pressure technology was Moissan, who thought he had made diamond from graphite by heating it under pressure and cooling it rapidly, the first person to make real progress in understanding this area was the late Professor P. W. Bridgman of Harvard, who received a Nobel Prize in 1944 for his discoveries. Genuine synthetic diamonds were first made in 1954 using high temperature and pressure, but it was only recently that research groups in the United States, France, Poland, Germany, Great Britain, and Japan started to apply this technology to the study of organic reaction mechanisms and to synthesis. A substantial body of new information was obtained concerning the details of organic reactions in solution. From this it was possible to deduce what types of reactions involving organic compounds should most likely be assisted by high pressures. These predictions, in a general way, have proved to be correct, but there are many very important details that are crucial to synthetic success, such as use of the correct solvent for a particular reaction, which can only be discovered by experiment or guessed by analogy. A significant number of compounds that are thermally unstable or that proved to be impossible to make under atmospheric pressure, have been obtained by using high pressures with homemade or commercially available equipment. The idea for this book, devoted mainly to preparative organic chemistry under high pressures, was developed in Japan. We thought that a state-of-the-art book on this subject would be of value to those working in synthetic organic chemistry and that it would help them to decide whether high pressure technology, with its advantages and limitations, might help them in solving their current problems.

We would appreciate receiving comments about this book and being notified of errors that are doubtless present, in spite of our attempts to eliminate them. We thank the individual contributors who made this book possible. We also thank the Ministry of Education, Science, and Culture for Grants-in-Aid (to KM) for Developmental Scientific Research (Numbers 284021 and 61840017) and Sandoz A. G. Basel for library facilities (RMA).

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*January 1991*

# **ORGANIC SYNTHESIS AT HIGH PRESSURES**

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# **PART I**

## **Basic Principles**



# 1 Introduction

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## 1. INTRODUCTION

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### 1.1 INTRODUCTION

When a new technology is in view, there is usually a considerable barrier to be overcome before new apparatus is bought, installed, and used for its initially intended purpose. At this point it is often found that the apparatus can be employed, usefully and without much extra effort, in a much wider context than that originally envisaged. This is the position that high pressure technology occupies in the field of organic synthesis at the present time.<sup>1</sup> Persuading chemical substances, which in some ways are quite like people, to react together in a desired manner is still an art. The exact conditions for the best results are often not easy to find. The reaction solvent (e.g., alcohol, too much or too little, can be disastrous), illumination (e.g., wavelength and intensity), and temperature are very important factors. If the correct conditions are not found, the application of high pressure can lead to the desired result, to a very interesting unexpected result, or to carbonization.

A number of commercial sources will supply suitable reactors for synthetic experiments,<sup>2</sup> and the cost is less than that of many widely used spectrometers. Usually, the compounds that are to be compressed are dissolved in a suitable solvent and are put into a poly(tetrafluoroethylene) (PTFE) or other flexible container, which is then filled with solvent and closed securely with a cap. This is then placed in a pressure vessel that is then filled with kerosene or another suitable liquid. This liquid is now compressed with a piston actuated by a suitable hand or electrically operated pump to the desired pressure when the pressure is transferred to the inner flexible container. The "pot" of a normal laboratory reactor is usually 1–50 mL in capacity and can be pressurized to about 2.0 GPa. Pressures of over 0.5 GPa are usually needed to assist organic synthesis whereas lower pressures may be sufficient in cases where information

concerning a reaction profile is required. A reactor of 1-L capacity that is capable of being used up to 10.0 GPa has been made.<sup>3</sup>

In contrast to gases, liquids lose relatively little volume on compression so that the precautions necessary to protect the operators of high pressure equipment involving liquids are relatively easy to take in almost any laboratory. Compressed liquids possess about 1% of the potential energy of similarly compressed gases.

The activation volume  $\Delta V^\ddagger$  is defined as the difference between the partial molar volume of the transition state and the initial states of the reactants in a chemical reaction. In the case of an ideal solution,  $\Delta V^\ddagger$  can be expressed by the thermodynamic equation:

$$\Delta V^\ddagger = -RT \frac{\delta \ln k}{\delta p}$$

The partial molar volume can be divided into structural and solvent dependent parts, and this enables deductions to be made concerning the transition state of the reaction in question. Activation volumes have been determined for many reactions,<sup>4</sup> but when they are not available the  $\Delta S^\ddagger$  value may be used as a guide, since a linear relationship has been found between  $\Delta V^\ddagger$  and  $\Delta S^\ddagger$  for a significant number of transformations.

Reactions with a negative volume of activation will be accelerated by increased pressures. Negative activation volumes are associated with bond formation, concentration of charge, and ionization during the formation of the transition state, whereas bond cleavage, dispersal of charge, neutralization in the transition state, and diffusion control, lead to positive activation volumes. The solvent can greatly affect the activation volumes through its interaction in the transition state. Reactions that are expected to speed up with increasing pressure therefore include any reaction where the molecularities of the reactants decrease in the products (including cycloadditions and condensations), reactions which proceed through cyclic transition states (e.g., Cope and Claisen rearrangements), those which take place through dipolar transition states (e.g., the alkylation of tertiary amines), and reactions inhibited by steric hindrance. Sometimes there is a critical pressure below which a reaction does not appear to take place (or to be accelerated). This may be due to a change of state, a change in mechanism, or both. The freezing points of many common solvents are raised by increasing the pressure, so potential reactants may be precipitated or forced to react in semisolid or solid phase conditions. The lining up of molecules of the reactants under these circumstances may be the key to success. The viscosity of liquids often doubles for each 0.1 GPa of applied pressure, which then makes diffusion control of reactions more important. In one case the mechanism of an alkylation reaction was shown to be altered by increasing the pressure,<sup>5</sup> and the discovery of other mechanistic changes caused by pressure must be expected.<sup>6</sup> In 1989 for pressure accelerated Diels–Alder reactions, it was shown<sup>7</sup> that the intrinsic contraction in bond formation in the transition state is small (3–5% of  $\Delta V^\ddagger$ ) and that most of the volume contraction that occurs is due to loss of empty space

surrounding the reactants and not from the reactants themselves. This is a very important conclusion, for it suggests that the data for activation and reaction volumes in the cases investigated should not be used for the deduction of the reaction mechanisms. Neither the concerted nor the diradical mechanism for the Diels–Alder reaction can be established from high pressure data. It is possible that the mechanism adopted by a particular Diels–Alder reaction may vary with the pressure.

Because a significant number of compounds, which for steric or other reasons cannot be synthesized at atmospheric pressure, but which nevertheless have been obtained by employing high pressures, it is clear that this type of technology can be of great value in organic synthesis.<sup>8</sup>

The SI unit of pressure (Pa, the Pascal) is used in this book and the exact numerical relationships between the various units of pressure are given in the following table:

|   | Units    |          |                        |          |
|---|----------|----------|------------------------|----------|
|   | (bar)    | (atm)    | (kg·cm <sup>-2</sup> ) | (MPa)    |
| 10 <sup>5</sup> Pa = 0.1 MPa = 10 <sup>-4</sup> GPa | 1.0      | 0.986924 | 1.019216               | 0.1      |
| 1 atm   | 1.013250 | 1.0      | 1.033227               | 0.101325 |
| 1 bar   | 1.0      | 0.986924 | 1.019216               | 0.1      |
| 1 kg·cm <sup>-2</sup>                               | 0.980665 | 0.967842 | 1.0                    | 0.098115 |

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# 2 Basic Principles and Mechanisms

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The thermodynamic and kinetic effects of pressure on liquid phase reactions are discussed in this chapter.



## 2.1 THERMODYNAMIC EFFECTS OF PRESSURE

Consider a general chemical reaction as expressed by Eq. (2.1).



The chemical potential of the component  $i$ ,  $\mu_i$ , is given by

$$\mu_i = \mu_i^\circ + RT \ln a_i \quad (2.2)$$

where  $\mu_i^\circ$  is the chemical potential of  $i$  in its standard state and  $a_i$  is the activity. At equilibrium, the overall chemical potential change equals zero.

$$l\mu_L + m\mu_M + \cdots - (a\mu_A + b\mu_B + \cdots) = 0 \quad (2.3)$$

Thus,

$$\sum v_i \mu_i^\circ = -RT \ln \frac{a_L^l a_M^m \cdots}{a_A^a a_B^b \cdots} = -RT \ln K \quad (2.4)$$

where  $v_i$  is the number of moles of the  $i$ th component involved in the reaction.

The pressure dependence of the equilibrium constant  $K$  is given by

$$\left( \frac{\partial \ln K}{\partial P} \right)_T = - \frac{1}{RT} \left( \frac{\partial \sum v_i \mu_i^\circ}{\partial P} \right)_T \quad (2.5)$$

and since

$$\left( \frac{\partial \mu^\circ}{\partial P} \right)_T = \bar{V}^\circ \quad (2.6)$$

we obtain

$$\left( \frac{\partial \ln K}{\partial P} \right)_T = - \frac{1}{RT} \sum v_i \bar{V}_i^\circ = - \frac{\Delta \bar{V}^\circ}{RT} \quad (2.7)$$

where  $\bar{V}_i^\circ$  is the partial molar volume of component  $i$  in its standard state and  $\Delta \bar{V}^\circ$  is the difference between the sum of the partial molar volumes of the products and that of the reactants in their standard state. In concentrated solutions, it is much easier to measure mole fractions ( $x_i$ ) of the reactants and products; they are related to the activities by

$$a_i = x_i \gamma_i \quad (2.8)$$

where  $\gamma_i$  is the activity coefficient. The thermodynamic equilibrium constant is, therefore, given by

$$K = \frac{a_L^l a_M^m \cdots}{a_A^a a_B^b \cdots} = \frac{x_L^l x_M^m \cdots}{x_A^a x_B^b \cdots} \cdot \frac{\gamma_L^l \gamma_M^m \cdots}{\gamma_A^a \gamma_B^b \cdots} = K_x K_\gamma \quad (2.9)$$