PHASE-TRANSFER CATALYSIS; MECHANISMS & SYNTHESES

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Phase-Transfer Catalysis

Mechanisms and Syntheses

Marc E. Halpern, EDITOR
PTC Technology

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Foreword

THE ACS SYMPOSIUM SERIES was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of this series is to publish comprehensive books developed from symposia, which are usually "snapshots in time" of the current research being done on a topic, plus some review material on the topic. For this reason, it is necessary that the papers be published as quickly as possible.

Before a symposium-based book is put under contract, the proposed table of contents is reviewed for appropriateness to the topic and for comprehensiveness of the collection. Some papers are excluded at this point, and others are added to round out the scope of the volume. In addition, a draft of each paper is peer-reviewed prior to final acceptance or rejection. This anonymous review process is supervised by the organizer(s) of the symposium, who become the editor(s) of the book. The authors then revise their papers according to the recommendations of both the reviewers and the editors, prepare camera-ready copy, and submit the final papers to the editors, who check that all necessary revisions have been made.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previously published papers are not accepted.

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Preface

CHARLES STARKS predicted 10 years ago that a vast number of new applications and more complex catalyst systems based on phase-transfer catalysis (PTC) await discovery and exploitation. Starks made this prediction 10 years ago in his overview in ACS Symposium Series 326, *Phase-Transfer Catalysis: New Chemistry, Catalysts, and Applications*. In his preface, Dr. Starks noted the exponential growth of PTC up to 1986. A decade has passed, and Dr. Starks's predictions have come true. The exponential growth of PTC continues in the laboratory synthesis and commercial manufacture of organic chemicals and polymers. This growth appears to sustain itself as a result of strong fundamental driving forces for high yield, short reaction time, replacement or elimination of solvent, and much more, all of which PTC provides. The driving forces of industry in the mid-1990s coincide with the capabilities of PTC to deliver the desired outcomes.

This book documents the research of many top contributors to the growth of PTC. Tracking down and recruiting these scientists was no easy task. Martin O'Donnell from Purdue University performed an outstanding service (investing truly exemplary planning and effort) to the academic and industrial PTC community by organizing the PTC symposium, upon which this book is based, at Pacifichem 95 in Honolulu, Hawaii, December 17–22, 1995. The speakers recruited by Professor O'Donnell and the papers presented addressed most of the major areas of PTC innovation, including mechanisms, research guidelines, chiral PTC, synthesis of organic chemicals, modification of polymers, triphase catalysis, and new catalysts. Several chapters in this book are landmarks in the field, including the chapters by Professor O'Donnell and coworkers. Other chapters provide excellent and unique historical and scientific perspective, particularly the mechanistic chapters in this book written by the founders of PTC.

Acknowledgments

The credit for this book goes to the authors, who invested great effort and elegant creativity; to Professor O'Donnell, who made it all happen;

and to the many reviewers, who executed the peer-review process with dedication and effort.

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Contents

Chapter 1

Recent Trends in Industrial and Academic Phase-Transfer Catalysis

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Phase-Transfer Catalysis ("PTC") continued to grow significantly during the past decade. The driving forces for industrial and academic PTC research are stronger than ever. Even in light of the impressive growth of PTC, much progress has yet to be made both in the fundamentals of PTC and its industrial application. Chemical companies which focus on cutting cost of manufacture and pollution prevention have much to gain by implementing PTC to reap great benefit. PTC trends, barriers and opportunities are discussed.

The last ACS Symposium Series book published on the subject of phase-transfer catalysis, "PTC," is about a decade old. During this decade, there have been changes in the chemical industry, changes in academic chemical research and changes in the state of the art of PTC. This paper represents a non-comprehensive attempt to characterize some of the progress of PTC over the last decade while stimulating thought about how PTC has or has not meshed with the needs of the changing environment in the chemical industry and academia.

Exactly 10 years ago, Dr. Charles Starks, who coined the term "Phase-Transfer Catalysis," wrote in the preface to ACS Symposium Series 326 on PTC that in the previous 15 years PTC "expanded greatly." Dr. Starks estimated that the "volume of phase-transfer catalysts totaled about 40,000 lb of catalysts per year in 1980 but grew to more than one million lbs of catalyst per year in 1985." In 1996, there are several commercial processes which use approximately one million lbs per year each of phase-transfer catalyst and I estimate that the non-captive market for phase-transfer catalysts is over $25 million per year. I estimate that the number of commercial PTC applications grew each year by 10-20%, although it should have been growing even faster due to industry trends for process requirements (described below). Ten years ago, Dr. Starks noted that Chemical Abstracts just

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started to issue CA Selects - Phase-Transfer Catalysis, which has since been very successful and useful to PTC chemists and casual PTC browsers. During the past six years, specialized courses on industrial PTC have been offered and provided to chemists at well over 100 companies and a new journal "Phase-Transfer Catalysis Communications" was launched (1994) with 1200 subscribers and growing rapidly. Today, you can search Phase-Transfer Catalysis on the Internet (which hardly existed 10 years ago) and find references to the work of many of the authors in this book (there is even one web site dedicated to PTC, which will seem trivial to a reader of this book 10 years from now).

Indeed, PTC is alive, well and growing because it provides benefit to chemists and engineers. Much has been written over the years about the multitude of advantages which PTC offers,[1,2] including increasing yield, reducing reaction time and/or temperature, eliminating or solvent, using alternate raw materials, enhancing selectivity and safety and more. An informal non-scientific survey[3] of chemists and engineers at 38 industrial sites in 1995/6 suggested that the primary driving force for considering PTC at the outset of a project is usually productivity and sometimes replacement or elimination of solvent. The most desired PTC outcome in both lab and plant in 1985 was increasing or achieving high yield. In 1996, this has been supplemented by PTC driving forces for reducing cycle time (to squeeze more profit from a fixed plant) and eliminating, reducing or replacing solvent (to comply with ever increasing environmental demands). **These driving forces, which fit well with the capabilities of PTC, are timeless and fundamental to performing chemistry in the lab and in the plant**. Considering these driving forces and considering that PTC is applicable to such a diverse range of organic and polymer reactions, PTC is not likely to be totally replaced by some as yet unknown competing technology in the near future. The ability of PTC to deliver benefit in the lab and plant will probably assure that another ACS Symposium Series on PTC will be published within another decade.

The key barriers to executing PTC projects are usually cited to be (1) lack of time to develop/optimize choice of catalyst, catalyst separation and other reaction or process parameters or (2) lack of confidence (i.e., expertise) that the reaction or process (including related unit operations) will actually work. As a general observation, it may be stated that deadlines and project overload are responsible for an enormous amount of non-optimized processes being commercialized, whether they involve PTC or not.

The economic conditions and massive R&D layoffs in the chemical industry in the early 1990's have created very strong conflicting needs which are relevant to PTC development. Chemists have always felt project pressures, however the demands on chemists in the mid-1990's are quite different from the demands in the mid-1980's. The number of R&D scientists and engineers in the US chemical industry (non-pharmaceutical) dropped from 46,100 in 1990 to 41,200 in 1995.[4] In this work environment, chemists are required to develop much more cost efficient manufacturing processes than ever and have less time and more workload than ever. On the one hand, PTC excels in reducing cost of manufacture and pollution prevention. On the other hand, PTC often requires added time for development. Constrained R&D resources often result in managers consciously foregoing million dollar per year profit opportunities in favor of allocating several $10,000's of development resource for a "higher priority" non-PTC project.

Progressive companies recognize the potential profit opportunities which are likely to result from implementing PTC. Progressive companies have overcome the barriers to PTC development by cultivating internal PTC experts, contracting with industrial PTC expert consultants or bringing in industrial PTC training. All of these activities reduce the investment in development resource to a tolerable level while maximizing the actual benefit realized by the company. Review of the patent literature shows that most of the same companies which issued impressive PTC technology patents prior to 1985 (such as, but not limited to, General Electric, DuPont, Dow, Bayer, Sumitomo, ICI, Ciba-Geigy, Merck, Eli Lilly and others) continued to do so through the 1990's. The new PTC patents continue to cover polymers, pharmaceuticals, agricultural chemicals and a very wide range of intermediates, specialty and fine organic chemicals.[5] It is interesting to observe that not all large companies have embraced PTC and some small companies use PTC very effectively. One may assume that the growth of PTC in many large and small chemical companies is due to the profit enhancing virtues of PTC. Whereas, I would like to think that the lack of growth of PTC at certain large and small companies is a result of corporate culture and organizational resistance to change, despite the proven profit track record of PTC.

Although there have been several extremely impressive industrial contributions to fundamental PTC, the basis for most PTC knowledge has come from academic institutions. During the past decade, academia has also suffered funding shortages. Federal funding for basic and applied chemical research in the United States increased at annual rates of only 0.6% and 2.7%, respectively, during the period 1989-1996.[4] In constant dollars, these amounts actually represent decreases in funding. Despite the funding difficulties, major advances in PTC have come from academia, primarily as a result of the highly dedicated and very high quality work of a few groups around the world. Many, though not all of these outstanding dedicated groups, contributed papers to the Symposium reported in the chapters of this book.

The past decade provided major advances in almost all categories of theoretical and applied PTC. The major areas of PTC progress during this decade are represented well in this book and include better understanding of general PTC mechanisms (Starks, Chapter 2; Makosza, Chapter 4; Landini et al[6]) the critical role of water (landmark work by Liotta et al, Chapter 3; more landmark work by Sasson et al, Chapter 12), solvent effects (Yufit et al, Chapter 5), catalyst structure (Sirovski, Chapter 6; Dehmlow, Chapter 9; Halpern, Chapter 8), solvent-free PTC[7] (Diez-Barra et al, Chapter 14), chiral PTC (landmark work by O'Donnell et al, Chapters 7 and 10; Shioiri, Chapter 11), modification of polymers (wide application by Nishikubo, Chapter 17; Nakamura et al, Chapter 18; Iizawa et al[8]) and carbohydrates (vast application by Roy et al, Chapter 13), polymerization,[9,17] triphase catalysis (Ohtani et al, Chapter 19; Dutta et al, Chapter 20; Doriswamy et al[10], Svec et al[11]), kinetic characterizations[12], inverse phase-transfer catalysis,[13] new catalysts (among them Balakrishnan et al, Chapter 21; Ouchi et al, Chapter 22; plus too many others to cite here) and many synthetic improvements (such as Takido et al, Chapter 15; Jiang et al, Chapter 16). Almost all of these advances were initiated in academia and soon after found application in industry as witnessed in the growing patent literature (see below). Other notable advances originating in academia include the integration of PTC with supercritical CO_2[14] and transition metal co-catalysis[15] to name just two. It is surprising to this author that there are no known commercial applications of transition metal co-catalyzed PTC. It may be anticipated that during the next decade both transition metal co-catalyzed PTC as well as supercritical fluid PTC will be commercialized.

Industrial R&D groups have been exploiting PTC's virtues to enhance productivity, quality, safety and environmental performance. During the past decade, General Electric continued to pioneer the discovery and use of thermally stable guanidinium salts as phase-transfer catalysts[16] and apply PTC to greatly reduce phosgene usage in the manufacture of polycarbonates.[17] A new area of "fluorous media" was innovated, in which a catalyst mediates between a perfluoroalkane (which is immiscible with hydrocarbons) a hydrocarbon and a gaseous phase.[18] Other impressive patents include multi-Michael additions,[19] dehydrohalogenation with efficient catalyst recycle,[20] high temperature fluoride displacement[21] and nucleophilic aromatic substitution.[22] Ton quantities of crown ethers are being used in commercial industrial PTC processes, which was nearly unthinkable ten years ago. Other recent industrial PTC innovations are reviewed in reference 5.

Almost all of the mechanistic and significant synthetic *breakthroughs* in PTC originate from groups focused on PTC (with significant PTC publications and patents). However, it is interesting to note that, as in the past, a great percentage of the PTC publications and patents which describe *applications*, continue to originate from groups which produce only 1-3 PTC publications or patents. As opposed to other topics in chemistry, PTC has such wide applicability that many researchers who focus on non-PTC areas follow the PTC literature and apply PTC when the need arises. Indeed, one of the reasons for the popularity of PTC is that it is applicable to such a wide variety of organic chemical reactions. With increased time management constraints and dwindling libraries, chemists have to be selective in which technologies they choose to follow. PTC offers too much advantage for too wide a scope of reactions to be ignored. Thirty years of growth suggest that PTC is not a fad...PTC offers real benefits which stand the test of time.

Although statistics can be manipulated and are often misleading, following are some statistics relating to the development of PTC literature and patents.[23] By August 1996, abstracted PTC publications numbered 8000 and PTC patents numbered 1500. The most popular phase-transfer catalyst cited by authors and inventors was tetrabutyl ammonium bromide, "TBAB," which was cited in 3257 publications and 846 patents.

The number of PTC publications and patents issued per year has been growing steadily. Some measures indicate that the rate of growth of PTC publications/patent remains high and other measures suggest a slight decrease in the *rate* of growth, though year to year growth is still clearly observed. For example, the five year average of TBAB patents issued per year in 1985 was 38, in 1990 it was 46 and in 1995 it was 57. The five year averages of overall PTC publications (including patents) and PTC patents (separately) issued per year were, respectively, 389 and 70 in 1985, 467 and 90 in 1990 and 484 and 100 in 1995. It appears that in the late 1980's and the early 1990's, growth in PTC patents outpaced growth in PTC publications (excluding patents), though the overall rate of growth may have slowed slightly. It should be emphasized again that the absolute number of *new* PTC publications and patents continues to grow year to year.

Another interesting observation results from examining the country of origin of PTC publications. A random examination of 157 PTC publications in 1989 showed that 18% each originated from Japan and the former Soviet Union, 11% each from China and France, 8% from the US, 7% from Germany and 5% from India. A random examination of 182 PTC publications in 1996 showed 23% originating in China, 13% from the former Soviet Union, 12% from Japan, 11% from the US, 9% from India, 5% from Germany and 4% from France. The absolute number of PTC publications has been rather steady from Poland, Italy, the UK, Israel, Spain, Canada, Hungary, Romania and Korea. Despite the smaller quantities, the quality of the publications from the latter countries is quite high and some represent the new landmarks in PTC progress. Countries represented in the PTC literature in the 1996 sample which did not appear in the 1989 sample included Vietnam, Switzerland, Morocco, Pakistan, Iraq, Turkey, Bulgaria, Egypt and New Zealand.

It is usually easy to set up and analyze PTC reactions, though they can be difficult to optimize. Good quality academic PTC research can be performed on a relatively low budget (mostly for flasks and chemicals, assuming graduate students are "free"), as long as a GC or HPLC (and preferably but not necessarily an NMR instrument) is available. Industrial PTC R&D requires time allocation as do other industrial projects, plus time for special scale up issues such as heat transfer and agitation for the multiphase PTC systems and catalyst separation/recycle unit operations. As we all know, the ease at which research can be performed often has an impact on how much of it is chosen to be performed. The data here suggest that PTC seems to be gaining popularity in all regions (with constrained or less constrained resources). Again, the driving forces for PTC and the resulting achievable benefits are fundamental to performing chemistry and are often obvious to academic and industrial researchers alike, regardless of country of origin.

In summary, phase-transfer catalysis has progressed very well during the past decade, with patents and publications achieving nearly three times the cumulative level of the previous two decades. As the following chapters in this book suggest, even though tremendous progress has been made in elucidating the fundamentals of PTC mechanism and applying them for commercial gain, much progress needs yet to be made. Scarce academic resources pose a threat to this advancement in PTC as well as to science in general. In parallel, dwindling industrial R&D groups are narrowly missing great opportunity to generate self-sustaining profit by failing to evaluate, let alone implement, PTC in manufacturing processes. Many corporations have realized great profit from implementing PTC, whereas other corporations are missing great profit opportunities by PTC retrofit (potential short term gratification for profit & loss executives) and don't even know it! The opportunities to benefit from PTC in both academia and industry are great. The rewards will be reaped by those individuals, companies and even countries (China, Russia, India and Japan are leading the growth in 1996) who take the initiative to pursue the PTC opportunities, have the PTC expertise and awareness of benefits and who allocate the resources to execute the PTC programs.

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