

Professor Mieczysław Mąkosza

A Tribute



Mieczysław Mąkosza, born November 16, 1934 became famous through his pioneering investigations of Phase Transfer Catalysis (PTC) and, subsequently, thanks to his studies of aromatic nucleophilic substitution, in particular Vicarious Nucleophilic Substitution (VNS).

Professor Mąkosza studied chemistry at the University of Rostow and then Leningrad (now: St. Petersburg). After graduating with distinction in 1956, he joined the staff of the Department of Chemistry of the Warsaw University of Technology (Politechnika Warszawska). In 1963 he was granted a PhD degree and in 1967 he received a DSc degree. In 1971 he spent a sabbatical leave working with Prof. G.A. Russel in Iowa State University (USA). From 1975-1977 he was the Director of the Institute of Organic Chemistry and Technology of the Warsaw University of Technology. In 1979 he was appointed the Director of the Institute of Organic Chemistry of the Polish Academy of Sciences (PAN).

After a few years of research on nitration of alkanes and chemistry of arylboronic acids, he became involved in a project directed towards industrial synthesis of 2-phenylbutyric acids. On the basis of a short note in the literature he worked out a process of alkylation of phenylacetonitrile with ethyl chloride in the presence of aqueous sodium hydroxide and triethylbenzylammonium chloride as catalyst. The successful solution of this problem, patented

in 1960, and published in *Roczniki Chemii* (presently *Polish J. Chem.*) **1965**, *39*, 1223 and expanded by other reactions which were published also in internationally recognized journals such as *Tetrahedron Lett.* **1966**, 4621; **1969**, 677 and *Tetrahedron* **1968**, *24*, 175 can be regarded as the beginning of studies of Phase Transfer Catalysis (PTC).

At the beginning of this research Mąkosza focused his attention on the vast practical applications of the two-phase system of the carrying out of organic reactions. He found that many important reactions of carbanions generated from C-H acids such as arylacetonitriles, ketones, halomethylsulfones and alkyl arylacetates, can be carried out in a very simple and efficient way by means of phase transfer catalysis. In 1969 he reported that by treatment of chloroform with aqueous sodium hydroxide, in the presence of a catalytic amount of tetraalkylammonium salt, dichlorocarbene could be generated efficiently; *Tetrahedron Lett.* 4659 (1969). Its reaction with alkenes gave dichlorocyclopropanes (the Mąkosza reaction). This was an important discovery because it was earlier believed that formation of carbenes requires strictly anhydrous conditions and, therefore, had limited practical application.

Continuing his research into phase transfer catalysis, Mąkosza pointed out that crown ethers could also serve as catalysts; *Angew. Chem., Int. Ed.* **1974**, *13*, 665.

In 1978 an armory of PTC was extended by him to solid-liquid systems containing anhydrous alkali metals carbonates. As a result of this important discovery it became possible to apply the method of phase transfer catalysis to reactions of carbanions of such compounds as alkyl malonates, cyanoacetates and acetylacetates which could not withstand the hydrolytic action of alkali hydroxides. The great practical advantage of this new and unconventional method lies in its simplicity; the expensive equipment, dangerous and costly solvents and reagents are eliminated from the process ensuring at the same time higher yields, better selectivity, and safety in comparison with traditional methods.

PTC is of limited effectiveness, however, in reactions of hydrophilic anions, e.g. hydroxy or fluoride anion, which may induce β -elimination or fluorination of halides. These problems are eliminated when co-catalytic procedures are used. For instance, fluorination of alkyl halides and sulfonates with potassium fluoride is efficiently catalyzed by a combination of tetraalkylammonium salts and triphenyltin fluoride.

The first mechanistic concepts concerning phase transfer catalysis were published by him in 1969. In 1973, at a conference at Cape Cod (USA) he formulated the mechanistic concept according to which the first step of the reactions of carbanions – deprotonation of C-H acids – took place on the boundary between two phases. The ion exchange with the catalyst and formation of the lipophilic ion-pairs occurs with such adsorbed carbanions in the interfacial region. Research carried out by Prof. Mąkosza and later on in other laboratories all over the world confirmed the concept that is now universally accepted.

More than twenty years ago, Prof. Mąkosza directed his attention to nucleophilic aromatic substitution; in this area of research his achievements have been equally spectacular. On the basis of a few early observations, he formulated a hypothesis that addition of nucleophiles to halonitroarenes proceeds faster at the position occupied by hydrogen than at that occupied by the

halogen. The σ^H adducts produced in the former process cannot form products by departure of hydride anion whereas the σ^X adducts produced in the latter process readily lose halogen anion to give products of S_NAr . This concept led him to the discovery of new reactions of fundamental practical importance and wide applications. The most important and general is a new reaction named by him Vicarious Nucleophilic Substitution of Hydrogen (VNS) which proceeds between electron-deficient arenes, particularly nitroarenes and nucleophilic agents containing a leaving group at the nucleophilic center. The most representative examples of such nucleophiles constitute α -halocarbanions produced by deprotonation of α -haloalkylsulfones, halonitriles, esters of α -haloacids, haloforms etc. The σ^H adducts of such α -halocarbanions to nitroarenes undergo a rapid base induced β -elimination to give corresponding *ortho* or *para* nitrobenzyl carbanions which, upon protonation, form products of VNS. The VNS reaction is of general character with respect to the carbanions which may contain any leaving group able to be eliminated and to the electrophilic arenes such as substituted nitrobenzenes, nitronaphthalenes and electrophilic heterocycles. It was shown that VNS reactions also proceed with such nucleophiles as alkyl hydroperoxides to convert nitroarenes into nitrophenols and also with a few hydrazine and hydroxylamine derivatives to afford direct amination of nitroarenes.

Prof. Małosza clarified specific features of the VNS reaction such as orientation, scope and limitation, and fine details of the mechanism and in so doing he demonstrated how to control the direction of the substitution.

Taking into account the stoichiometry of the reaction and its outcome, VNS can be considered as a process analogous to the Friedel Crafts reaction proceeding with a reversed polarity. Great practical value of VNS processes has been demonstrated by new syntheses of indoles, quinolines and other heterocycles and also by the use of this process in the synthesis of natural products.

Prof. Małosza has shown that as an alternative to VNS, the σ^H adducts of nucleophiles to nitroarenes can be converted into products of nucleophilic substitution of hydrogen *via* oxidation which removes hydride anion. Such process could be effectively performed by the use of potassium permanganate in liquid ammonia. He has shown also that a new process of oxidation of σ^H adducts of nitroarenes with dimethyloxirane is of particular interest since it directly converts the σ^H adducts into substituted phenols. So, in one operation the replacement of hydrogen (by the carbanion moiety) and the nitro group (by hydroxyl) takes place.

Apart from practical advantages of Małosza's achievements in the field of nucleophilic aromatic substitution, their importance for our knowledge, also in the field of the mechanism of organic reactions, should be emphasized. The crowning achievement of these investigations was a generalization, formulated by him, which changed the hitherto existing views on the nucleophilic aromatic substitution and coherently explained the known empirical facts. According to the generalization formulated by Małosza, the nucleophilic aromatic substitution is a complementary reaction to electrophilic substitution and is governed by similar rules. So far, in many textbooks and numerous monographs an opposite view has prevailed. Examination of

present original literature reveals, however, a growing appreciation of his interpretation of the experimental facts and the application of his new methodologies.

The importance of Mąkosza achievements for applied chemistry should be underlined. Both, PTC and nucleophile aromatic substitution found their broad application in production of a variety of organic compounds on an industrial scale.

Prof. Mieczysław Mąkosza has been given many awards, at home and abroad as listed abroad:

- Kostanecki Medal of the Polish Chemical Society in 1979
- Jurzykowski Foundation Award in 1987
- The State Award – 1st degree in 1988
- Prize of Prime Minister of Poland in 1995
- Maria Skłodowska-Curie & Wilhelm Klemm Honorary Lectureship of German and Polish Chemical Societies in 1995
- Maria Skłodowska-Curie & Pierre Curie Honorary Lectureship of French and Polish Chemical Societies in 1996
- Alexander von Humboldt Research Award in 1996
- Śniadecki Medal of the Polish Chemical Society in 1997
- Honorary Fellow of the Florida Center for Heterocyclic Compounds in 1997
- The Doctor Honoris Causa from Indiana University, Purdue University at Indianapolis (USA) in 1989, from the Russian Academy of Sciences in 1994, from Silesian Technical University, Gliwice (Poland) in 1998, from Ural State Technical University, Ekaterinburg (Russia) in 2001, and from Rostov State University, Rostov (Russia) in 2001.

He is a member of the Polish Academy of Science, the Polish Academy of Arts and Sciences, the Academia Europea and Deutsche Akademie der Naturforscher Leopoldina.

He has been a member of international advisory boards of many scientific journals of high standing such as Tetrahedron, Tetrahedron Letters, Synlett, Journal of Physical Organic Chemistry, Mendeleev Communications, Organic Preparations and Procedure International, Polish Journal of Chemistry.

He is a respected scientist with a long and impressive list of publications to his name. He is the author of over 325 original scientific publications, more than 50 review articles and 70 patents.

He is often invited to give lectures at prestigious international scientific conferences. He was a visiting professor at the universities: in Spain (Barcelona), France (University Paris-Sud) and USA (the Indiana University, Purdue University at Indianapolis) and honorary professor of St. Petersburg University.

Marek Chmielewski
Janusz Jurczak