

Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts

Editor

PROFESSOR TSUTOMU ISHIKAWA

Graduate School of Pharmaceutical Sciences, Chiba University, Japan



A John Wiley and Sons, Ltd, Publication

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To the late Professor Hisashi Ishii and Kimiko

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Preface

Science has developed progressively from the late nineteenth century to the twentieth century and, without stopping, has continuously been evolving through the twenty first century to explore new technologies in various fields. These new technologies give us their benefits with the result that our standard of living is improving. However, negative aspects behind their application to economic development, such as public pollution and global warming etc., have accompanied them and lead to the destruction of the natural environment in some cases. Reconstruction of environmental conditions at a global level is the biggest problem to be solved by us and, therefore, as scientists we should always keep in mind the mission for the next generation.

There are without exception the same pressures on the field of chemistry. Synthetic organic chemistry especially has grown quickly through the design of new intelligent reagents and the discovery of innovative and widely applicable reaction methods. Now, total synthesis of target compounds with an even more complex structure can be formally achieved by the skilful combination of conventional and new methods; there is strong competition between research groups throughout the world to do this.

In spite of the large contribution of chemistry to the improvement in our standard of living, the negative and dangerous image of chemistry has been spread in human society because of destructive damage, such as big explosions in chemical factories in some cases. Therefore, chemistry should progress with the creation of a comfortable world in harmony with nature.

High efficiency based on environmentally benign concepts is strongly required of synthetic organic chemistry in twenty first century. The efficiency involves not only a short reaction process and higher yield in each step, but also lower energy costs and reaction with less waste (high atom economy), and of course from the economical aspect the selection of cheap and easily available materials for the reaction sequence. An important mission of organic chemistry in twenty first century is the establishment of new sustainable chemistry and, in order to achieve the mission, the efficient and repeated use of limited resources is essential. Thus, various types of new recyclable catalysts with high potency have been extensively explored. Organosuperbases are one compound group of promising catalysts in organic chemistry because of their easy molecular modification, possible recyclability, and non or lower toxicity.

Recently, nitrogen-containing organobases, such as guanidines and amidines, have been attracting much attention in organic synthesis due to their potential functionality. It is known that nitrogen–phosphorus hybrid organobases such as phosphazenes show stronger basicity than the nitrogen bases. This book will review the multi-functional ability of these organosuperbases and related molecules in organic synthesis and will discuss their possible

perspective as intelligent molecules. I am very happy if this book is able to give a hint in research activity to organic chemists who are interested in organobase catalysts.

I am responsible for this book as editor. Thus, please do not to hesitate to contact me benti@p.chiba-u.ac.jp with any questions.

Tsutomu Ishikawa
Chiba Japan, June 2008

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This book was completed not only by through the hard work of my team mates, Drs Davor Margetic, Yoshinori Kondo, Hiyoshizo Kotsuki, Kazuo Nagasawa, Takuya Kumamoto and Waka Nakanishi, but also by editorial support from John Wiley, especially Richard Davies. Paul Deards gave me the chance to write this book. I express my sincere appreciation of their cooperation and I am proud to work together with them. My family and laboratory members of the Graduate School of Pharmaceutical Sciences, Chiba University, should be thanked also for their encouragement during the writing.

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1

General Aspects of Organosuperbases

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In the field of organic chemistry, a base is generally defined as a reagent capable of abstracting proton to yield a carbanion species. At a basic textbook level, organobases are normally limited to amines, which are categorized as very weak bases according to the above definition. The introduction of an imine function ($=\text{NH}$) to the α -carbon of amines affords more basic amine species, amidines, which correspond structurally to amine equivalents of carboxylic esters (carboxylic acid imidates). Guanidines, which carry three nitrogen functions (one amine and two imines) and correspond to amine equivalents of ortho esters (carbonimidic diamides), show the strongest Brønsted basicity among these amine derivatives [1]. Thus, basicity is proportional to the number of the substituted nitrogen functions at the same carbon atom; representative examples are shown in Figure 1.1. The basicity of guanidine is comparable to the hydroxyl ion (OH^-) [2]. Basic amino acids, lysine and arginine, have amino and guanidine groups, respectively, at the side chains as additional functional groups and can act as base catalysts responsible for important biological actions, such as enzymatic reactions in living organisms, through hydrogen bonding networks caused by these basic characters [3]. On the other hand, histidine belongs to an acidic amino acid in spite of carrying an imidazole ring involving an amidine function as a partial structure [4].

The basicity of these amine derivatives is due to the construction of highly effective conjugation system after protonation under reversible conditions; primitively, it is a reflection of the number of canonical forms, especially isoelectronic forms, in the resonance system (Figure 1.2). This is one of the reasons why guanidines are stronger bases than amidines [5].

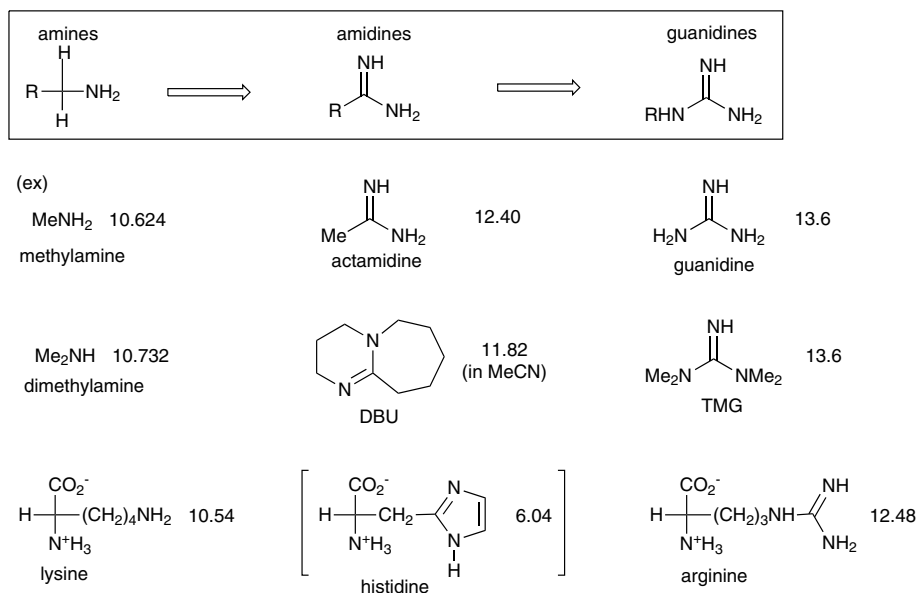


Figure 1.1 Structures of amine derivatives and their representative examples (pK_a of the conjugated acids in H_2O): DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene; TMG = 1,1,3,3-tetramethylguanidine

Thus, a pentacyclic amidine (vinamidine) [6] and biguanide [7] with a vinylogous conjugation system show very strong basicity [8], as expected by the above account (Figure 1.3).

An alternative stabilization effect on the protonation to these two bases leading to their highly potential basicity is through bidentate-type hydrogen bond formation as shown in Figure 1.4. Alder also discussed the effects of molecular strain on the Brønsted basicity of amines [9].

In 1985, Schwesinger [10] introduced phosphazenes (triaminoiminophosphorane skeletons), which contain a phosphorus atom [P(V)] bonded to four nitrogen functions of three amine and one imine substituents, as organobases containing a phosphorus atom. They are classified as P_n bases, based on the number (n) of phosphorus atoms in the molecule [11].

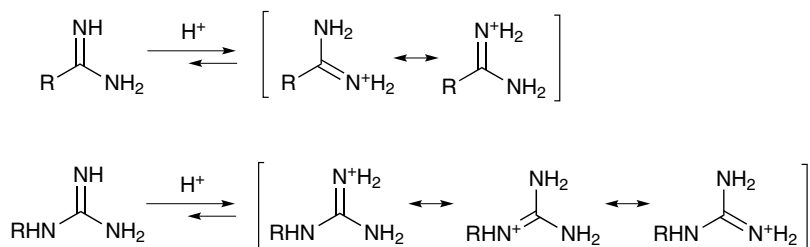


Figure 1.2 Conjugation of amidinium and guanidinium ions

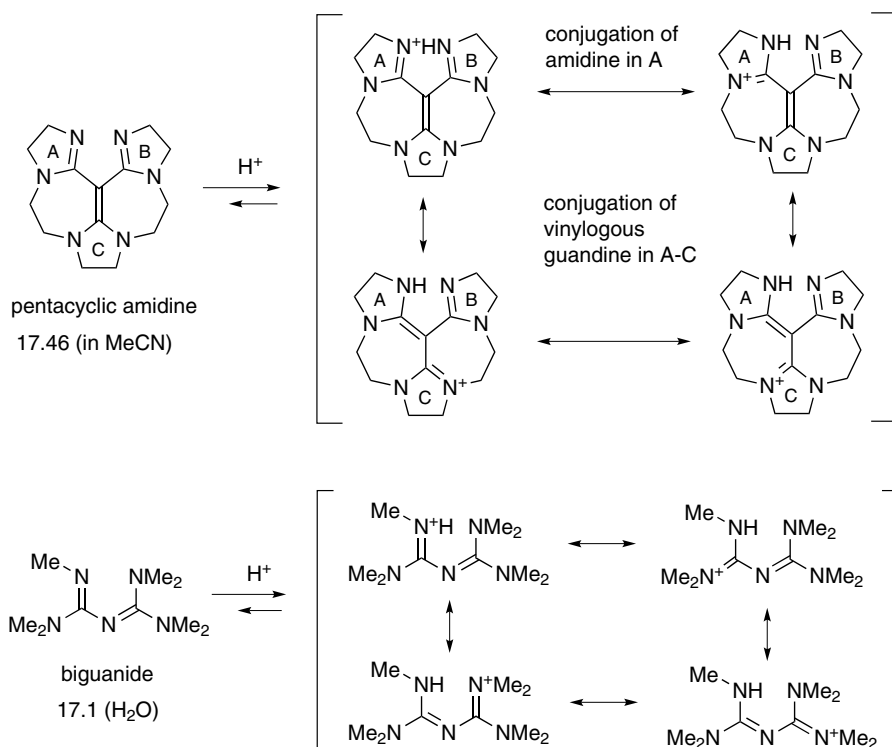


Figure 1.3 Amidine and guanidine derivatives with a vinylogous conjugation system

The examples of simple P1 and P4 bases are shown in Figure 1.5. Their basicity is basically reflected by the number of the triaminoiminophosphorane units and, thus, P4 bases, the strongest phosphazene bases, show basicity comparable to organolithium compounds. Schwesinger *et al.* [12] reported that the strong basicity of phosphazene bases could be caused by the efficient distribution of positive charge through conjugation system in the molecules. However, crystallographic analysis indicates a tetrahedral-like structure around the phosphorus atom in solid state. Phosphazene bases are easily soluble in common organic solvents and stable to not only hydrolysis but also attack by electrophiles owing to their steric bulk [13].

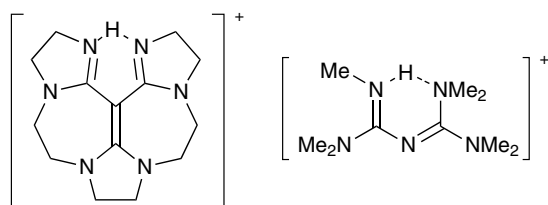


Figure 1.4 Stabilization effect through hydrogen bonding

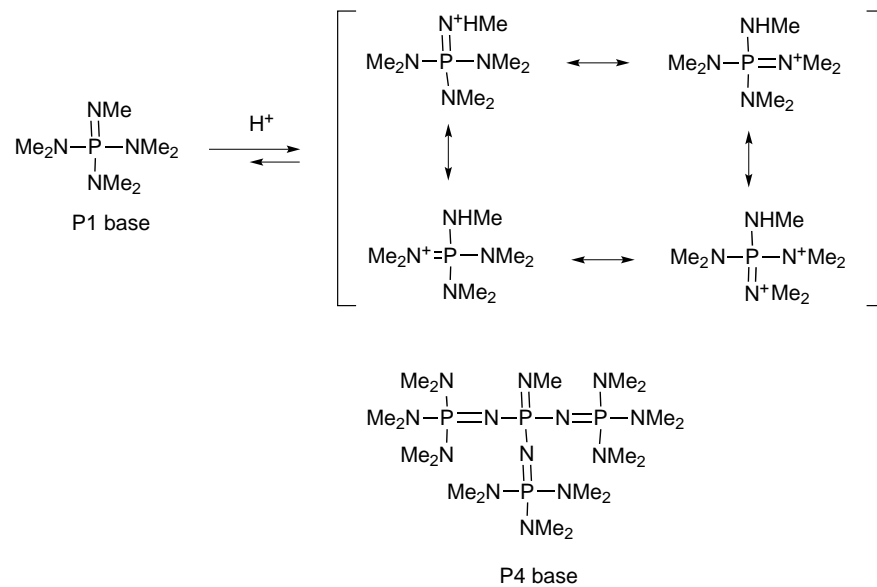


Figure 1.5 Examples of P1 and P4 phosphazene bases

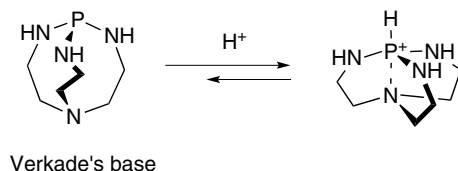


Figure 1.6 Typical structure of Verkade's base and its basicity due to *trans*-annular P–N formation

Verkade [14] discovered proazaphosphatranes (cycloazaphosphines) as alternative phosphorus-containing organobases, in which a P(III) atom bonded to three amino groups is located at the bridge head. The basicity of Verkade's bases is comparable to those of P2-type phosphazene bases. The corresponding phosphonium salts formed by protonation on the phosphorus atom are stabilized through effective *trans*-annular N–P bond formation, to which the fourth nitrogen atom located at the alternative bridge head position participates; this result in propellane-type compounds with tricyclo[3.3.3]dodecane skeletons, as shown in Figure 1.6.

In 1968, Alder [15] reported the preparation of 1,8-bis(dimethylamino)naphthalene (DMAN) by *N*-methylation of 1,8-diaminonaphthalene. DMAN shows exceptional proton affinity through bidentate-type coordination by the two dimethylamino groups located at *peri* position of the naphthalene skeleton, in spite of being categorized as a weakly basic aromatic amine (Figure 1.7). Thus, DMAN is called a 'proton sponge'.

1,8-Bis(tetramethylguanidino)naphthalene (TMGN) [16] and guanidinophosphazenes [17], such as tris[bis(dimethylamino)methylene]amino-*N*-*tert*-butylaminophosphorane [(tmg)₃N^{*t*}Bu], are designed as hybrid organobases by the introduction of the guanidine function into the proton sponge and phosphazene skeletons, respectively (Figure 1.8).

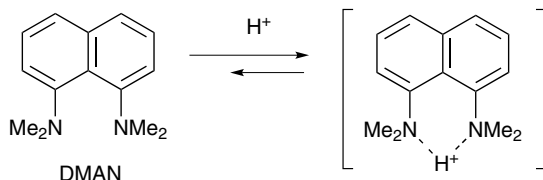


Figure 1.7 Bidentate-type chelation of DMAN

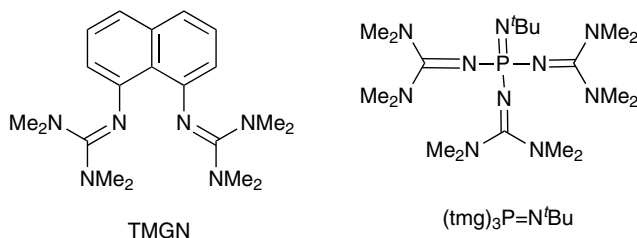
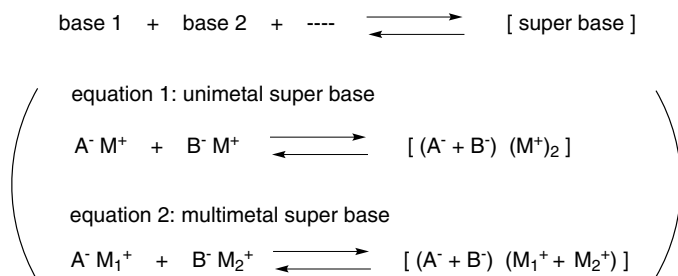


Figure 1.8 Examples of hybrid organobases



Scheme 1.1 Schematic equation for the definition of superbases proposed by Caubère

Computational calculation of their proton affinities indicates that these new generations are, as expected, stronger than the original ones [12,18].

Organic chemists often use the words ‘strong’ or ‘super’ as the intensive expression of basic property; however, the criteria are ambiguous and dependent upon the chemists who use the expression. Therefore, the expression such as ‘strong’ or ‘super’ is ambiguous and causes confusion among organic chemists. Caubère has proposed the definition of superbases as follows in his excellent review [19]: *The term ‘superbases’ should only be applied to bases resulting from a mixing of two (or more) bases leading to new basic species possessing inherent new properties. The term ‘superbase’ does not mean a base is thermodynamically and/or kinetically stronger than another, instead it means that a basic reagent is created by combining the characteristics of several different bases.* The general equation for the definition of a ‘superbase’ is illustrated in Scheme 1.1, in which the examples of ‘unimetal superbase’ introduced by Caubère and a ‘multimetal superbase’ by Schlosser [20] are given. Thus, the term superbases in general applies to ionic metal-containing bases acting under irreversible proton abstraction.

One of important and beneficial characteristics of an organic base, especially from the view point of environmental aspects, is the ability of recycling use in repeated reaction, in which reversible proton transfer occurs between the base and a substrate, an acidic counterpart. Thus, powerful organic bases that may be applicable in various organic syntheses as base catalysts have attracted much attention. According to Caubère’s definition, organic superbases should be a mixture of two or more different kinds of amine species and show a new property. In this book nonionic powerful amine derivatives of amidines, guanidines, phosphazenes and Verkade’s bases with comparable or higher basicity to that of DMAN are *arbitrarily* classified as organic superbases and discussed on their chemistry due to basic characteristics, mainly focusing on their applications to organic synthesis as potentially recyclable base catalysts. Related intelligent molecules are also discussed.

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2

Physico-Chemical Properties of Organosuperbases

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2.1 Introduction

From the physical-organic point of view, the most interesting physico-chemical property of neutral organosuperbases is their exceptional basicity associated with high kinetic activity in proton exchange reactions. Because of their high basicity and relatively weak nucleophilicity, these nonionic compounds have found wide application as catalysts for organic reactions. By definition [1] the superbases are stronger bases than a 'proton sponge' [1,8-bis(dimethylamino)naphthalene: DMAN], that is, they have an absolute proton affinity (APA) larger than $245.3 \text{ kcal mol}^{-1}$ and a gas phase basicity (GB) over $239 \text{ kcal mol}^{-1}$.

The basicity of organic molecules can be measured by various physical methods, in gas phase or condensed media experiments, or calculated by quantum chemical methods. Several solvents, including dimethyl sulfoxide (DMSO), acetonitrile (MeCN), and tetrahydrofuran (THF), have found wide application as media for studies of strong bases. Acetonitrile has been the most popular solvent and a vast number of basicity measurements in acetonitrile have been carried out. Nevertheless, various reference bases have been used for gas phase measurements. Hence, a variety of results obtained by different authors and by different methods has been collected in this review. Material collected in tables has been arranged in descending order of basicity. A number of other organobases approaching a superbasicity threshold have been also measured; however, due to limitations in space here, these molecules have been omitted. This review is divided according to the chemical classes

of bases, and starts with the proton sponges, then gradually moves to stronger groups. In addition, superbases predicted by calculation have been included, with a separate section on quantum chemical methods used for basicity estimation and the study of superbases.

2.2 Proton Sponges

2.2.1 'Classical' Proton Sponges

Proton sponges (PS) are organic diamines with unusually high basicity. The exceptional basicity of the very first proton sponge, DMAN (**1**) was reported by Alder in 1968 [2]. This compound has a basicity about 10 million times higher ($pK_a = 12.1$ in water) than other similar organic amines (its experimentally measured proton affinity (PA) in the gas phase is 246.2 [3], while the calculated value [4] is 246.5 and 258.7 kcal mol⁻¹, using 6-31G*//6-31G + ZPE and 6-31G methods). Proton sponges and their complexes have attracted considerable interest from chemists, giving rise to over 70 structural and 100 spectroscopic papers (Table 2.1) [5]. The name proton sponge is given because of the high thermodynamic basicity combined with a kinetic inactivity to deprotonation that resembles the affinity of a sponge for water.

The general feature of all proton sponges is the presence of two basic nitrogen centres in the molecule, which have an orientation that allows the uptake of one proton to yield a stabilized intramolecular hydrogen bond (IMHB). A dramatic increase in basicity of aromatic proton sponge can be achieved on account of: destabilization of the base as a consequence of strong repulsion of unshared electron pairs; formation of an IMHB in the protonated form; and relief from steric strain upon protonation [6]. Two general concepts to raise the thermodynamic basicity or PA are established. One is to replace the naphthalene skeleton by other aromatic spacers, thus influencing the basicity by varying the nonbonding N...N distances of the proton-acceptor pairs. The other concept focuses on the variation of basic nitrogen centres or its adjacent environment ('buttressing effect').

The trend that proton sponges with high thermodynamic basicity typically have a low kinetic basicity (kinetic activity in proton exchange reactions) is a serious limitation of proton sponges: the captured proton does not usually take part in rapid proton exchange reactions, which would allow such neutral superbases to serve as catalysts in base-catalysed reactions. Their further limitations are moderate solubility in aprotic nonpolar solvents and stability towards auto-oxidation.

From a physical organic point of view, there is continuing debate about whether the enhanced basicity in proton sponges is due mainly to strain relief on protonation, or to the special properties of the hydrogen bonds in their monoprotinated ions.

Experimental and theoretical studies have shed light on the structural factors that influence the high basicity of proton sponges. Their abnormally high basicity is accepted to be produced by various contributions: the effective PA for one of the amine groups (assuming asymmetric protonation at one nitrogen); the relief of strain (possibly also accompanied by an increase in aromatic stability) caused by loss of destabilizing lone pair-lone pair repulsion on protonation; the formation of a hydrogen bond which stabilizes the protonated species; the difference in solvation energies of the base and protonated cation in solution.