Comments on the Terminology for Applications of Temporarily Attached Solubility-Modifying Moieties in Combinatorial Chemistry

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In their excellent article on glycopeptide and oligosaccharide libraries published recently in this journal, St. Hilaire and Meldal carefully explain the distinction they feel is necessary between combinatorial libraries and sets of compounds prepared in parallel by methods not leading to exponentially growing numbers of chemical entities in each synthetic cycle.[1] However, their understanding of the term "combinatorial" in this respect is much stricter than the IUPAC recommendations and therefore might not be generally acceptable.[2]

Nevertheless, the constant struggle for precision in scientific terminology is highly desirable and the article by St. Hilaire and Meldal can be regarded as an invitation to start a discussion on terms used in the dynamic field of library synthesis that should be reconsidered.

High-throughput chemical transformation strategies used in combinatorial approaches require that products can be easily isolated from reaction mixtures without needing to resort to time-consuming work-up operations. Strategies that make use of solid supports and other temporarily attached solubility-modifying moieties have gained considerable impact in the generation of molecular libraries.[3]

The range of solid supports currently available is already very broad and it is still growing fast. Virtually all kinds of material originating from man-made or naturally occurring resources, such as organic or inorganic polymers, as well as nonpolymeric material, have been suggested as supports in solid-phase organic synthesis (SPOS).[4]

The most important feature that is shared by these different supports from a synthetic point of view is their ability to modify the solubility of the attached growing product in order to facilitate work-up procedures. A simple phase-separation step, such as the collection of solid material by filtration, is usually envisioned to separate support-bound molecules from excess reagents or impurities in solution. During this compulsory phase-separation step the temporarily attached solubility-modifying groups typically lead to the formation of the desired solid phase. The physical state of the support during reactions is of minor importance in SPOS and need not necessarily be a solid phase.[5] On the contrary, much effort has been undertaken to design supports that display functional groups in a "solutionlike" environment to circumvent the inherent difficulties that are connected with syntheses in heterogeneous phases or on-bead screening protocols.[5]

Unlike virtually nonswelling, macroporous, highly cross-linked polystyrene (PS) or inorganic systems, for example, controlled-pore glass supports, swelling is crucial for materials such as cellulose derivatives and the frequently used standard resins, such as polystyrene with 1% cross-linking, for their utility as supports in organic synthesis. Hence, it is generally accepted that reactions occur more or less in a gel-type phase, and not literally on a solid phase. This is true as well for polystyrene beads with polyethylene glycol (PEG) tentacles or second-generation grafted PS-PEG supports with various molecular architecture or the cross-linked PEG copolymers introduced by Renil and Meldal as well as Rademann et al., respectively.[6]

For the reasons given above it is not advisable to concentrate on the proper physical characterization of phases during synthesis. Clearly a focus on the ability of the supports to "phase switch" as suggested by Curran is much more helpful, and the "phase-switching/phase-trafficking" terminology developed by Flynn is comprehensible and practical for this purpose, but may only be appreciated by specialists working in the field.[7]

However, despite its shortcomings the term solid-phase organic synthesis is widely accepted and generally understood by the scientific community. This is not the case for the term liquid-phase organic synthesis (LPOS), which is meant to indicate that a soluble polymer is used as a support that can aid product isolation from liquid reaction mixtures by using membrane technologies, ultrafiltration, or, more commonly applied, by conventional filtration following precipitation. Thus, the name LPOS clearly suffers from a vague description of the underlying concept. In fact, this term neither indicates that solubility-modifying supports such as linear polystyrene, polyethylene glycol, or block copolymers are used nor that a phase separation by filtration is envisioned.

LPOS reactions take place, as most of the reactions in organic synthesis do, in a liquid solution formed by dissolving a solid, namely a polymer, in a solvent. These solutions are, of course, "liquid phases", but this is not a special feature that justifies the preservation of this term.[8] For example, appro-

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priate cheap waxlike solid polyethylene glycol mono methyl ethers can be dissolved in a broad range of solvents, for example, toluene, and reactions on molecules attached to the hydroxyl function can be performed and monitored in solution. After a given synthetic operation, the polymer-bound molecules are precipitated by the addition of diethyl ether to the reaction mixture, and can easily be separated from the residual solution by filtration using standard laboratory equipment. Thus, the use of the soluble polymer supported synthesis rediscovered and pioneered by Janda et al. combines the advantages of synthesis in solution, such as straightforward reaction monitoring, and operative advantages brought about by the ease of phase separation of the solid formed upon precipitation.[8d]

Recently a technique that applies small organic molecules as temporarily attached solubility-modifying groups was reported and entitled "Liquid-phase synthesis with solid-phase workup".[9] Again, reactions take place on a temporarily dissolved solid in solution; a phase switch for work-up is achieved by precipitation upon protonation of a covalently attached heterocycle, a small molecule instead of a soluble polymer, called a "quinoline precipitation device".[9] Consequently, the term synthesis in the "liquid phase" can no longer be regarded as the equivalent term for the commonly accepted and descriptive term "soluble polymer-supported organic synthesis (in solution)", as initially suggested and lately used side by side with the term LPOS by Janda et al.[10] Thus, it seems practical to indicate the use of soluble polymer-supports in organic synthesis as such, that is, by the abbreviation SPSOS instead of LPOS when necessary.

Given that it is not generally accepted that the terms solid-phase synthesis or immobilization should be applied in such a loose way to strategies using small molecule precipitation devices (which can not be called supports), the use of soluble organic polymers and fluorous hydrocarbons as covalently attached solubility modifiers are covered, it might be desirable to establish a general term that may serve as a keyword for the entire heterogeneous arsenal of built-in product-separation strategies. Discussion on this topic seems highly desirable. We propose the keywords "solubility control auxiliary" for all kinds of solubility-modifying devices attached to products or reagents in combinatorial or general organic chemistry as alternatives to the term "phase labeling" suggested by Curran.[7a]

Since it is advisable to eliminate ambiguous terms before they lead to permanent misconceptions that are hard to eradicate the terms liquid-phase organic synthesis or "synthesis in the liquid phase" and the abbreviation LPOS should not be selected anymore to describe synthesis using soluble polymer supports as a solubility control auxiliary.

[1] a) P. M. St. Hilaire, M. Meldal, *Angew. Chem.* **2000**, *112*, 1210 – 1228; *Angew. Chem. Int. Ed.* **2000**, *39*, 1162 – 1179; methods in which the number of the synthesized compounds increases exponentially with the number of the executed series of coupling steps have been dubbed "real combinatorial" procedures: b) A. Furka in *Handbook of Combinatorial & Solid Phase Organic Chemistry*, *Vol. 1* (Eds.: W. Bennet, J. Christensen, L. Hamaker, M. Peterson, M. Rhodes, H. Saneii), Advanced ChemTech, Louisville, **1998**, pp. 7 – 22.

[2] Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998 prepared for publication by C. G. Wermuth, C. R. Ganellin, P. Lindberg, L. A. Mitscher, *Pure Appl. Chem.* **1998**, 70, 1129 – 1143): "A combinatorial library is a set of compounds prepared by combinatorial synthesis." "Combinatorial synthesis is a process to prepare large sets of organic compounds by combining sets of building blocks." (See also (http://www.chem.qmw.ac.uk/iupac/medchem/).)

[3] a) S. H. DeWitt, A. W. Czarnik, *Acc. Chem. Res.* **1996**, *29*, 114 – 122; b) K. Gordon, S. Balasubramanian, *Curr. Opin. Drug Disc. Dev.* **1999**, *2*, 342 – 349; c) J. W. Ellingboe, *Curr. Opin. Drug. Disc. Dev.* **1999**, *2*, 350 – 357; d) C. J. Andres, D. J. Denhart, M. S. Deshpande, K. W. Gillman, *Comb. Chem. High Throughput Screening* **1999**, *2*, 191 – 210; e) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436 – 2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288 – 2337; f) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19 – 46; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17 – 42; g) M. B. Francis, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 987 – 991; *Angew. Chem. Int. Ed.* **1999**, *38*, 937 – 941; h) Th. R. Boussie, C. Coutard, H. Turner, V. Murphy, T. S. Powers, *Angew. Chem.* **1998**, *110*, 3472 – 3475; *Angew. Chem. Int. Ed.* **1998**, *37*, 3272 – 3275.

[4] a) D. E. Bergbreiter, *Med. Res. Rev.* **1999**, *19*, 439 – 450; b) C. Blackburn, *Biopolymers* **1999**, *47*, 311 – 351; c) B. A. Bunin, J. M. Dener, D. A. Livingston in *Annual Reports in Medicinal Chemistry*, *Vol. 34* (Eds.: A. Doherty, G. L. Trainor), ACS, San Diego, **1999**, pp. 267 – 286.

[5] a) P. Hodge, *Chem. Soc. Rev.* **1997**, *26*, 417 – 424; therefore the term SPOS is ambiguous to some extent: in an article by b) G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.* **1998**, *4*, 2467 – 2474, the selected keyword solid-phase synthesis was chosen to describe the reaction of solid reagents in the absence of a solvent; c) it might be argued as well that the terms "organic" and "phase" are of historical origin and not free from limitations.

[6] a) W. Rapp in *Combinatorial Peptide and Nonpeptide Libraries: A Handbook* (Ed.: G. Jung), VCH, Weinheim, **1996**, pp. 425 – 464; b) J. Rademann, M. Grotli, M. Meldal, K. Bock, *J. Am. Chem. Soc.* **1999**, *121*, 5459 – 5466; c) M. Renil, M. Meldal, *Tetrahedron Lett.* **1996**, *37*, 6185 – 6188.

[7] a) D. P. Curran, *Angew. Chem.* **1998**, *110*, 1230 – 1255; *Angew. Chem. Int. Ed.* **1998**, *37*, 1175 – 1196; b) D. L. Flynn, *Med. Res. Rev.* **1999**, *19*, 408 – 431.

[8] a) The terms LPOS and LPCS (liquid-phase combinatorial synthesis) were constructed correctly in analogy to the "liquid-phase synthesis of peptides" reported by Mutter and Bayer,[8c] but cannot be regarded as descriptive, academically speaking; b) M. Mutter, H. Hagenmaier, E. Bayer, *Angew. Chem.* **1971**, *83*, 883 – 884; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 811 – 812; c) E. Bayer, M. Mutter, *Nature* **1972**, *237*, 512 – 513; d) H. Han, M. M. Wolfe, S. Brenner, K. D. Janda, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419 – 6423; e) on p. 2468 in [5b] the term liquid phase is used to describe "reaction of the melt" as opposed to the same reaction in solution.

[9] H. Perrier, M. Labelle, *J. Org. Chem.* **1999**, *64*, 2110 – 2113.

[10] a) D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489 – 509; b) P. Wentworth, Jr., K. D. Janda, *Chem. Commun.* **1999**, 1917 – 1924; c) A. D. Wentworth, P. Wentworth, Jr., U. F. Mansoor, K. D. Janda, *Org. Lett.* **2000**, *2*, 477 – 480; d) F. Sieber, P. Wentworth, Jr., J. D. Toker, A. D. Wentworth, W. A. Metz, N. N. Reed, K. D. Janda, *J. Org. Chem.* **1999**, *64*, 5188 – 5192; e) F. Sieber, P. Wentworth, Jr., K. D. Janda, *J. Comb. Chem.* **1999**, *1*, 540 – 546; f) N. N. Reed, K. D. Janda, *Org. Lett.* **2000**, *2*, 1311 – 1313.

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