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Viewpoint

Path toward "Net Zero Organic Synthesis"

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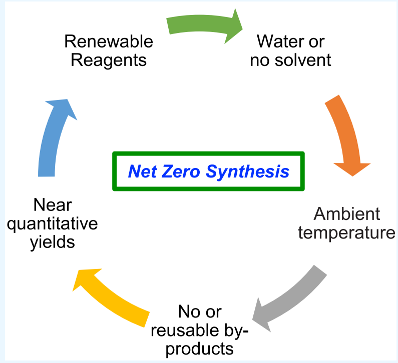
ABSTRACT: Researchers over the past ∼200 years have accomplished the synthesis of simple to very complex molecules; however, the concept of ideal synthesis has still not reached maturity. Of late, the "Net Zero" concept has captured the imagination of many fields of technology, in tune with Ideal Synthesis. The current Viewpoint covers the principles of ideal synthesis being discussed in the literature and how one could take up the synthesis of organic molecules considering the Net Zero concept to make this central science well-accepted by critics of this important field.



INTRODUCTION

$$E = mc^2$$

The most powerful equation drawn by German Physicist Albert Einstein provides the theory of relativity, which expresses the fact that mass and energy are the same physical entity and interchangeable.

The growth engine (GE) for comfortable living on our planet is always driven by the same two parameters: mass (materials) and energy. The materials include agrochemicals (for food security), medicines (for health security), and shelter (protection from the external environment). All of these materials require energy (derived from fossil fuels, biomass, solar, wind, and more recently hydrogen for interconversion of materials to products of reference).

> ***"The earth has enough resources to meet the needs of all but not enough to satisfy the greed of even one person"*** *Mahatma Gandhi.*

The biggest challenge for the GE of the human race, especially since the beginning of the industrial revolution, is the unprecedented pace at which the environment is getting warmed up by greenhouse gases, which are resulting in natural disasters such as melting of ice from the Arctic/Antarctic regions and receding glaciers in the Himalayan region, higher events of typhoons, cyclones, sudden and catastrophic flooding, extreme heat, and cold waves, depletion of the ozone layer, etc. The alarm bells rung by environmentalists raised time and again have to be addressed soon (it may already be too late) before all life forms become extinct from this planet. The awareness created by this community has reached even the most remote parts of the planet.

One of the branches of science which has acted as the work horse of GE undoubtedly is chemistry. The contributions of chemistry in the coatings, pigments, pharma, agrochemical, and construction sectors cannot be downplayed despite the overwhelming criticism that the chemical sciences has faced for Green House gas emissions, solid wastes as a hazard to life, ozone depletion, and pollution in water bodies and soils. Thus, it is imperative for the practitioners of chemistry, more so the synthetic organic chemists, to not only create a positive perception to the critics and law makers but also build and practice the principles which are essential to reduce the burden on the environment. In line with this, the 12 principles of green chemistry[1] have been advocated (introduced by Paul Anastas and John Warner). These 12 principles are interlinked and provide broad guidelines to address the challenges posed by the environment to organic chemistry.

DISCUSSION

The art of Organic Chemistry began with the first synthesis of the most influential molecule, urea, by Wohler,[2] which transformed the productivity of agriculture beyond the world's imagination almost two centuries ago. This revolutionary synthesis opened up new vistas in this branch of science and has been developed as the one of the most well studied and

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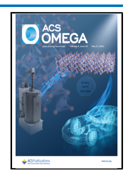

understood fields of science today. "*No matter how complex, any natural product discovered in nature can, in principle, be replicated in laboratory by chemical means given sufficient funding and time*", as stated by K.C. Nicolaou,[3] aptly supports the level of acknowledgment to this subject. The molecules which were conquered by total synthesis,[4] in the 190 year old journey of synthetic organic chemistry, include erythromycin,[5] penicillin,[6] morphine,[7] azithromycin,[8] strychnine,[9] rapamycin,[10] calicheamicin,[11] and halichondrin,[12] and the count is unlimited. This success is fully attributed to various innovators of reactions, named after the individuals who developed them.[13] These include Grignard,[14] Wittig,[15] Diels–Alder,[16] Cannizaro,[17] Claisen,[18] and Woodward[19] in the early 19th/20th century and Grubbs',[20] Sharpless,[21] Suzuki,[22] Corey,[23] etc. of recent origin. These reactions could use mostly stoichiometric quantities of reagents; catalysts have been used in some of these reactions; and very few required neither reagents nor catalysts and are driven by heat/light. These reactions have played a great role in making molecules not only in academic laboratories but also in large factories for commercial purposes, for human wellbeing but not necessarily for planetary wellbeing. New trends to minimize the complexity of natural products while retaining the functionality through "function-oriented synthesis"[24] and "diversity-oriented synthesis"[25] have also been adapted to mimic nature while reducing the load on the environment. All these contributions enabled organic chemistry, the most agile and productive science, to create comfort for *Homo sapiens sapiens*.

The environmentalists' concerns and alerts were addressed to some extent in this marathon journey, as evidenced by the invention of catalytic reactions, reagentless reactions (thermal, photochemical, etc.), and solvent-free reactions (Ball & Mill) and the use of green solvents and multicomponent and domino reactions, etc. Industrial houses have also started raising their bars with new trends of quality by design (QBD), manufacturing 4.0, evaluation of *e*-factor, Process Mass intensity, etc.; **however, affordability and production at lower cost than competitors' have been primary drivers for the industry**. Many creative minds continue to challenge themselves to design better and adaptive processes to address the concerns of the environment. The concept of "Ideal Synthesis" was born out of this. Almost 50 years ago Hendrickson[26] defined "*an "ideal synthesis" as one which would start from available small molecules so functionalized as to allow constructions linking them together directly, in a sequence only of successive construction reaction involving no intermediary refunctionalisations and leading directly to the structure of target not only its skeleton but also its correctly placed functionality*". Wender[27] (1996) further gave a comprehensive definition of "ideal synthesis". "*An ideal (the ultimate practical) synthesis is generally regarded as one in which the target molecule (natural or otherwise) is prepared from readily available, inexpensive starting materials in simple, safe, environmentally acceptable, and resource effective operations that proceed quickly and in quantitative yields*". Two ways to achieve ideality are (i) the use of strategy level reactions such as Diels–Alder or tandem or domino sequences that allow for a great increase in target relevant complexity in one operation and (ii) the design and development of new reactions and sequences that allow for an increase in complexity relevant to the target molecule.

Advancing further, Baran[28] (2010) defined a formula for calculating ideality as the percentage of the sum of construction reactions and strategic redox reactions divided by number of all synthetic steps.

$$\%\,\text{ideality} = \frac{[(\text{No. of construction reactions}) + (\text{No. of strategic redox reactions})] \times 100}{\text{Total number of steps}}$$

Baran then carried out an introspection of his own group's contributions and evaluated 22 of his syntheses on the parameters of ideality (32 to 83% ideal).

This elementary formula certainly provides early indications of how far the steps are from ideal situations. Our self-introspection of a recent synthesis of Nirmatrelvir[29] resulted in ~50% ideality. While any scores above 75% provide a "feel good" factor to the researchers engaged, they will still have many challenges to handle, especially the overall yield (has to be close to 100%); all byproducts and side products should have a mass close to 0%; the catalyst(s)/ reagent(s) need to be fully recovered and reused at least for several cycles; and all solvents used should be green in nature and recoverable to near 100%. In addition, preferably all chemical reactions engaged have to be performed at ambient temperature with minimal energy consumption. While being the most matured branch of all the sciences, organic synthesis is still taking baby steps toward ideality.

In contrast, the global warming alerts are demanding for "Net Zero" emissions (Box 1),[30] which have to be achieved at lightening speed for the planet to be sustainable in reasonable measures. All of the principles and philosophies advocating for greenness have been very qualitative. Most of the reactions discovered so far have not focused on Net Zero synthesis. Thus, it is a thought-provoking consideration whether the most sought after "Net Zero" principles of minimum greenhouse gas emissions, circularity of the resources, energy generation from renewable sources, especially green hydrogen, etc., which have been the focus of all UN member countries, could be implemented by the organic chemistry community with a commitment to reach Net Zero Synthesis. Undoubtedly, it will be a near nightmare for an organic chemist, especially engaged in total synthesis involving multisteps, to achieve "Net Zero" synthesis.

Box 1. Steps to Net Zero Emissions

Net Zero is defined as "A target of completely negating the amount of greenhouse gases produced by human activity can be achieved by reducing emissions and implementing methods of absorbing carbon dioxide from the atmosphere."

Major steps to achieve "Net Zero" in emissions are (a) Carbon neutrality balancing emissions and removal on a global scale; (b) emission reductions and negative emissions (removals); (c) marketing of low-carbon products; (d) carbon finance by industry; and (e) increase in carbon sinks.

It is possible to achieve "Net Zero" in a single-step reaction sequence such as building bicyclocarboxylic acid in a one-step [4 + 2] cycloaddition reaction between furan and ethyl acrylate, without any solvent, as both are liquids, and if the reaction proceeds at room temperature or heating is provided by sunlight or green hydrogen then it could be claimed as a Net Zero reaction. Hydrogenation reactions, such as the Wilkinson[31] and Noyori reduction[32] with complete recycling of catalyst, can be considered here as excellent reactions to reach Net Zero. Unfortunately, the reactions available to

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organic chemists with such efficiency are few. Very few such reactions can be considered as contributors to Net Zero synthesis without the formation of byproducts, such as Claisen rearrangement, *ene* reaction, aldol reaction, etc. (provided solvent used is renewable, no heating is required, and yields are 100% without column chromatographic purifications). Overcoming the challenges to achieve "Net Zero" boundaries in a multistep synthesis with today's available reactions is certainly an impossible task. An achievable approach, as a first step, may be "*near Net Zero*" (NNZ), with defined boundaries and scores set for each parameter. This is an analogy taken from practitioners of medicinal chemistry who have a checklist (Box 2) to move a molecule from hit to lead to lead optimization followed by taking it forward to preclinical studies.

Box 2. Key Indicators in Drug Discovery for "Go No-Go" Decisions[33]

Aqueous solubility, microsomal stability, CYP enzyme inhibitions, hepatotoxicity, cytotoxicity, permeability, etc. are some of the critical criteria followed in drug discovery to develop a HIT into a Lead. Other important points considered include target validation, lead identification and development, safety, and efficacy in humans which include clinical trials and marketing approvals. From a commercial point of view, scalability of the drug is a major concern, as there could be many players and competitors.

To expand the analogy to chemical synthesis, we propose the processes to be "near Net Zero", and all the parameters should be renewable and recyclable and result in zero effluents. For any standard reaction, the processes and materials required include starting materials (minimum 2), reagents, catalyst(s), solvent (low to high boiling), reaction conditions (cold, hot, ambient temperature), and workup, including quenching and extraction followed by chromatographic purification. An ideal synthetic scheme should have the following parameters for consideration as "near Net Zero" synthesis (Box 3).

Box 3. Parameters for Achieving Near Net Zero Synthesis

a. The sum molecular weight of the reactants has to be equal to the molecular weight of the product(s) (exact match the best)
b. % Catalyst loss (zero being the best)
c. % Solvent loss (minimum the better)
d. Water as the medium of reaction with no byproducts/reagents dissolved
e. Reaction at ambient (room) temperature or solar energy for heating
f. No chromatographic purification (preferably product separates from the reaction medium)
g. % Reagent loss (replenishable source and reusable elsewhere regardless of the byproduct formed out of reagent)
h. % Yield (100% being best)
i. No byproducts formed or water is the byproduct

To have a very robust and quantitative matrix to consider any synthesis as "Net Zero", all the parameters need to be included: *viz*., source of raw materials (nonfossil and renewable sources [the fossil fuels are predicted to be exhausted in the near future: oil in ~50 years, natural gas in ~53 years, and coal in ~114 years]), no reagents or reagents from a renewable source without any waste (at least the byproduct needs to be useful elsewhere), yields (near 100%), no chromatography, and only the use of class 3 solvents (avoid classes 1 and 2) and any other parameter can be given a perfect score on a scale of 10 if it is really ideal or given a score worthy of identifying to be reaching near net zero (like the referees decide the journal publication fate) based on the quantitative scores.

Researchers from academia and industry have considered many options to reach the ideal synthesis. The ideal synthesis calculations focus on the yields of the reactions and the formation of the byproducts but do not consider contributions of solvents which are ~56% of the total contributors. Principles of green chemistry, e-factor, recyclable solvents, and process mass intensity are all being considered now when new projects are considered. Thus, all the efforts initiated so far have limitations, and hence, there is a need to identify a formula/matrix that can result in Net Zero or at least Near Net Zero synthesis. This formula has to be as robust and widely applicable as Einstein's mass energy equation incorporating scores, as shown in Box 3. It is desirable that all of the parameters in Box 3 form the basis of determining the best synthetic route, with each parameter as close to the desirable points as possible, to achieve a Net Zero or Near Net Zero Synthesis. The observations "*The future will be either green or not at all*" by Bob Brown and "*We are the first generation to feel the impact of climate change and the last generation that can do something about it*" by Barack Obama summarize the urgency and the need for Near Net Zero if not "Net Zero Synthesis".

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; p 30.
(2) Wohler, F. Ueber künstliche Bildung des Harnstoffs. *Annalen der Physik und Chemie.* **1828**, *88*, 253–256.
(3) Nicolaou, K. C.; Rigol, S.; Yu, R. Total Synthesis Endeavors and their contributions to science and society: A personal account. *CCS Chem.* **2019**, *1*, 3–37.
(4) Nicolaou, K. C.; Montagnon, T. *Molecules that changed the world*; Wiley-VCH, 2008.

(5) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. Total Synthesis of Erythromycin. *J. Am. Chem. Soc.* **1981**, *103*, 3215−3217.

(6) (a) Sheehan, J. C.; Henery-Logan, K. R. The Total Synthesis of Penicillin V. *J. Am. Chem. Soc.* **1957**, *79*, 1262−1263. (b) Sheehan, J. C.; Henery-Loganm, K. R. The Total Synthesis of Penicillin V. *J. Am. Chem. Soc.* **1959**, *81*, 3089−3094.

(7) Gates, M.; Tschudi, G. The Synthesis of Morphine. *J. Am. Chem. Soc.* **1956**, *78*, 1380−1.

(8) Djokic, S.; Kobrehel, G.; Lopotar, N.; Kamenar, B.; Nagl, A.; Mrvos, D. Erythromycin series. Part 13. Synthesis and structure elucidation of 10-dihydro-10-deoxo-11-methyl-11-azaerythromycin A. *J. Chem. Res.* **1988**, *19*, 152−153.

(9) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. O.; Hunger, A.; Daeniker, H. U.; Schenker, K. The Total Synthesis of Strychnine. *J. Am. Chem. Soc.* **1954**, *76*, 4749−4751. (b) Woodward, R. B. The total synthesis of strychnine. *Experientia* **1954**, *76* (Suppl 2), 213−228.

(10) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. Total Synthesis of Rapamycin. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420.

(11) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *Total synthesis of calicheamicin* γ_1. *J. Am. Chem. Soc.* **1992**, *114*, 10082−10084.

(12) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. Total synthesis of halichondrin B and norhalichondrin B. *J. Am. Chem. Soc.* **1992**, *114*, 3162−3164.

(13) *March's advanced Organic chemistry: reactions, mechanisms and structure*, 7th ed.; Smith, M. B., Eds.; Wiley, 2015.

(14) Grignard, V. C. Sur quelques nouvelles combinaisons organométalliques du magnésium et leur application à des synthèses daalcools et d'hydrocarbures. *Compt. Rend. Hebd. Śeances Acad. Sci.* **1900**, *130*, 1322−24.

(15) Wittig, G.; Schöllkopf, U. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien I. *Chem. Ber.* **1954**, *87*, 1318.

(16) (a) Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe, I. *Justus Lieb. Ann. Chem.* **1928**, *460*, 98−122. Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe, II. *Ber. Deutschen Chem. Gesellschaft* **1929**, *62*, 554−562.

(17) Cannizzaro, S. Ueber den der Benzoësäure entsprechenden Alkohol. *Lieb. Ann. Chem. Pharmacie.* **1853**, *88*, 129−130. [On the alcohol corresponding to benzoic acid].

(18) Claisen, L.; Claparede, A. Condensationen von Ketonen mit Aldehyden. *Ber. Deutsch. Chem. Gesellschaft* **1881**, *14*, 2460−2468.

(19) Woodward, R. B. Biographical NobelPrize.org. Nobel prize Outreach AB, 2024.

(20) (a) Grubbs, R. H. *Handbook of Metathesis*, 1st ed.; Wiley-VCH: Weinheim, 2003. (b) Grubbs, R. H.; Trnka, T. M. Ruthenium-Catalyzed Olefin Metathesis; *Ruthenium in Organic Synthesis*; Murahashi, S., Ed.; Wiley-VCH: Weinheim, 2004; pp 153−177.

(21) Hentges, S. G.; Sharpless, B. K. Asymmetric induction in the reaction of osmium tetroxide with olefins. *J. Am. Chem. Soc.* **1980**, *102*, 4263−65.

(22) (a) Miyaura, N.; Yamada, K.; Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979**, *20*, 3437−3440. (b) Miyaura, N.; Suzuki, A. Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst. *Chem. Commun.* **1979**, 866−867.

(23) Corey, E. J. Facts NobelPrize.org. Nobel prize Outreach AB, 2024.

(24) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008**, *41*, 40−49.

(25) Schreiber, S. L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **2000**, *287*, 1964−1968.

(26) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784−5800.

(27) Wender, P. A. *Chem. Rev.* **1996**, *96*, 1−2.

(28) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657−4673.

(29) Shekhar, C.; Nasam, R.; Paipuri, S. R.; Kumar, P.; Nayani, K.; Pabbaraja, S.; Mainkar, P. S.; Chandrasekhar, S. Total synthesis of antiviral drug, nirmatrelvir (PF-07321332). *Tetrahedron Chem.* **2022**, *4*, 100033.

(30) *Integrity Matters: Net Zero commitments by businesses, financial institutions, cities and regions. Report from the United nations' high-level expert group on the net zero emissions commitments of non-state entities*, November 2022.

(31) Osborn, J. A.; Wilkinson, G.; Mrowca, J. J. Tris-(triphenylphosphine)halorhodium (I). *Inorganic Syntheses* **1967**, *10*, 67.

(32) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. Asymmetric hydrogenation of b-keto carboxylic esters. A practical purely chemical access to b-hydroxy esters in high enantiomeric purity. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(33) Hughes, J. P.; Rees, S.; Kalindjian, S. B.; Philpott, K. L. Principles of early drug discovery. *Br. J. Pharmacol.* **2011**, *162*, 1239−1249.

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