'SIGNIFICANT GREEN CHEMISTRY METRICS: ROLE OF ATOM ECONOMY AND REACTION MASS EFFICIENCY IN CHEMICAL PROCESS'.

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ABSTRACT:
As the population of world is increasing enormously, there arise a challenge to develop the ways that address the needs of present generation without compromising the ability of future generation to meet their own needs, such kind of development is called Sustainable development .It results in lowering natural harm and reduces the wastage of resources. Applying such manageable development to chemical industries is simply called as 'GREEN CHEMISTRY'. Its basic idea is to prevent pollution, counteract contamination and production of wastes instead of producing them and tidying them up. There are 12 basic principles of green chemistry that have to be kept in mind while outlining a synthetic process in a greener way.
So, then after developing a reaction procedure concerned with all such principles of green chemistry where ever possible and then the next step is to evaluate the greenness of reaction quantitatively, Thus we require certain Metrics/Standards which are generally termed as green chemistry metrics / simply process chemistry metrics. This formal assessment provides an insight on various metrics so far been introduced and an exhaustive view of importance of Atom economy and Reaction mass efficiency in calculating efficiency of reactions.

KEYWORDS: Sustainable development, Atom economy, Reaction Mass Efficiency, Catalysts.

1. INTRODUCTION:

The concept of green chemistry emerged as essential tool for promoting sustainable development in laboratories and industries, For instance, we may have 2 or 3 different methods for synthesis of a substance, the selection of suitable method rely on the process which have usage of less hazardous materials, which are economical, that even reduce production of byproducts and so on. Along with these, maximization of starting material into desired product has gained more popularity to make reaction more economical.

Condensed principles of green chemistry:
P – Prevent wastes
R – Renewable materials
O - Omit Derivatization step
D – Degradable chemical products
U – Use safe synthetic methods
C – Catalytic reagents
T – Temperature, pressure ambient
I – In process monitoring
V –Very few auxiliaries
E – E- factor
L – Low toxicity of chemical products
Y –Yes, it is safe.

Coupled with the need to invent ecofriendly chemical reaction, there is equal need to quantify the greenness of reaction by using so-called green chemistry metrics.

2. SIGNIFICANT GREEN CHEMISTRY METRICS

IMPORTANCE OF GREEN CHEMISTRY METRICS:

Process chemistry metrics are a system or standards of measurement of various aspects in a chemical process .They Serves to quantify efficiency of process and allows for easy identification of the best and worst reactions in a process or Sequence. Such relative efficiencies of a reaction help to evaluate convenient synthetic routes of Preparation. These standards rank the greenness of reaction process as quantitative as possible. Number of metrics has been proposed so far to make chemist aware of need to select method which generates less wasteful byproducts. Implementation of these metrics particularly, in pharmaceutical industries is gaining more access as these industries are singled out as the one producing more waste per gram of target product.

A good metric must be clearly defined simple, measurable, and objective rather than subjective. Few of them are:
Percentage yield
E-factor
Mass intensity

Solvent and catalyst environmental impact factor

Stoichiometric factor

Effective mass yield

Carbon efficiency

Among these metrics the most prominent ones include:

Atom economy

Reaction mass efficiency

Table no.1: Summarized table of green chemistry metrics

METRIC	FORMUALE	APPLICATION	COMMENT
PERCENTAGE YIELD(% YIELD)	$\frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$	Means to compare theoretical yield and actual quantity of product.	Considers only one reactant and one product.
E-FACTOR	$\frac{\text{total waste generated in Kg}}{\text{total product in Kg.}}$	Exposes relative wastefulness of different parts of chemical processing industries.	Lack of clarity depending on how total waste is ultimately defined.
MASS INTENSITY	$\frac{\text{total mass used in process}}{\text{mass of product}}$	Yield, solvents reagents, Stoichiometr, of a reaction are taken into account.	MI=1(for ideal synthesis) that is when total mass input is equal to mass of product.
CARBON EFFICIENCY	$\frac{\text{amount of carbon in product}}{\text{total amount of carbon in startingmaterials.}}$	Estimates the % of carbon from reagents that remain in the final product.	Evaluation of greenness of synthesis solely based on carbon accounting.
SOLVENT AND CATALYST ENVIRONMENT--AL IMPACT FACTOR(f)	$\frac{\sum \text{mass of reaction and post reaction solvents} + \text{mass of catalyst used}}{\text{mass of final product}}$	It takes into account actual mass of materials used in process.	It has value of 0 only if all materials used in process (solvents, catalysts) are recycled otherwise f is greater than 0.
STOICHIOMETRIC FACTOR	$1+\frac{(AE)\sum \text{massof excess reagents}}{\text{expected product mass at 100\% yield}}$	Used if more than one reagents are taken in a process in excessive amount.	When reaction is stoichiometric then it has value of 1 otherwise SF>1.

EFFECTIVE MASS YIELD	$\frac{\text{mass of final product}}{\text{mass of non benign reagents}}$	To find out the proportion of final product made from nontoxic materials.	Defining 'non benign' (not harmful) is difficult when working with complex reagents that have limited environmental/occupational toxicity.

3. ROLE OF ATOM ECONOMY IN A CHEMICAL PROCESS:

'Key metric associated to greenness of reaction with respect to raw materials usage is <u>ATOM ECONOMY'</u>. With the target of achieving synthetic efficiencies in transforming starting materials into desired products chemists turned their focus onto process that were inherently atom efficient.

Concept of (AE) was introduced by Barry Trost in 1991 at Stanford university, simply stated that 'Atom economy is calculation of how much of reactant is getting transformed into final product.' [Note: Solvents, reagents and chemicals of catalytic quantities are omitted from analysis as they do, not contribute atoms for product].

IMPORTANCE: It can meet the needs of basic principles of 'green chemistry'. It can also be as an important means of comparing the efficiency of chemical reaction. Atom economical approaches are getting more popular due to raise in cost of raw materials, energy consumption , nature of wastes generated and value of final product to be generated .

$$\text{Atom economy} = \frac{\text{MW of product}}{\sum \text{MW of all reactants}} \times 100$$

For generic reactions,

$$A + B \xrightarrow{\text{reagents , solvents}} C$$

$$\%\text{atom economy} = \frac{GMW(C)}{GMW(A) + GMW(B)} \times 100$$

For a linear synthesis,

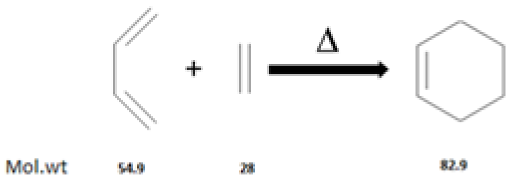
$$A + B \rightarrow C$$
$$C + D \rightarrow E$$
$$E + F \rightarrow G$$

$$\text{atom economy} = \frac{GMW(G)}{GMW(A + B + D + F)}$$

In linear sequential synthesis atom economy calculation ignores the intermediates as those that are formed in one step are been consumed in the next step. Atom economy depends upon the reagents and type of reaction involved Chemists viewed that Addition and Rearrangement reactions are most atom economical contrast what Eliminating and Substituting reactions do.

Ex: Reactions with 100% atom economy are

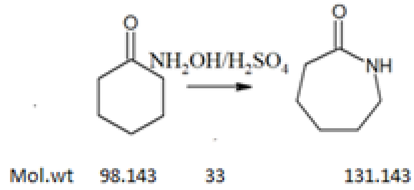
1. Addition reaction of ethane and butadiene



$$\%\text{atom economy} = \frac{82.9}{54.9+28} \times 100 = 100\%.$$

Scheme 1:Atom economy Calculation for Addition Reaction of 1,3 Butadiene and ethene.

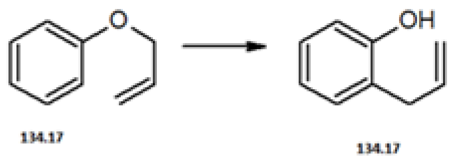
2. Beckmann rearrangement



$$\% \text{ atom economy} = \frac{131.15}{98.143+33} \times 100 = 100\ \%$$

Scheme 2:Atom economy Calculation for Rearrangement reaction of Cyclohexanone to Caprolactum.

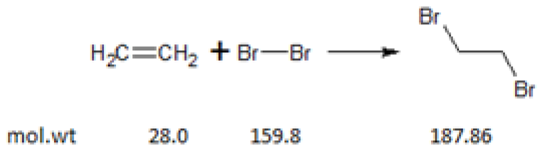
3. Allyl phenyl ether rearrangement to O-alyl phenol.



$$\%\text{atom economy} = \frac{134.17}{134.17} \times 100 = 100\%$$

Scheme 3: Atom economy Calculation for Allyl Phenyl ether Rearrangemet reaction

4. Bromination of alkene.

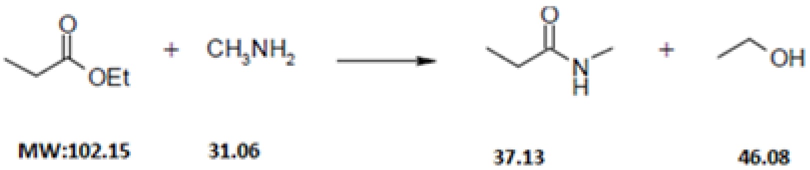


$$\% \text{ atom economy} = \frac{187.86}{28.0+159.8} \times 100 = 100\%$$

Scheme 4: Atom economy Calculation for Bromination of Alkene

Examples of reactions with reduced A.E due to substitution and elimination types.

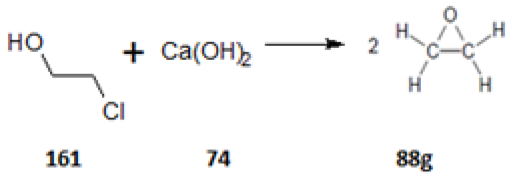
5. Substitution of methyl amine and ethyl propionate in amide formation.



$$\% \text{ atom economy} = \frac{87.13}{31.06+102.15} = 65.40\%$$

Scheme 5: Atom economy Calculation for Substitution Reaction of Methyl Amine and Ethyl propionate

6. Formation of ethylene oxide from 2-chloro ethanol and calcium hydroxide involving elimination of calcium chloride and water.

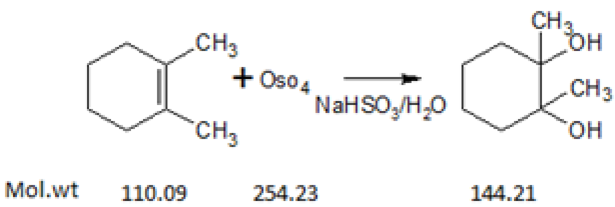


$$\%\text{atom economy} = \frac{88}{161+74} \times 100 = 37.4\%$$

Schem 6:Atom economy Calculation of reaction involved in Synthesis of Ethylene Oxide.

Addition reactions may often not provide 100% atom economy in certain cases one such an example is osmium tetroxide mediated dihydroxylation.

These inefficiencies provide opportunities to design new reactions with the goal of improving atom economy.

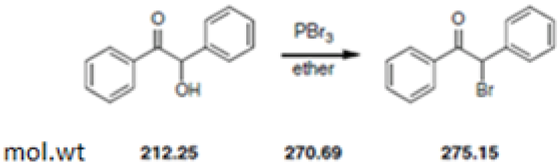


$$\%\text{atom economy} = \frac{144.21}{110.09+254.23} \times 100 = 34\%$$

Scheme 7:Atom economy Calculation of Dihydroxylation Reaction invilving Osmium Tetroxide.

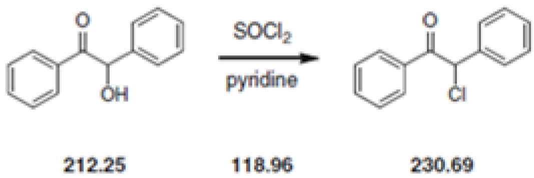
Although such substitution and elimination reactions are intrinsically wasteful, there exist an opportunity to design reaction of better atom economy ex: preparation of alkyl halides from alcohols. Choosing appropriate substituent depends on gaining access to better leaving group for further reaction or step with high atom economy.

Ex: below reactions can be observed to find the effect of substituent in alkyl halide formation reaction using PBr_3 and $SOCl_2$.



$$\%\ \text{Atom Economy} = \frac{275.15}{212.25 + 270.69} \times 100\% = 57\%$$

Scheme 8:Atom economy Calculation for Bromination Reaction of Secondary Alcohol



$$\%\ \text{Atom Economy} = \frac{230.69}{212.25 + 118.96} \times 100\% = 70\%$$

Scheme 9:Atom economy Calculation for Chlorination of Secondary Alcohol using Sulfonyl chloride.

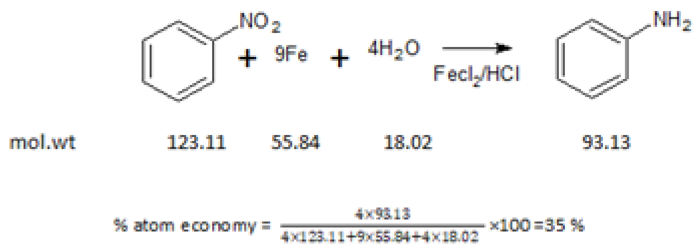
3.1 Role of catalyst in performing Atom efficient reactions :

Considering a chemical reaction involving a catalyst, where it is always used in place of a stoichiometric reagent, So its effect on atom economy can be neutral where the alternative reagent can reduce the atom economy, thus catalytic methods offer better atom efficiencies than alternative non-catalytic. In another way, as the catalytic quantities are very low, there will be less mass input into the process, which increases ratio of atom economy calculation. With the use of homogenous, heterogeneous and biocatalysts it is possible to reduce experimental constraints such as extra synthetic steps, stoichiometric components and energy inputs along with efficiency in atom economy.

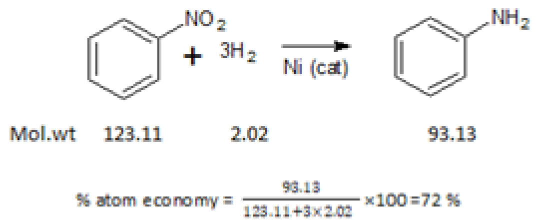
3.1.1 HETEROGENOUS CATALYSIS:

The reactions where both catalyst and reactants are in two different phases and process occurs by adsorption of reactant molecules onto surface of catalyst. The best example is nickel catalyzed hydrogenation of nitrobenzene to accommodate global demand for aniline; nickel was picked up as cheap, easily available and recoverable catalyst with an atom efficiency of 72% where original process has only 35% economy.

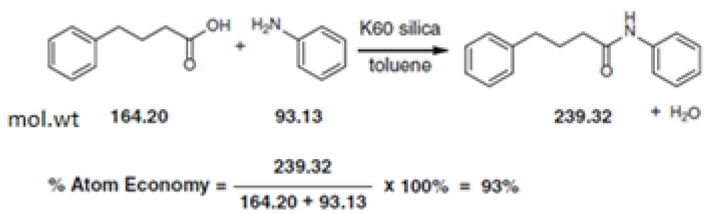
Another promising approach is the emerging use of thermally activated k60 silica as a readily available and affordable catalyst for amide bond formation in order to eliminate the use of inefficient reagents like carbodiimides, phosphonium or uranium salts etc.



Scheme 10.Atom economy Calculation for Traditional synthesis of Aniline.



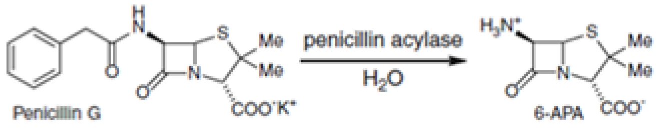
Scheme 11. Atom economy Calculation for Nickel Catalysed Aniline Synthesis.



Scheme 12.Atom economy Calculation for Catalytic Synthesis of 4-N-Diphenylacetamide.

3.1.2 BIOCATALYSIS: Enzymes promote chemical reactions which have numerous green chemistry advantages like biodegradability, safety, high selectivity etc. In terms of atom economy, synthesis of 6amino penicillanic acid from penicillin G highlights power of biocatalysts.

Sheldon et..at in 2001 explained the development of biocatalytic process for synthesis of 6Amino pencillinic acid using stable penicillin G acylase enzyme resulting in dramatic reduction of wastes and with milder reaction condition compared to the traditional 4 step deacylation of penicillin G to give 6APA which accounts just an atom economy of 28%.



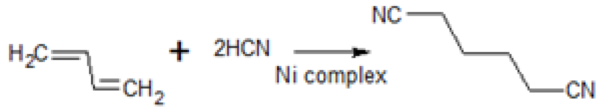
mol.wt 372.48 216.26

$$\% \text{ Atom Economy} = \frac{216.26}{372.48} \times 100\% = 58\%$$

Scheme 13: Atom economy Calculation for Penicillin acylase mediated synthesis of 6 amino penicillanic acid.

3.1.3 HOMOGENOUS CATALYSIS: As distinguished from heterogeneous catalysis, here the reactants and catalysts are found to be in same phase.

Ex: In 1970 DuPont Adiponitrile Synthesis catalyzed by nickel tetrakis phosphate complex as an example of major industrial process involving homogenous catalysis occurring with 100%AE.



Mol.wt 54.09 27.03 108.14

$$\%\text{atom economy} = \frac{108.14}{54.09+2\times 27.03} \times 100 = 100\%.$$

Scheme 14:Synthesi of Adiponitrile Mediated by Nickel catalyst.

LIMITATION : In some instances, atom Economy is limited in process efficiency when the reaction can proceed with high atom economy but having yield of less than 50%.ex: synthesis of 2,4 diphenylquinoline where AE=93% and yield is less than or equal to50%.

Here, Reaction Mass Efficiency produces robust and global perspective of greenness in such cases.

Relationship.

3.2 REACTION MASS EFFICIENCY:

Steinbach and Winkenbach introduced the term balanced yield which is synonymous to present term Reaction Mass Efficiency, and which is the measure of productivity rather than wastes generated.

$$\text{Balance yield} = \frac{\text{Main product amount}}{\text{Balance sheet total input}}$$

In 2001, GSK presented their list of green metrics to promote sustainable development among them RME was emphasized as realistic metric for greenness of reaction.

$$\text{RME} = \frac{\text{Product mass}}{\text{Sum of Mass of all Reactants Appearing in the Chemical equation}} \times 100$$

An excess of either of reactants to maximize the selectivity or yield of reaction are not included in atom economy But, in reaction mass efficiency equation which was put forth by curzos eventually recognized Reaction mass efficiency accounts for Yield ,Atom economy and stoichiometry factor. Following generic reaction is taken to derive such relationship

$$.\text{RME} = \text{Yield} \times \text{Atom economy} \times \frac{1}{\text{stoichiometric factor}} \times 100$$

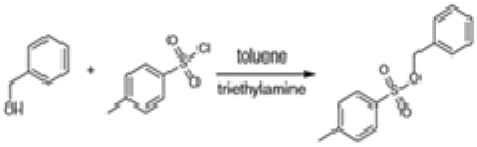
Figure:1

A + B ⟶ C

MASS	M1	M2	M3
MOLES	MW1	MW2	MW3
GMW	X	Y	Z

$$\text{RME} = \frac{Z}{X} \cdot \frac{MW3}{MW1+MW2} \cdot \frac{1}{(Y-X)MW2/X(MW1+MW2)}$$

Example: By applying the derived equation following reaction of esterification of benzyl alcohol and p-toulene sulfonyl chloride.



MASS	10.81	21.9	23.6g
MOLES	0.10	0.115	0.09
GMW	108.14	190.64	262.32g

$$RME = \frac{23.6}{10.81 + 21.9} = 0.72 \qquad YIELD = \frac{0.09}{0.10} = 0.90$$

$$ATOM\ ECONOMY = \frac{262.32}{190.64 + 108.14} = 0.88$$

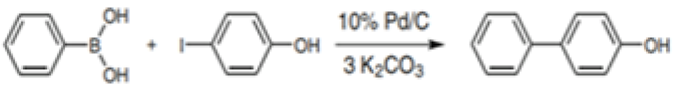
$$STOICHIOMETRIC\ FACTOR = 1 + \frac{(0.115 - 0.10) \times 190.64}{0.10 \times (108.14 + 190.64)} = 1.10$$

$$RME = YIELD.ATOM\ ECONOMY.1/STOICHIOMETRIC\ FACTOR = 0.90 \times 0.88 \times \frac{1}{1.10} = 0.72$$

Scheme 15Reaction mass efficiency Calculation for esterification reaction of benzyl alcohol.

Note: Results are expressed in absolute form ranging between (0-1), to make RME values meaningful as percent values cannot achieve this.

Through his work on Green metrics in 2005, Andros recognized RME to be accounted for all the materials involved in chemical process and thus proposed a generalized mass efficiency equation which can be broken down into product of yield, atom economy, stoichiometric factor and (material recovery parameters) ie; accounts for solvents, catalysts, workup /purification materials.



MASS	0.122g	0.22g	0.415g	0.115g
MOLES	1.00mmol	1.00m mol	3m mol	0.675m mol
GMW	121.93	220.01	414.6	170.21

Catalyst mass = 0.003g

Reaction solvent mass = 11g

Workup mass = 38.1g

Atom economy = 0.225

Yield = 0.675

Kernel RME = 0.225×0.675 = 0.152

$$Curzos\ RME = \frac{0.115}{0.122+0.220+0.415} = 0.152$$

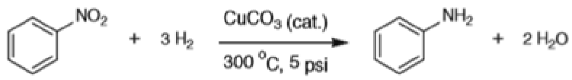
$$Generalized\ RME = \frac{0.115}{0.122+0.220=0.415+0.003+11+38.1} = 0.0023$$

Scheme 16 : Reaction mass effficiency Calculation of suzuki reaction.

Here the Kernel RME is equal to Curzos as excess reagents are not used, but when mass of remaining reagents are used RME is decreased as the solvents occupy 98% of mass involved in experiment.

3.2.1 APPLYING REACTION MASS EFFICIENCY TO CATALYSIS:
Apart of always being atom efficient, few catalytic reactions have shown that atom economy is limited at its ability to measure process efficiency. Ex: Synthesis of 2,4diphenylquinoline have shown 93% atom economy with an yield of less than 50% thus attaining less in terms of achieving reaction efficiency and productivity. Applying reaction mass efficiency metric to catalytic reactions have gained more global perspective on greenness.
3.2.2 HETEROGENOUS CATALYSIS:
Ex: Among 5 industrial routes in converting benzene to aniline, efficient process includes Nitration via electrophilic substitution reaction and hydrogenation catalyzed by copper carbonate on silica.RME calculations for industrial production of aniline are as follows: Here in this reaction generalized RME is much greater than Suzuki reaction representing as industrial process should be much more efficient than laboratory preparations.

Mass	589.7Kg	480.8kg	907.2 kg
GMW	78.11	63.01	123.11



Mass	907.2 kg	43.6kg	671.3kg
GMW	123.11	6.05	93.13

Catalytic mass -5.03 kg

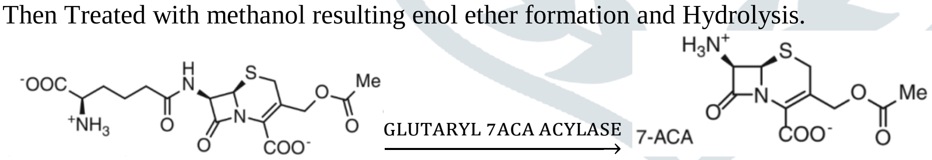
Workup and purification material mass – 9.1 kg

Reaction solvent mass – 753 kg

$$\text{Generalized RME} = \frac{671.3}{589.7+480.8+43.6+5.03+753+9.1} = 0.357$$

scheme17: reaction mass efficiency calculation for catalytic synthesis of aniline.

3.2.3 BIOCATALYSIS:
Ex: Synthesis of 7 amino cephalosporonic acids from potassium salt of cephalosporin C. It has been traditionally made by a four step route developed in 1980 with an atom economy of 36%.which first includes the Acyl chloride protection of amine and COOH groups of potassium salt of cephalosporin C. Followed by Treatment with Phosphorous penta chloride to form imodyl chloride. Then Treated with methanol resulting enol ether formation and Hydrolysis.



SCHEME18: Conversion of potassium salt of cephalosporin C to 7ACA mediated by biocatalysts.

Where as, Biocatalytic route had given 90 fold reduction in overall waste and seven fold reduction in solvent emissions. Cephalosporin C salt is stirred with immobilized DAO and reacted with oxygen gas to produce keto intermediate. This react spontaneously to produce glutaryl 7 ACA .further, Enzyme is again recycled and reaction is stirred with glutaryl 7-ACA acylase to form 7 Aminocephalosporonic acid .
NOTE: RME Values less than 0.15 are unproductive and less efficient. As, this metric accounts for most of all reactant masses and also as it is a combined metric of atom economy, yield and stoichiometic factor ,it can be considered To be a helpful greenness measurement.

4. CONCLUSION: Green chemistry is been considered as added value to organic chemistry.
Greenness assessment tools that can well assess e-impact of chemical process and reaction efficiencies are to well understand before going through a chemical synthesis.
Assessment of greenness with large input datasets have to be made by developing more efficient metrics.
Atom economy is one way to measure the idealness of said synthesis.
New software and tools are expected to be developed for easy calculations of standards and also there is a need for popularization of existing metrics.
Atom economy even cannot be considered as a stand-alone metric, can be used as organizing concept and in combination with other metrics.

Yield can remain as ubiquitous metric in economic standpoint and for high value added materials like in pharmaceuticals. RME combines most of key properties of process and chemistry and represents a simple, objective and a well derived metric and it drives for invention of likely chemical process and technologies that lead to more sustainable development.

REFERENCES:

1. Trost BM (1991) The atom economy—a search for synthetic efficiency. Science 254:1471–1477. doi:10.1126/science.1962206.
2. Constable DJC, Curzons AD, Cunningham VL (2002) Metrics to "green" chemistry—which are the best? Green Chem 4:521–527. doi:10.1039/b206169b
3. McMurry J (2012) Organic chemistry, 8th edn. Brooks/Cole, New York, pp 319–320
4. Andraos J (2009) Application of green metrics analysis to chemical reactions and synthesis plans. In: Lapkin A, Constable DJC (eds) Green chemistry metrics: measuring and monitoring sustainable processes. Wiley-Blackwell, Chicester
5. Trost BM (2012) Atom economy: a challenge for enhanced synthetic efficiency. In: Li CJ (ed) Handbook of green chemistry volume 7: green synthesis. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
6. Sheldon RA (2012) Fundamentals of green chemistry: efficiency in reaction design. ChemSoc Rev 41:1437–1451. doi:10.1039/c1cs15219j
7. Moores A (2009) Atom Economy—principles and some examples. In: Crabtree RH (ed) Handbook of green chemistry volume 1: homogeneous catalysis. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
8. Kumagai N (2011) Development of atom-economical catalytic asymmetric reactions under proton transfer conditions: construction of tetrasubstitutedstereogeniccenters and their application to therapeutics. Chem Pharm Bull 59:1–22. doi:10.1248/cpb.59.1
9. . Weissermel K, Arpe H-J (1997) Industrial organic chemistry, 3rd edn. Wiley-VCH, Weinheim, pp 143–144
10. Grant S, Freer AA, Winfield JM, Gray C, Lennon D (2005) Introducing undergraduates to green chemistry: an interactive teaching exercise. Green Chem 7:121–128. doi:10.1039/ b412664e
11. Mercer SM, Andraos J, Jessop PG (2012) Choosing the greenest synthesis: a multivariate metric green chemistry exercise. J ChemEduc 89:215–220. doi:10.1021/ed200249v
12. Rothenberg G (2008) Catalysis: concepts and green applications. Wiley-VCH Verlag, New York, pp 4–28
13. Comerford JW, Clark JH, Macquarrie DJ, Breeden SW (2009) Clean, reusable and low cost heterogeneous catalyst for amide synthesis. ChemCommun 2562–2564. doi:10.1039/ b901581g
14. Crabtree RH (2009) The organometallic chemistry of the transition metals, 5th edn. Wiley, Hoboken, pp 248–249
15. Straathof AJJ, Panke S, Schmid A (2002) The production of fine chemicals by biotransformations. CurrOpinBiotechnol 13:548–556. doi:10.1016/S0958-1669(02)00360-9
16. Weissenburger HWO, van der Hoeven MG (1970) An efficient nonenzymatic conversion of benzylpenicillin to 6-aminopenicillanic acid. ReclTravChim Pays Bas 89:1081–1084. doi:10. 1002/recl.19700891011
17. Wegman MA, Janssen MHA, van Rantwijk F, Sheldon RA (2001) Towardsbiocatalytic synthesis of β-lactam antibiotics. Adv SynthCatal343:559–576.doi:10.1002/1615-4169(200108)343:6/73.0.CO;2-Z
18. Steinbach A, Winkenbach R (2000) Choose processes for their productivity. ChemEng 107:94–104
19. Curzons AD, Constable DJC, Mortimer DN, Cunningham VL (2001) So you think your process is green, how do you know?—Using principles of sustainability to determine what is green—a corporate perspective. Green Chem 3:1–6. doi:10.1039/b007871i
20. Andraos J (2005) Unification of reaction metrics for green chemistry: applications to reaction analysis. Org Process Res Dev 9:149–163. doi:10.1021/op049803n
21. Andraos J (2005) Unification of reaction metrics for green chemistry II: evaluation of named organic reactions and application to reaction discovery. Org Process Res Dev 9:404–431. doi:10.1021/op050014v
22. Andraos J, Sayed M (2007) On the use of "green" metrics in the undergraduate organic chemistry lecture and lab to assess the mass efficiency of organic reactions. J ChemEduc 84:1004–1010. doi:10.1021/ed084p1004
23. Constable DJC, Curzons AD, Cunningham VL (2002) Metrics to "green" chemistry—which are the best? Green Chem 4:521–527. doi:10.1039/b206169b
24. Mayo DW, Pike RM, Forbes DC (2013) Microscale organic laboratory with multistep and multiscale syntheses, 6th edn. Wiley, Hoboken, pp 421–427
25. Dicks AP, Batey RA (2013) ConfChem conference on educating the next generation: green and sustainable chemistry—greening the organic curriculum: development of an undergraduate catalytic chemistry course. J ChemEduc 90:519–520. doi:10.1021/ ed2004998
26. Kulkarni A, Torok B (2010) Microwave-assisted multicomponent domino cyclizationaromatization: an efficient approach for the synthesis of substituted quinolines. Green Chem 12:875–878. doi:10.1039/c001076f
27. Mercer SM, Andraos J, Jessop PG (2012) Choosing the greenest synthesis: a multivariate metric green chemistry exercise. J ChemEduc 89:215–220. doi:10.1021/ed200249v

28. Henderson RK, Jimenez-Gonzalez C, Preston C, Constable DJC, Woodley JM (2008) EHS & LCA assessment for 7-ACA synthesis A case study for comparing biocatalytic and chemical synthesis. IndBiotechnol 4:180–192. doi:10.1089/ind.2008.4.180
29. Ascher G (1980) U.S. Patent 4322526
30. Bayer T (2004) 7-Aminocephalosporanic acid—chemical versus enzymatic production process. In: Blaser HU, Schmidt E (eds) Asymmetric catalysis on industrial scale: challenges, approaches and solutions. Wiley-VCH Verlag GmbH & Co, KGaA, Weinheim
31. David J. C. Constable,a Alan D. Curzonsb and Virginia L. Cunninghama/Metrics to 'green' chemistry—which are the best?/ First published as an Advance Article on the web 17th October 2002.
32. Kenneth M. Doxsee/ University of Oregon/Reaction Efficiency/2010.
33. Roger A. Sheldon/Fundamentals of Green Chemistry: Efficiency in Reaction Design/The Royal Society of Chemistry 2011.

34. Dicks, Andrew, Hent, Andrei/Green Chemistry Metrics/SpringerBriefs in Green Chemistry for Sustainability/2015.