Tools and new metric to tackle the environmental impact of macrocyclization reactions

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ABSTRACT

Albeit the numerous scientific advantages provided by macrocyclic compounds, there is still a significant gap between the "proof of concept" research and their application. This is a direct consequence of the challenging macrocyclization reactions generally involved in their production. Indeed, macrocyclizations are one of the greatest offenders to the principles of Green Chemistry, as long reaction times, high dilution conditions, and solvent-consuming purification techniques are commonly needed. However, new tools -catalysts, templates, preorganization, flow chemistry- are blossoming to develop environmentally friendly approaches for synthesizing macrocycles. Here, we present some of these tools together with a simple metric to assess the environmental impact of several reported macrocyclic systems. The metric has been proved as a useful way to scrutinize macrocyclizations, even in the cases where other environmental metrics such as E-Factor and Emac did not show conclusive results.

Keywords: Macrocycles, Metric, Sustainable Chemistry, Catalysis, Flow Chemistry

1. INTRODUCTION

Macrocyclic compounds have found a wide range of applications in several fields.[1,2,3] However, synthesis and functionalization of macrocycles is still limited by the challenging protocols involved in their production.[4] High-dilution techniques usually govern the success in the synthesis of macrocyclic structures with good yields.[5] This approach does not only result in enormous amounts of chemical waste, but it also brings upon cost issues and difficulties in scale-up.[6] In an era where most chemical processes are scrutinized according to their environmental impact, macrocycle synthesis can be one of the greatest offenders to the principles of green chemistry,[7] further hampering their use in industrially relevant processes. Consequently, many efforts have been devoted to developing greener approaches towards efficient macrocyclization reactions.[8] The utilization of preorganized reagents,[9] templating agents,[10] and flow protocols,[11] have fostered remarkable advances in the field, leading to highly selective macrocyclizations even at high concentrations.[12,13]

Several antecedents can be found in literature describing useful metrics for assessing the environmental implications of chemical reactions.[14,15] Nevertheless, the definition of a specific metric, that takes into account the intrinsic requirements of macrocyclizations may help to evaluate this specific type of synthetic protocols.[16] As a matter of fact, J. C. Collins and K. James introduced a practical metric (Emac) that accounted for the concentration and yields afforded in the syntheses of several pharmaceutically active macrocycles.[17] Notwithstanding, this metric does not consider the environmental efficiency, nor the reaction time required for reaching the desired yields.

We believe that these overlooked synthetic implications are fundamental to properly assess the impact of macrocyclization reactions. Thus, we report herein our efforts to establish a simple metric that permits the estimation of the environmental impact of macrocyclizations. This tool encompasses both productivity and waste generated during the macrocyclization process. Several reported macrocyclization reactions have been evaluated with this metric, discussing how state-of-the-art synthetic tools enable effective methodologies to minimize the environmental impact of the macrocyclizations while maximising yield and productivity (Fig. 1).

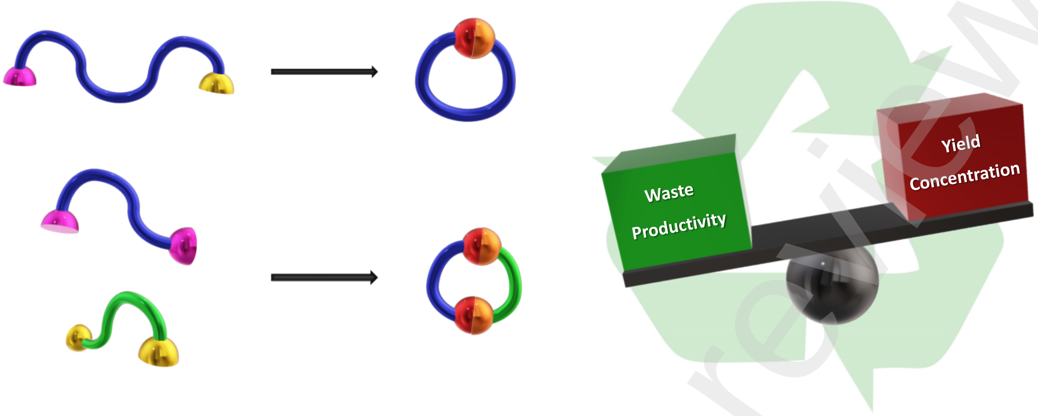

Fig. 1 General schematic representation of unimolecular (above) and bimolecular (below) macrocyclization reactions.

2. DISCUSSION

2.1. Macrocyclization Environmental Impact (MEI)

Inspired by former environmental metrics, a simple and new metric that simultaneously accounts for the macrocyclization efficiency in terms of productivity and waste generated during the synthesis and isolation of the macrocycles is defined: Macrocyclization Environmental Impact (MEI, Eq. 1). For this metric, the higher is the MEI value obtained, the higher is the environmental impact of the process

$$\text{MEI} = \text{E-Factor} / \text{Productivity} \quad (g_{waste} \times L \times h / g_{macrocycle}^{2}) \qquad \textbf{(Eq. 1)}$$

The amount of waste should include the residues generated in both the synthesis and the isolation of the macrocycle. The productivity will be the grams of products obtained divided by the reactor volume (L) and time (h), as factors related with the productivity and the dilution used in the process. As evidenced by the equation, the ideal scenario would be to have a macrocyclization with low E-Factor and high productivity giving low MEI values.

In general, the higher is the amount of waste generated per gram of macrocycle the higher the MEI value would be, emphasizing the need to decrease the waste produced. This is of major importance in macrocyclizations, where large amounts of solvent waste are generated due to the low concentrations required and to the tedious purification protocols generally involved. Hence, the cost and CO_2 footprint associated with purchasing, evaporating, and disposing such additional volume of solvent is indirectly considered, as well as the larger equipment and safety issues related with its handling. Another drawback of employing high-dilution conditions is the prolonged reaction times often needed for reaching high macrocyclization yields, significantly reducing the productivity for the whole process. In line with these considerations, the MEI score must consider the dilution and time requirements to achieve the optimised yield, with the higher these parameters are, the lower the macrocyclization efficiency, and, therefore, the higher the score of the MEI.

In order to validate the applicability of the proposed metric, different reported macrocyclization reactions (Fig. 2) were analysed calculating the amount of waste generated, including excess of reagents, co-reagents (*i.e.* base/acids), catalysts, and solvents used (with the exception of water) in the synthesis and isolation of the product. Although the selection of the macrocycles is far from systematic, a direct comparison of the MEI scores with other established metrics (*e.g.* Emac and E-Factor) shows meaningful information. In addition, the MEI values can also suggest the best pathways and tools to reduce the environmental impact of these type of synthetic protocols.

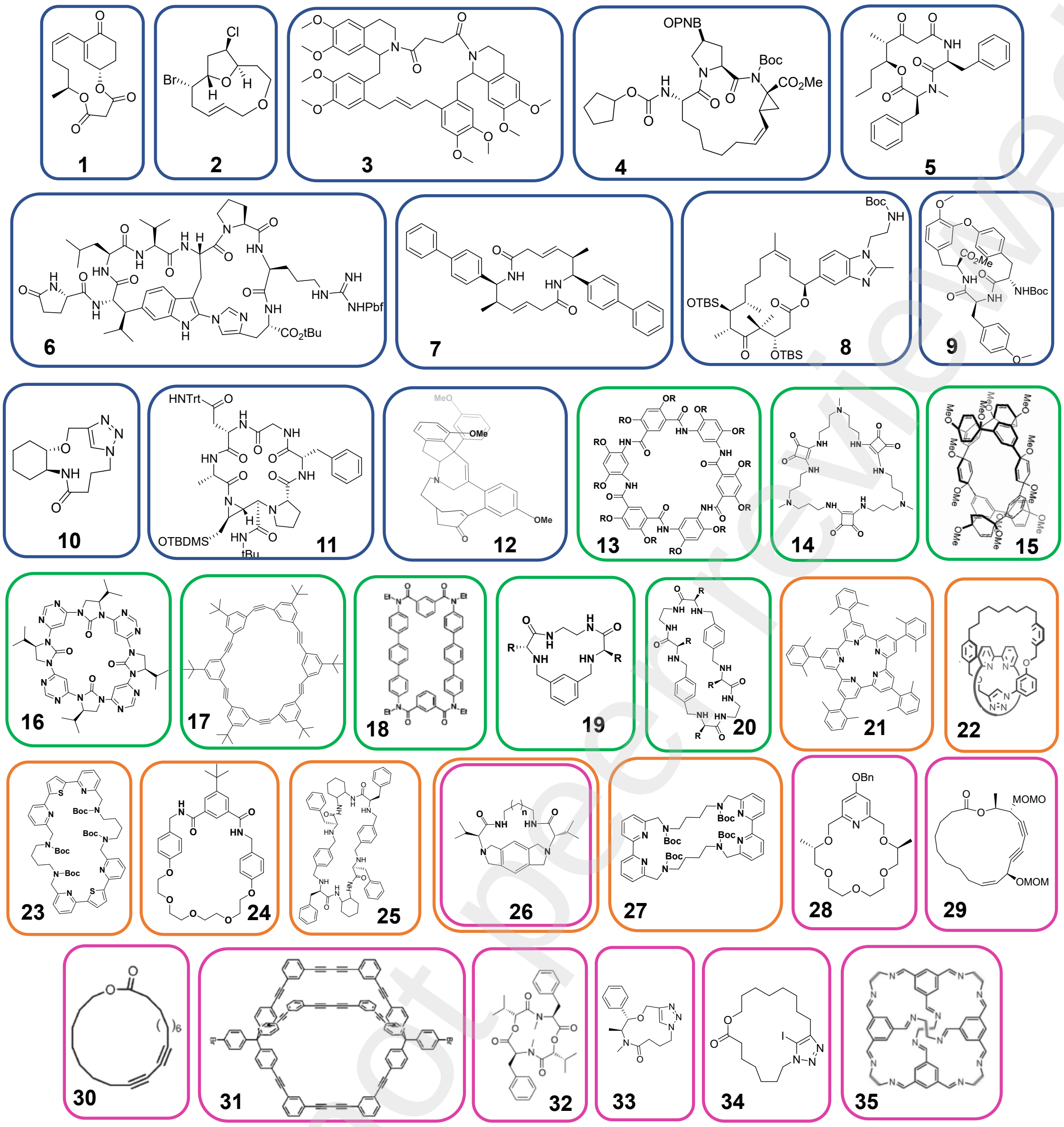

Fig. 2 Chemical structures of the different macrocyclic compounds considered in this work. Macrocycles highlighted in blue (**1-12**) can be classified in pharmaceutically relevant macrocyclizations. Macrocycles highlighted in green (**13-20**) can be classified in preorganized macrocyclizations. Macrocycles highlighted in orange (**21-27**) can be classified in template-assisted macrocyclizations. Macrocycles highlighted in pink (**26, 28-35**) can be classified in flow-mediated macrocyclizations. See Tables 1, 2, 3, and 4 in the manuscript for references.

2.2. MEI in pharmaceutically relevant macrocyclizations

One of the main fields of application for macrocyclic species is their use as highly active drugs. These macrocycles, especially those being peptide-based, present several unique features like their large polar surface areas that renders on an enhanced cellular permeability and bioavailability.[18] Moreover, another pharmacological advantage is associated to their higher level of preorganization compared with analogous open-chain compounds, avoiding entropic losses during substrate-binding that would decrease the affinity.[19]

The MEI values have been determined for several reported macrocyclization reactions of biologically active cyclic compounds (Table 1). To emphasize and discriminate the environmental impact of the different macrocyclizations in a simple and straightforward manner, a colour code is used where: MEI >5000 (light red, enormous environmental impact), MEI 1501-5000 (orange, high environmental impact), MEI 151-1500 (light blue, significant environmental impact), MEI 10-150 (light green, low environmental impact), and MEI <10 (green, minimal environmental impact.

Table 1 Macrocyclization environmental efficiency (MEI) calculated for different reported systems according to Eq. 1.

Entry	Comp.[a]	Reaction type		Conc (mM)	Yield (%)	Productivity (g_p/L·h)[b]	Em ac	E-Factor[c]	MEI (g_w·L·h/g_p^2)
1 [20]	**1**	RCM	Intramolecular	3	80	0.028	6.2	3253	116178.6
2 [21]	**2**	RCM	Intramolecular	2	34	0.012	4.9	3816	318000.0
3 [22]	**3**	RCM	Intramolecular	2	35	0.027	4.9	2078	76963.0
4 [23]	**4**	RCM	Intramolecular	100	95	49.296	7.9	52	1.1
5 [24]	**5**	Lactam	Intramolecular	2	47	0.012	5.3	2813	234416.7
6 [25]	**6**	Lactam	Intramolecular	3	83	0.300	6.2	3668	12226.7
7 [26]	**7**	Lactam	Intramolecular	550	73	11.333	8.3	13	1.2
8 [27]	**8**	Lactone	Intramolecular	2	57	0.186	5.6	786	4225.8
9 [28]	**9**	Negishi	Intramolecular	2	35	0.031	4.9	2005	64677.4
10 [29]	**10**	Huisgen	Intramolecular	2	71	0.593	5.9	2185	3684.7
11 [30]	**11**	Ugi-like	Intramolecular	200	88	30.000	8.1	16	0.5
12 [31]	**12**	S_N2	Intermolecular	2	79	0.019	6.0	2237	117736.8

[a] The macrocyclic structures have been summarised in Fig. 2. [b] Calculated considering the concentration, time, and yield reported. [c] The waste generated during the chromatographic purification has not been considered in the waste calculation due to lack of information. Colour code: MEI >5000 (light red, enormous environmental impact), MEI 1501-5000 (orange, high environmental impact), MEI 151-1500 (light blue, significant environmental impact), MEI 10-150 (light green, low environmental impact), MEI <10 (green, minimal environmental impact).

The MEI scores very differently according to the nature of the macrocyclization reaction considered (Fig. 2). As surmised, MEI values highlight the key importance of the reaction concentration. In general, the macrocyclization reactions performed under non-diluted conditions are those leading to remarkably low MEI values (< 1.5) (Entries 4, 7, and 11, Table 1). It must be noted that these macrocyclizations are based on reactions classified among the most efficient in terms of productivity (ring-closure metathesis (RCM), Ugi-like reactions, and lactam synthesis).[32] The high selectivity of these reactions permitted the use of higher concentrations, leading to significantly improved productivities. However, the other cyclization reactions were performed under diluted conditions (*ca.* 2-3 mM). These concentration values are close to the average macrocyclization concentration reported (3.7 mM).[17] The high-dilution conditions employed in these cases rendered low volumetric productivities and huge solvent waste, leading to enormous environmental impacts (See entries 1-3, 5, 6, 9, and 12; macrocycles **1-3**, **5**, **6**, **9**, and **12** in Fig. 2).

One should highlight the results obtained for macrocycles **8** and **10** (see Fig. and Table 1, entries 8 and 10). Despite these macrocyclizations are also conducted under high-dilution conditions (2 mM), they scored much lower MEI values than the other macrocyclizations performed under similar dilutions. This observation is the direct result of the reduced reaction times required for achieving the desired yields of the macrocycle. As a matter of fact, macrocycle **10** was produced in only 0.67 h. Consequently, its productivity is much higher than that of related macrocyclizations, significantly decreasing its environmental implications

The comparison of the MEI values for macrocyclization reactions with a simple well-established green metric such as the E-factor shows, in general, a similar trend. Both values are significantly reduced when the productivity and reagent concentrations are increased. However, for those cases where the E-factor score similar values, the MEI values allow to discriminate the efficiency of the macrocyclization reaction. For instance, the macrocycles **3**, **9**, **10** and **12** led to comparable E-factors (*ca*. 2000). In contrast, the MEI values for these reactions varied in two orders of magnitude. Thus, the macrocycles can be classified attending to their environmental impact as follows **12** > **3** > **9** > **10** (Entries 3, 9, 10 and 12. Table 1).

2.3. MEI in preorganized macrocyclizations

Successful macrocyclizations have been achieved using open-chain precursors preorganized in a folded conformation that allows the reacting sites of corresponding precursor/s to be closed by either intra- or intermolecular macrocyclization reaction (Fig. 3).[33]

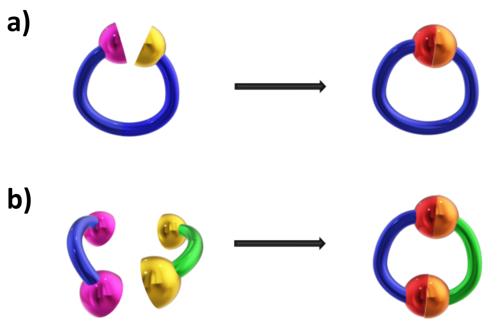

Fig. 3 General schematic representation of preorganized reagents for macrocyclizations. a) Intramolecular. b) Intermolecular.

The optimal preorganization of the reagents/intermediates generally results in a remarkable increase in macrocyclization efficiency.[9] Indeed, for an intramolecular process, the proper spatial disposition of the reacting sites usually provides an unambiguous orientation for macrocyclization, leading to a more selective and faster process than for the competing intermolecular reactions.[34]

Table 2 Macrocyclization environmental efficiency (MEI) calculated for different preorganized systems according to Eq. 1.

Entry	Comp.[a]	Reaction type		Conc (mM)	Yield (%)	Productivity $(g_p/L\cdot h)$[b]	Emac	E-Factor	MEI $(g_w\cdot L\cdot h/g_p^2)$
1 [35]	**13**	Amide formation	Intermolecular	65	82	4.980	7.6	30[c]	6.0
2 [36]	**14**	Squaramide formation	Intramolecular	37	81	1.667	7.3	40[c]	24.0
3 [37]	**15**	Suzuki-Miyaura cross-coupling	Intermolecular	5	29	0.205	5.1	1623[d]	7917.0
4 [38]	**16**	Buchwald-Hartwig cross-coupling	Intermolecular	20	85	0.418	7.1	91	217.7
5 [39]	**17**	Cross-coupling	Intramolecular	11	75	0.327	6.7	123[d]	375.8
6 [40]	**18**	Peptoid formation	Intermolecular	50	55	1.529	6.9	136[c,d]	89.3
7 [41]	**19**	S_N2	Intermolecular	8	65	0.208	6.3	207[c,d]	995.0
8 [42]	**20**	Imination	Intermolecular	50	67	1.886	7.2	28[c,d]	15.0

[a] The macrocyclic structures have been summarised in Fig. 2. [b] Calculated considering the concentration, time, and yield reported. [c] The waste generated during the chromatographic purification has not been considered in the waste calculation due to lack of information. Colour code: MEI >5000 (light red, enormous environmental impact), MEI 1501-5000 (orange, high environmental impact), MEI 151-1500

(light blue, significant environmental impact), MEI 10-150 (light green, low environmental impact), MEI <10 (green, minimal environmental impact).

Table 2 shows the values calculated for the different macrocycles (compounds **13-20**, Fig. 2) based on the preorganization of their precursors. In general, the higher reaction selectivities in the preorganized systems allows for the use of higher concentrations than those described in Table 1. These increased concentrations result in enhanced productivities, and thus, lower MEI values. With this approach, some of the macrocyclizations did not require tedious chromatographic protocols for purifying/isolating the desired product. This fact is of prior importance when discussing the environmental impact of chemical reactions, as purification by means of chromatography produces enormous amounts of solvent waste.[43] Indeed, macrocycles **13**, **14**, and **16** could be isolated without any chromatographic methodology.

The only macrocyclization leading to high environmental impacts was the synthesis of compound **15**. In this case, the low yields (*ca.* 29 %) and the relatively diluted conditions (5 mM) precluded the environmentally-friendly production of the macrocycle. Notwithstanding, comparing this MEI score with the ones studied in Table 1, the value is still one order of magnitude lower than those for the unpreorganized systems presenting similar macrocyclization yields (Entry 3 in Table 2 *vs.* Entries 2, 3, 5, and 9 Table 1). These results evidence that the MEI and, therefore, the environmental impact of the macrocyclization reactions can be reduced by developing strategies that preorganize the reagents in an optimal disposition for the formation of the macrocycle.

The MEI value provides a simple score to differentiate systems with similar E-Factor and Emac values. This can be illustrated when macrocycles **13** and **20** are compared (Entries 1 *vs*. 8, Table 2). Whereas both E-Factor and Emac scored similar values, the MEI for the macrocycle **20** is 2.5-times higher than the value found for **13**. This difference can be attributed to the higher productivity of **13**, which reduced the environmental impact of the reaction. Entries 5 and 6 of Table 2 also demonstrate the practicality of the metric for evaluating the environmental efficiency. According to the E-Factor, the more efficient macrocyclization should be the synthesis of **17** (Entry 5). However, the *ca*. 5-times greater productivity achieved in the synthesis of **18**, compared to the one of **17**, promotes lower MEI scores, indicating that this macrocyclization results in a lower environmental impact overall.

2.4. MEI in templated macrocyclizations

An interesting alternative for the cases in which the precursors are not precisely preorganized is the use of catalysts -templating agents- that promote a favourable conformation for macrocyclization.[9,10] The most frequent mechanism for template-assisted macrocyclizations is the precursor(s)/intermediate wrapping around the templating species, approaching the two reactive groups (Fig. 4). Hence, the introduction of the template helps to change the unfavoured disposition and to induce an appropriate conformation for the macrocyclization step.

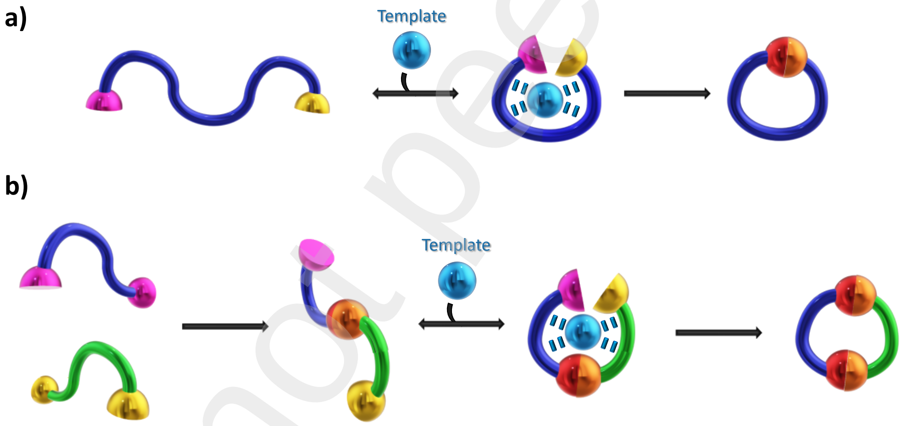

Fig. 4 General schematic representation of template-assisted macrocyclizations. a) Intramolecular. b) Intermolecular.

This strategy is especially relevant for intermolecular macrocyclization, as the template effect enhance the selectivity of the process in comparison with untemplated systems. One of the main species used as templates are cations, although anions have been also explored.[44] It must be noted, however, that this approach can be against the eight principles of Green Chemistry, as it relies on supramolecular derivatisation.[7] The template will not be incorporated in the final macrocycle, generating therefore additional waste.

Table 3 summarizes the different values calculated for the template-assisted macrocyclizations considered. The syntheses of macrocycles **21** and **22** were performed through metal-templation, with Ni^{2+} and Cu^{+} species, respectively. Despite the lower concentration used for the synthesis of **22** than that of **21** (see Entries 1 and 2 in Table 3), the lower reaction times and higher yields for the former preceded to enhanced macrocyclization productivity. Taking into account the E-Factor values, the synthesis of **21** should be about 2-times more environmentally-damaging than the analogous **22** macrocyclization. MEI scores show the opposite trend (825.0 and 547.7 $g_w \cdot L \cdot h/g_p^2$, respectively for **21** and **22**), as the intensification variable encompassed within this metric, namely the productivity, results in lower environmental drawbacks overall.

Table 3 Macrocyclization environmental efficiency (MEI) calculated for different template-assisted systems according to Eq. 1.

Entry	Comp.[a]	Reaction type		Conc (mM)	Yield (%)	Productivity ($g_p/L \cdot h$)[b]	Emac	E-Factor	MEI ($g_w \cdot L \cdot h/g_p^2$)
1 [45]	**21**	Yamamoto coupling	Intermolecular	40	57	0.280	6.9	231[d]	825.0
2 [46]	**22**	Azyde-alkyne cycloaddition	Intermolecular	6	98	1.017	6.8	557[d]	547.7
3 [47]	**23**	Olefin metathesis	Intermolecular	10	82	2.250	6.7	278[d]	123.6
4 [48]	**24**	Amide formation	Intermolecular	14	32	1.067	5.7	530[c,d]	496.7
5 [49]	**25**	Imination	Intermolecular	55	65	0.718	7.2	63[c,d]	87.7
6 [50]	**26**	S_N2	Intermolecular	2	82	0.252	6.0	1030	4087.3
7 [51]	**27**	Olefin metathesis	Intermolecular	10	93	2.200	6.9	285	129.5

[a] The macrocyclic structures have been summarised in Fig. 2. [b] Calculated considering the concentration, time, and yield reported. [c] The waste generated in the purification prior to the chromatography has not been considered due to lack of information. [d] The waste generated during the chromatographic purification has not been considered in the waste calculation due to lack of information. Colour code: MEI >5000 (light red, enormous environmental impact), MEI 1501-5000 (orange, high environmental impact), MEI 151-1500 (light blue, significant environmental impact), MEI 10-150 (light green, low environmental impact), MEI <10 (green, minimal environmental impact).

Templated macrocyclizations have also been assayed based on hydrogen bonding between the reagents and the auxiliary species (Entries 3-6, Table 3). Macrocyclization reactions illustrated in

Entries 3 and 5 (Table 3) gave quite low MEI scores. This is a direct result of the remarkable productivity achieved in the synthesis of **23** and the small E-Factor obtained in the synthesis of **25**.

The synthesis of macrocycle **26** displays the ideal scenario for templated macrocyclizations. In this case, the proper design of the reagents permitted to have a positive template effect rendered by the leaving groups of the macrocyclization reaction (Entry 6, Table 3). With this approach, the chemical waste is not necessarily increased due to additional amounts of catalysts. Moreover, the desired macrocycle was isolated without the need of chromatographic protocols, drastically reducing the solvent waste generated.

In a similar fashion to hydrogen bonds, halogen bonding has also been used as driving force for template-assisted macrocyclizations. For example, macrocycle **27** could be obtained in excellent yields at relatively high concentrations (Entry 7 in Table 3) using iodoperfluorophenyl ethers as catalysts.

All these results indicate that, although introducing additional supramolecular derivatization shall result in increased waste and the need of demanding purification protocols, the overall environmental impact of the macrocyclization can be surmounted as result of the higher concentrations, selectivities, and yields enabled by the presence of adequate templates.

2.5. MEI in flow-assisted macrocyclizations

Continuous flow chemistry has emerged as a potential tool to increase the efficiency in the synthesis of complex molecules while reducing the environmental impact in comparison with the batch synthetic processes.[52,53] Albeit the exceptional opportunities offered by continuous flow processes, macrocyclizations under continuous flow conditions are still barely exploited.[11,13,54] The success of this seldom explored approached relies on the precise control of reagent concentration *via* static mixers, the use of supported reagents and catalysts, and the superior heat and mass transfer only achievable under flow conditions (Fig. 5).[55]

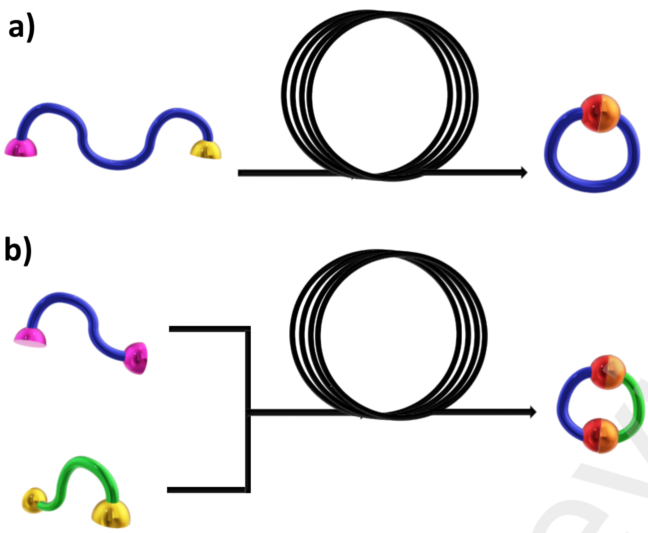

Fig. 5 General schematic representation of flow-enabled macrocyclizations. a) Intramolecular. b) Intermolecular.

To evaluate the suitability of flow chemistry as an enabling tool in macrocyclizations, MEI, Emac, and E-factor values have been calculated for some selected continuous-flow macrocycle syntheses and compared with those obtained under batch conditions (Table 4). In most of the cases, the MEI score decreased when the macrocyclization was performed under continuous flow conditions, independently of the type of transformation considered. This can be related, even when low concentrations were used, with the higher productivity generally achieved under flow. Only the case for compound **34** (Entry 7, Table 4) rendered a higher MEI score under flow than that using batch conditions, most likely due to the larger volume of the reactor used under flow conditions.

Although the productivity and the Emac can both be indicative of macrocyclization efficiency, especial attention should be paid to entries 1, 3, and 9 (Table 4). In these examples, the batch macrocyclizations scored higher Emac values than the flow protocols, mainly because of the higher yields obtained. However, the productivity values infer that the macrocyclization reaction is one (or two, in the case of macrocycle **26**) order of magnitude more efficient when performed in continuous flow. This is a result of the shorter reaction times required, leading to lower MEI values than those obtained for the batch processes. In terms of the E-Factor, flow protocols reduced the waste generated in the vast majority of macrocyclizations studied. Again, the MEI value can be used to discriminate in cases where the E-factor takes similar values. For instance, macrocycle **28** (Entry 1, Table 4) was synthesized using the two alternative approaches (batch vs flow) under similar conditions with comparable yields (ca. 75%). However, the higher productivity obtained for the flow process led to a much lower MEI value, indicating that the flow process is more efficient in terms of macrocycle production and environmental implications.

Table 4 Macrocyclization environmental efficiency (MEI) calculated for different reported continuous-flow systems according to Eq. 1.

Entry	Comp.[a]	Reaction type		Method	Conc (mM)	Yield (%)	Productivity (g_p/L·h)[b]	Emac	E-Factor	MEI (g_w·L·h/g_p^2)
1 [56]	**28**	S_N2	Intermolecular	Batch	13	76	0.236	6.8	159[c]	673.7
				Flow	12	74	10.057	6.7	164[c]	16.3
2 [57]	**29**	Glaser-Hay	Intramolecular	Batch	24	30	0.913	5.8	390[c]	427.2
				Flow	24	52	1.267	6.5	289[c]	228.1
3 [12]	**30**	Glaser-Hay	Intramolecular	Batch	24	81	1.037	7.1	167[c]	161.0
				Flow	24	91	4.400	7.3	151[c]	34.3
4 [58]	**31**	Glaser-Hay	Intermolecular	Batch	2	20	0.038	4.2	16748[c]	440736.8
				Flow	1	21	0.200	4.0	34753[c]	173765.0
5 [59]	**32**	Amide bond	Intramolecular	Batch	10	17	0.041	4.7	4071[c]	99292.7
				Flow	3	68	24.391	6.0	2206[c]	90.4
6 [60]	**33**	Azide-alkyne	Intramolecular	Batch	17	52	3.946	6.4	14652[c]	3713.1
				Flow	17	73	18.313	6.8	209[c]	11.4
7 [61]	**34**	Azide-alkyne	Intramolecular	Batch	24	95	0.553	7.3	112[c]	202.5
				Flow	50	83	0.154	7.5	59[c]	383.1
8 [62]	**35**	Imination	Intermolecular	Batch	154	83	0.271	7.9	41	151.3
				Flow	50	95	51.000	7.6	159	3.1
9 [63]	**26**	S_N2	Intermolecular	Batch	2	82	0.252	6.0	1030	4087.3
				Flow	2	69	2.977	5.8	155	52.1

[a] The macrocyclic structures have been summarised in Fig. 2. [b] Calculated considering the concentration, time, and yield reported. [c] The waste generated during the chromatographic purification has not been considered in the waste calculation due to lack of information. Colour code: MEI >5000 (light red, enormous environmental impact), MEI 1501-5000 (orange, high environmental impact), MEI 151-1500 (light blue, significant environmental impact), MEI 10-150 (light green, low environmental impact), MEI <10 (green, minimal environmental impact

In a similar manner, according to the E-Factor values, the flow synthesis of macrocycle **32** only promoted a *ca*. 2-times improvement in comparison to the batch analogue. Nevertheless, if one takes into account the productivity enhancement under flow conditions, it becomes evident that the reaction is clearly more environmentally respectful when performed under continuous flow (MEI three orders of magnitude smaller, Entry 5 in Table 4). A similar scenario is found in Entry 8. In spite of the lower concentrations used under flow conditions, the macrocyclization productivity is more than 2 orders of magnitude higher than for the related batch synthesis, leading to an astonishing decrease in the MEI score.

3. Conclusions

We have scrutinized several macrocyclization reactions to highlight how different strategies and enabling tools can be used to reduce the environmental impact of these reactions. In general, macrocyclization reactions promote enormous amounts of chemical waste because of the high-dilution conditions generally involved. A simple metric that allows quantifying in a simple fashion the macrocyclization environmental impact has been introduced and validated. Several macrocycle syntheses have been studied with this novel metric, comparing the scores with well-established environmental and efficiency metrics such as E-Factor and Emac.

The analysis of the MEI values allows to suggest the right direction to reduce the environmental impact of the macrocyclization processes: i) selection of the best reaction type and catalysts for the desired transformation. Ring-closure metathesis (RCM), Ugi-like, and click reactions are among the greenest synthetic methodologies; ii) generally, the use of sophisticatedly preorganized reagents leads to higher macrocyclization efficiencies, reducing the waste generated; iii) in the systems where the reagents cannot be properly oriented for macrocyclizations, templating agents can be envisioned as a useful tool. Although this additional supramolecular derivatisation can also contribute to increase the waste, the macrocyclization selectivity enhancement reduces the overall waste produced. The ideal templated-macrocyclization would be a system where the macrocyclization step releases active templating agents in the reaction course; iv) to explore flow processes for macrocyclization reactions. This approach can not only facilitate a macrocyclization efficiency enhancement, while reducing the environmental impact, but it can also enable a simple conditions optimization and scale-up.

All these novel techniques generally result in remarkable MEI values, mainly because of the higher productivities and reduced chemical waste attained in the syntheses. Besides, in the cases where Emac and E-Factor do not permit a clear scrutinization between macrocyclizations, the MEI metric has been proved as a powerful tool for easily evaluating such reactions.

CRediT authorship contribution statement

Conceptualization: F.E., E.G.V.; Methodology: F.E., E.G.V; Validation: F.E.; Formal analysis: F.E., B.A., S.V.L., E.G.V; Investigation: F.E., E.G.V.; Data Curation: F.E.; Writing original draft: F.E.; Writing – editing: F.E., B.A., S.V.L., E.G.V; Visualization: F.E., E.G.V..; Supervision: E.G.V.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgements

This work was financially supported by the projects UJI-B2019-40 and UJI-B2021-31 (Pla de Promoció de la Investigació de la Universitat Jaume I), AICO/2021/139 (Generalitat Valenciana), and RTI2018-098233-B-C22 (FEDER/Ministerio de Ciencia e Innovación – Agencia Estatal de Investigación).

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