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A Predictive machine-learning model for propagation rate coefficients in radical polymerization†

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Using a ridge regression, the propagation rate coefficients for radical polymerization are correlated with basic molecular properties. These are either available from literature, or from simple and non-time-consuming calculations. Parameters under consideration are molecular weights, boiling points, and dipole moments. The model is applicable to both acrylates and methacrylates with linear and branched structures, as well as monomers that are known to be influenced strongly by H-bonding, allowing to fit all data in a single approach. The model also successfully correlates monomers such as styrene and acrylonitrile. Absolute rate coefficients, as well as Arrhenius activation parameters can be described with good accuracy. With the presented model it is thus possible to describe practically all monomers for which kinetic data is available simultaneously and to carry out predictions for monomers for which no experimental data exist.

Introduction

The correct assessment of reaction kinetics, and the determination of reliable rate coefficients for reactions is often tedious and requires sophisticated methods.[1] This is especially true for kinetic rate coefficients in radical polymerization. In polymerizations, to make it more complicated, rate parameters do not merely predict the rate of a polymerization. They also play a crucial role in the design and synthesis of novel materials since individual reaction rates influence the structure of a polymer. A meaningful prediction of monomer conversions, molecular weights, and polymer dispersities is only achievable if reactivity information of the monomers can be correlated with the rate coefficient of chain propagation and termination at minimum.[2] The invention of the pulsed laser polymerization - size exclusion chromatography (PLP-SEC) method 35 years ago marked a turning point in investigations in polymerization kinetics by providing highly reliable measurements of

propagation rate coefficients in a comparatively simple fashion.[3] Over the years, a number of monomers has been investigated by this technique, and IUPAC working groups have benchmarked data for a number of important monomers.[4] PLP-SEC allows for determinations with relatively high precision – typically an error of 10 to 20% is estimated. Yet, no unifying approach exists to date that correlates the structure of a monomer with its rate of propagation, and therefore no meaningful prediction of kinetic data can be made. Within specific families of monomers, most notably the (meth)acrylates, some trends are known.[5] For example, the – on first glance counterintuitive to most chemists – increase of the propagation rate coefficient (k_p) with the length of the ester side chain. Yet, already smaller differences in structure such as branching *vs.* linear ester chains are not captured in the literature.[6] The traditional way to predict k_p is to use high level *ab initio* quantum chemical calculation.[7,8] While by themselves highly interesting, these calculations have for some monomers confirmed experimental values, but they struggle to make absolute predictions.

It is largely known that the propagation rate coefficients of monomers depend on a series of factors. Molecular weight is certainly important. Similarly, resonance stability of the propagating radical plays a major role. Also, H-bonding has been identified to cause significant rate effects and polarity is speculated to impact k_p.[9] These effects have, however, always only been investigated as insular effects, and no general theory could so far be formed that would unify all different aspects in

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one approach. Part of this issue might be that in the classical approach, physical chemists look for scientific understanding rather than for a correlation or pure association.[10] In complex interdependent systems, this can be a difficult endeavour since accurate data is often difficult to find, and actual causations might not be obvious. Association is much simpler to establish though *via* purely statistical approaches. Machine-learning (ML) harnesses this relative simplicity to predict complex behaviour of systems.[9,11,12] Hence, the question could be raised if it is possible to correlate complex propagation rate coefficients with fundamental and readily available information of monomers without the attempt to establish exact equations reflecting the underpinning processes. If such an approach was successful the resulting correlation can ideally be used to reach a better theoretical understanding. More importantly though, if statistical association is successful (without necessarily identifying the underlying causal mechanism), then rate coefficients would in principle become predictable. Propagation rate coefficients provide an ideal scenario for testing this hypothesis since relatively accurate coefficients are available for a series of molecules. In the following, we discuss if these kinetic rate coefficients can indeed be predicted on a purely statistical basis rather than using high level *ab initio* calculations using transition state theory. It should be mentioned that very recently, work has been published that follows a in principle similar approach using DFT calculations of features, which underpins the validity of our methodology.[13] In that work, the biggest difference to our approach is, next to using only computational data rather than including physical properties as features, that experimental k_p from different temperatures is directly fitted, while we use the evaluated Arrhenius parameters per monomer, hence averaged values. This reduces the size of the available dataset in comparison, which has the effect that while we work from a statistically more robust databasis, larger errors are received in the regression models, since relative errors of the regressions are correlated with the number of datapoints processed. This is a particularly important difference since an IUPAC working party recently demonstrated that not the amount of available data per monomer is determining its accuracy, but rather the number of different labs providing data.[12]

Results and discussion

Scientific discovery *vs.* scientific understanding

Ab initio methods, as much as all other chemical approaches to understand the structure property relationships of propagation rate coefficients have to date been based on an accurate calculation of specific influences, based on quantum chemical methods, or based on equations that directly relate properties based on physical laws. In our current approach we have turned this approach upside down. Rather than understanding relationships and correlations on the basis of physical understanding, we aimed to identify correlations purely based on statistical methods. As such, the tool we describe address pure

scientific discovery, as outlined in a recent perspective.[9] In this approach, a deeper understanding for the reason of correlation of parameters is *per se* not required. However, once correlations are established, this information can be used to infer new scaling laws, eventually leading to a better physical understanding. As for the basis of correlation, we have chosen physical properties of monomers that can be easily measured[14] or calculated by simple means. The aim is hereby to provide a framework that is as simple and accessible as possible.

Training data and initial feature selection

Any statistical model approach requires a dataset that can be used to train a model. As mentioned above, k_p is ideal since the IUPAC has benchmarked rate coefficients for a series of monomers.[4] k_p data for these monomers can be assumed to be fairly accurate.[15] In fact, recently an online database was established that allows to retrieve these coefficients directly.[16] In order to benchmark a monomer, IUPAC typically requires more than one laboratory to provide data. In addition, several laboratories have provided sole PLP-SEC data that can still be regarded as fairly reliable. We collated data for close to 40 monomers that we deemed reliable (it should be noted that the IUPAC also defined reliability criteria that make such selection possible). We omitted acidic monomers, since it is known that they are governed largely by pH, and hence are outliers in the complete set of available data.[17] Most data is available for the monomer families of acrylates and methacrylates. It is known that these monomers can be correlated within their respective families, allowing for some inference from one family to the other. All other monomers have no known quantitative correlation, even though it is common knowledge that radical stability plays a major role in predicting their reactivity. A full list of monomers and their respective values in Arrhenius form are given in the ESI.† For the sake of this work in this study, four distinct groups of monomers have been identified, these being as described above (i) acrylates, (ii) methacrylates (iii) monomers exhibiting strong H-bonding effects and (iv) 'others', such as the important monomer styrene. When considering monomers in radical polymerization, several molecular properties, in the following referred to as 'features' in line with data science terminology, are obvious to consider. It is known from literature that polarity is an important quantity that has direct influence on propagation kinetics. Thus, the dipole moment of the monomer is of general interest. Note that experimental data is mostly available for bulk polymerization, hence where the polarity of the monomer concomitantly influences radical reactivity and the solvent environment. Further, the length of ester side chains in (meth)acrylates are known to at least indirectly correlate with k_p.[5] Thus, molecular weight was added as a further feature. Already when collating experimental data on dipole moments, it is unfortunately evident that gathering such data is by far not trivial, and generally leads to scattered datasets. To solve this issue, we decided to include calculated data as features in our analysis. To this end, we used the General Atomic and Molecular Electronic Structure System software

package (GAMESS, version: 2018, R1). interfaced with the software ChemDraw 3D, and used also data provided by ChemSpider, and the ACD/Labs Percepta Platform - PhysChem Module predictions listed therein. *Via* GAMESS, we accessed dipole moments, boiling points, melting points and Gibbs free energies for each monomer under investigation (relative to ethylene as the simplest radically polymerizable monomer possible), using a low-level HF calculation method. ChemSpider provided some experimental data on boiling points and refractive index, and predictions for the same, plus predictions for surface tension and polarizability. Comparison of calculations with available experimental values showed that the theoretical values are certainly not perfect when examining absolute values, but are reasonable when comparing series of monomers with each other.

An important point is that we used literature data on Arrhenius relations rather than absolute measured k_p's. Hence, for each monomer, we use an overall averaged parameter stemming from a series of experiments, partially from experiments across several research groups. This makes the k_p data for each monomer statistically very robust and minimizes the experimental error. For the sake of practicality, we did all initial correlations on k_p values calculated for 25 °C from the Arrhenius parameters. Later we then demonstrate how also the Arrhenius parameters themselves can be correlated and predicted.

Methodology

Various machine-learning algorithms were initially tested to treat the available data, such for example a random forest. Yet, not enough datapoints are available to make use of such more advanced methods. Thus, data was fitted *via* multivariate linear regression, which is a combination of multiple linear regressions on independent variables for one dependant variable. Specifically, fitting was performed by regularised least squares, *i.e.*, by minimising the sum of squared errors plus a positive regularisation term that penalises large regression coefficients and, thus, avoids overfitting. This term is either the sum of squared regression coefficients (ridge regression) or the sum of magnitudes of the regression coefficients

(LASSO regression), in both cases multiplied by a tuneable hyper-parameter λ (see ESI†). This parameter is used to calibrate the degree of flexibility of the model to fit a set of training data. When λ increases, the model bias increases and the model variance decreases. In this context, bias describes how well a model tends to match a data set, whereas variance describes how much a model tends to change when it is trained with a different training set. The sum of the squared bias and the variance determines the expected squared error of a model (averaged over all possible training sets and independent test points). To choose an optimal λ and to perform overall model evaluation with limited data, unbiased model error estimates where obtained using leave-one-out cross validation (LOOCV). In an outer LOOCV, the model was fitted n times, each time using n-1 monomers as training data and the remaining monomer as test point. An overall scaled squared error estimate (r^2) was obtained through the average squared error across these n model fits. Similarly, an inner LOOCV was performed to determine an optimal λ for each training set. The resulting nested cross validation scheme (Scheme 1) uses n times n-1 model fits to obtain an overall unbiased performance estimate for the model when refitting it with all available data (and again using a LOOCV for choosing λ). Fitting and performance estimation were performed for a number of increasingly complex models (sets of dependent variables) as outlined below. It should be noted that this procedure yields in principle a prediction for each monomer under consideration, hence predicted values can be compared to experiments. All following figures use this comparison to demonstrate the quality of regressions. It is noteworthy to add that some monomers will be better represented by certain models. This can occur because the regression model tends to predict certain types of monomers better than others – or be a simple coincidence. It is thus important to evaluate the total r^2 of a fit rather than single values in order to avoid overinterpretation of the results.

Visualizing the state of the art

Before describing the regressions on the complete feature set, it is worthwhile to examine the state-of-the-art in predicting
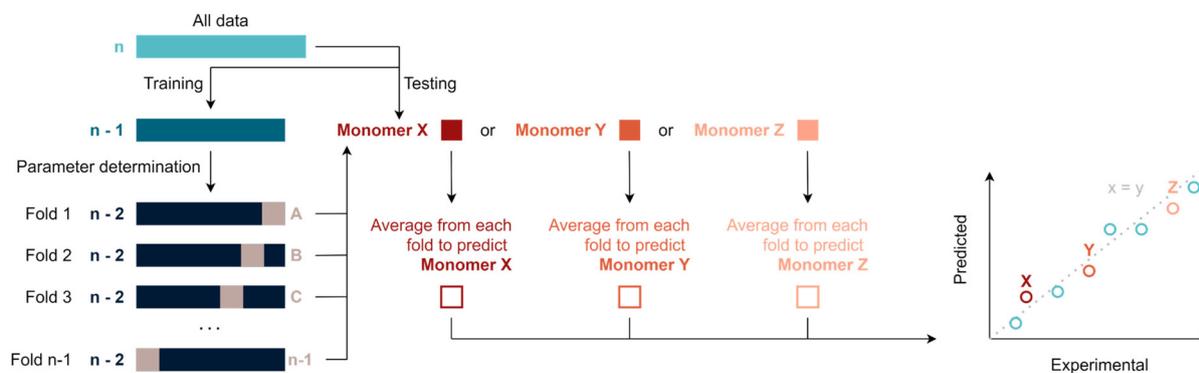
Scheme 1 Overview of the nested leave one out cross validation (LOOCV) approach for hyper-parameter selection and overall evaluation of the regression model.

propagation rate coefficients. Two influences are known with fairly high accuracy, that is that the propagation rate coefficient increases with the length of the ester side chain in (meth)acrylates; and acrylates propagate up to a factor 100 faster than methacrylates. For all other monomers, no clear correlation has to date been quantified. Thus, in principle, for acrylates and methacrylates individually linear regressions with molecular weight can be carried out. Based on literature assumptions, this should yield some predictivity. Indeed, when plotting experimental k_p as a function of molecular weight, a slight tendency towards increasing molecular weight can be observed. The overall correlation is, however, less than satisfactory. This is due to the list of monomers containing examples that have branched side chains, or that are associated with H-bonding. Nonetheless, this simplistic model can be used to derive a more general visualization of data. Using the LOOCV method, individual k_p was predicted for each linear acrylate and methacrylate. For this, we fitted each group of monomers individually as would classically be done. This results in a predicted value for each of the monomers. This residual, predicted value is then plotted against its measured value. Ideally, if the experiment was error free and if the prediction was 100% accurate, a linear plot with the slope of 1 should be observed. The sum of squares of this line can hence be used to quantify the predictivity of the underlying model used. The outcome of this data procedure is shown in Fig. 1. It should be noted that for all predictions, the logarithm of k_p was used rather than its actual value; this prevents the model from predicting non-physical negative values. As can be seen from the figure, the linear regression representing the state of the art basically predicts two plateaus, one for methacrylates and one for acrylates. Rather than predicting an increasing k_p with molecular weight, it thus results in not more than a rough average per monomer group. This shows that the perceived correlation between ester side chain length and k_p of

each monomer is not statistically robust (while not necessarily wrong). It cannot be used to predict any unknown propagation rate coefficient from a statistical point of view. This is, taking the large scatter of data into account, not really surprising.

Coming from this rather sobering result, we then extended the feature set of the regressions, taking all available physical properties into account, hence molecular weight, dipole moment, melting and boiling point and Gibbs free energy values. The outcome of such prediction is given in Fig. 2. As can be seen, no correlation is obvious and the plot seems almost random. Hence, we moved forward by adding further information to the feature set. To achieve this aim, we first broke the number of datapoints down, and isolated the (meth) acrylates from the list. Then, we introduced a binary differentiation for acrylates (one) and methacrylates (zero), see Fig. 3a. This alone lead to a reasonable representation of data, showing that the calculated physical properties of monomers have a positive effect, and are aiding in the prediction of rate coefficients. However, several difficulties remained. For example, hydroxy ethyl acrylate was not appropriately predicted. Also branched monomers, while improved compared to the state-of-the-art representation in Fig. 1, still showed significant deviations. To solve these issues, the feature set was extended by two parameters. One parameter described the inductive effect of the side chain, the other quantifies H-bonding between monomers (see ESI for details†). For both effects, literature was screened, and property tables provided by quantum mechanical calculation were used.[18,19] It should be hereby noted that H-bonding is not easy to quantify, and only the presence of major functional groups was accounted for. Despite the shortcomings of this process, a very good prediction is obtained in this way. Fig. 3a depicts the case fitting of acrylates and methacrylates without inclusion of strongly H-bonding monomers. It should be noted that both LASSO and Ridge regressions yield similarly reasonable results, while conventional linear regressions perform significantly less well. Nonetheless, the r^2 value of the plot shown in Fig. 3a is 0.991, underpinning its overall high quality. Statistical analysis of the
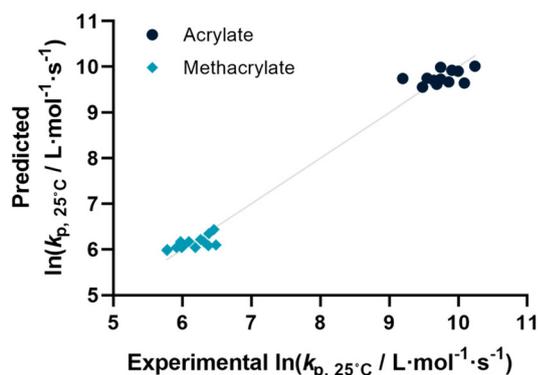

Fig. 1 The predicted *versus* experimental values of the ln(k_p) at 25 °C for a dataset containing only meth(acrylates) using the leave one out cross validation on a linear regression. Predictions are determined using a binary indicator whether the monomer is an acrylate (black) or methacrylate (turquoise) and only molecular weight as feature to represent the state-of-the-art in non-ML k_p predictions (r^2 = 0.980, RMSE = 0.206).
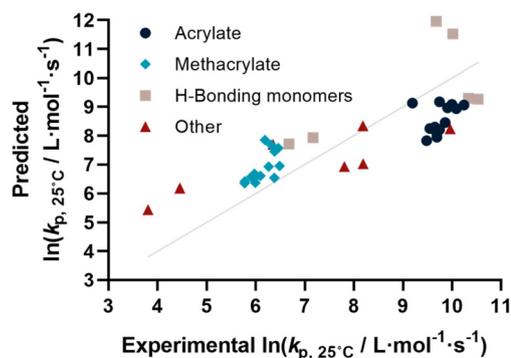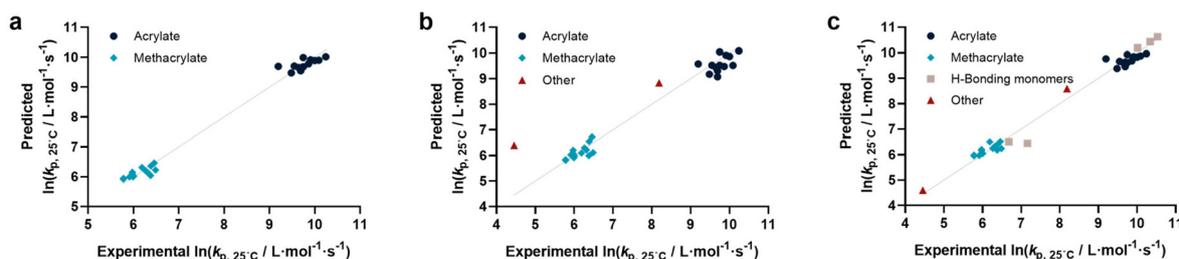

Fig. 2 The predicted *versus* experimental values of the ln(k_p) at 25 °C for a dataset n = 41 using the leave one out cross validation on a linear regression. Predictions are determined using Mr, inductive effects, DP, BPK, MPK, and GFE (r^2 = 0.631, RME = 1.167).

Fig. 3 (a) Comparison of predicted *vs.* experimental ln(k_p) for isolated acrylates and methacrylates (r^2 = 0.991, RMSE = 0.174), (b) after inclusion of non-meth(acrylate) monomers (r^2 = 0.940, RMSE = 0.460) and (c) all monomers using available data (r^2 = 0.985, RMSE = 0.227).

LASSO regression shows that either the melting point or the boiling point can be used, both information is not required since they display high collinearity. The same was true for surface tension data and refractive index data. Both features were practically redundant when polarizability was used. All other features do contribute to the results.

Yet, when including all monomers back into the fit, also this procedure still yielded an unsatisfactory result. The obvious reason for this is that none of the features sufficiently describes resonance effects, which play a major role in reactivity of monomers.[20] Surprisingly, while qualitative orders of reactivity are obviously known for practically all polymerizable vinyl monomers, no quantitative data on the resonance stability, or radical stability could be found in the literature. The closest information that we identified were dissociation constants of macroalkoxyamines, that were determined for nitroxide-mediated polymerization from EPR spectroscopy on the alkoxyamine dissociation. At least for styrene, acrylonitrile, as well for an average of methacrylates and acrylates, numeric values could be assigned. We normalized these dissociation constants, and provide our best prediction, shown in Fig. 3b. Finally. Since this plot yielded a very reasonable fit, we then directly also included the H-bonding monomers, as depicted in Fig. 3c. Fig. 3c displays the final result of our correlation work, and all used features for the given fit are highlighted in colour in Table S3.† Again, it is an interesting observation, that correlation of H-bonding has also a positive predictive effect for example for styrene (the datapoint with the lowest overall k_p). As can be seen, both acrylonitrile and styrene (orange triangles) fall very well on the line with the (meth)acrylates. r^2 in this case is 0.986, which is a very good result considering that both added monomers have nothing in common with the other monomers in question regarding all other used features. It can be assumed that if actual data for resonance stability of propagating radicals become available for other monomers (such as vinyl acetate for example), that also these monomers can then be adequately correlated. Overall, the ridge regression analysis for weighting of the various features shows that resonance stability by far is the most important feature, overshadowing the importance of dipole moments and substituent effects. Yet, this is at the moment only a qualitative observation that needs further study. Table 1 below gives an overview on the fit parameter and relative contributions to

Table 1 Fitted regression coefficients using all data; ordered according to importance of each parameter (computed as absolute coefficient times standard deviation of variable). See Table S3† for input feature data

Parameters	Coefficients	Importance
Dissociation constant A2	−0.00676	2.203144
Molecular weight MW	0.01508	1.308853
Polarizability	−0.10046	1.120701
Dissociation constant A1	1.09465	1.038845
Inductive effect A	−0.57508	0.596737
Inductive effect of ester R	−0.13211	0.255578
Effect of H-donor H_don	−0.06727	0.096749
Effect of H-acceptor H_acc	−0.00045	0.001883

the final model. However, as stated earlier, we believe such quantitative data should be read with care at this stage (fit coefficients for the other plots see ESI†).

A further consideration is that data for some features may be more accurate than others. This can in principle be accounted for by introducing a weighting for each individual feature to force the regression to put more emphasis on these features. We found though that doing this reduced the quality of regressions overall, and indeed in machine learning this is usually discouraged in order to not introduce biases.

With this method at hand, we tested if not only individual k_p can be predicted, but also activation parameters. To this end, we calculated k_p for 25, 50, 75 and 100 °C based on reported activation energies and frequency factors. As for the 25 °C data in Fig. 3, similarly reasonable fits were obtained. For each individual monomer the predicted k_p values at the four temperatures were fitted to the Arrhenius equation, yielding a predicted Arrhenius factor A and a predicted activation energy EA. Using the same representation as for k_p, it can be shown (Fig. 4a and b) that also the activation parameters are well predicted by our model. Specifically, E_a is represented very well, while ln(A) shows some more scatter. This scatter is a result of the sensitivity of A on small variations in E_a and correlates with the typically also higher scatter of experimental data for this value. This approach may appear somewhat indirect. In principle one can also directly correlate E_A and A with our methodology. However, this would require a simultaneous regression of both parameters, since A and E_a are highly interdependent. If fitted individually for E_a, a reasonable direct correlation is found, yet not for A. The approach to
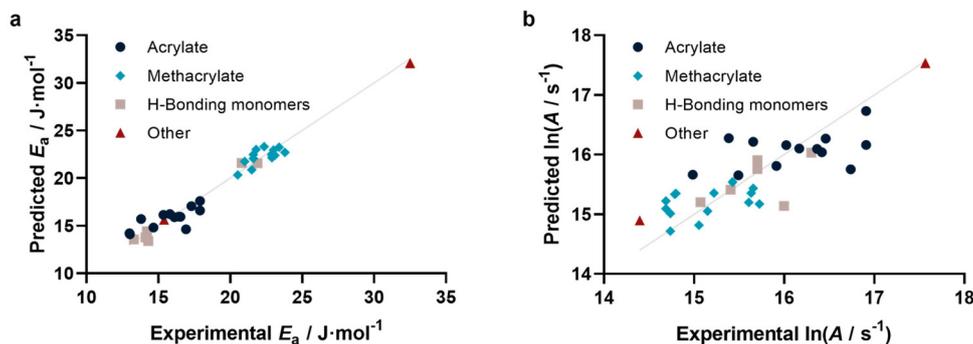
Fig. 4 (a) Activation energies ($r^2 = 0.963$, RMSE = 0.823) and (b) Arrhenius factors ($r^2 = 0.666$, RMSE = 0.427) determined from prediction of individual k_p at four different temperatures.

determine both values *via* individual k_p's' is hence more successful and reliable. Fig. 4a and b depict the activation parameter correlation.

From correlation to prediction

Until this point we only demonstrated that the data can be successfully correlated. Of course, the aim of any such investigation is to predict rate coefficients for monomers for which no experimental k_p data is available. With the good correlation demonstrated in Fig. 3c, predictions of rate coefficients should be possible as long as the unknown monomer largely falls into a similar category as the training data, *i.e.* doesn't feature exotic functional groups or represents a monomer with very different radical stability. Since practically all features in our model are based on calculated features, it is fairly straight forward to include further monomers into the list. As monomers in question we chose ethyl acrylate, propyl acrylate, cyclohexyl acrylate and propyl methacrylate. Arguably, the rate coefficients of these monomers are fairly simple to predict with ballpark figures even without advanced regression models. It is known that propagation rate coefficients increase generally with the size of the ester side chain for both acrylates and methacrylates, and reference data are available for the corresponding methyl and butyl (meth)acrylates. While the predictions made thus seem to be not too ambitious, they provide a reasonable test in order to see if the regression model can produce numbers within expectations. All ML-predicted k_p values are given in Table 2 alongside errors derived from the overall r^2 of the fit in Fig. 3c.

Table 2 Model predictions of propagation rate coefficients and their standard deviation for monomers for which no experimental k_p data is available. Predictions are based on the data shown in Fig. 3c (rounded to the next tens)

Monomer	k_p(25 °C)/L mol^{-1} s^{-1}
Ethyl acrylate	9300 < 13 210 < 18 770
Propyl acrylate	9540 < 13 560 < 19 260
Cyclohexyl acrylate	10 260 < 14 570 < 20 700
Propyl methacrylate	270 < 390 < 550

As a first observation of the data in Table 1, one can see that qualitatively the order of predicted propagation rates in the acrylates is correct, based on what is generally known about the behaviour of k_p with increasing side chain lengths.[5] A slight increase in rate for the ethyl to the propyl acrylate is seen, while the cyclohexyl acrylate monomer exhibits the highest rate coefficient. For both the acrylate and methacrylate the correct order of magnitude is predicted (which is, given the large number of monomers used in the correlation from these two families not surprising). Starting from the experimental propagation rate coefficients for methyl and butyl methacrylate, a k_p between 323 and 370 would be expected. The value for propyl methacrylate is very close in the range of expectations. Given that size-exclusion chromatography, which is key to experimental k_p determinations is commonly associated with an error of up to 20%, this match is exceptionally good, and outperforms any prediction based on *ab initio* calculations provided so far. For the acrylates, using the same comparison, a k_p between 13 130 (methyl acrylate) and 16 380 (butyl acrylate) would be expected. Again, the predictions made by our regressions meet this range. For cyclohexyl acrylate, the produced value seems also to be a reasonable estimate when compared to early PLP data provided by Tanaka *et al.*, who found that cyclohexyl k_p is similar to that of butyl acrylate.[21] It will be interesting to see in the future if these values will be confirmed by experiments. The error limits given in Table 1 are rather large, and disparate towards higher and lower values. This is due to predictions being made on a log scale. The overall error estimate is probably rather conservative, and reflects also the error in all used training data, which of course is not absolute at all. Regardless, we have made our Python script for the prediction available *via* the github platform, so that other researchers can make their own predictions based on need.

Conclusions

The predictions made based on the model presented herein may not be able give a 100% accurate representation of small effects such as ester side chain length, yet they provide very reasonable data that can be used for future work. Accuracies

are within standard error limits of experimental determinations, and relative effects are accurately predicted. With the exception of the predictions presented by Shi *et al.*,[10] no prediction of k_p values with the same accuracy by any other theoretical method has to date been provided. With increasing data coming available from experiments, and potentially with further refinement of feature calculations, we hope the accuracy of our method can be further refined in future work. The match of data currently seen for monomers with available experimental data on boiling points should be extendable to the full dataset. Generally, it is remarkable that only very little experimental data input is required in all predictions. We suggest that radical stability should be probed experimentally and theoretically in order to provide more valuable data that can refine the machine learning approach in this work. We envisage that in future a full predictivity with even higher accuracy will become available, allowing researchers to simply dial in a monomer and to obtain an accurate estimate of k_p. We also believe that with further data it will become possible to predict k_p in a broader monomer space, and not only (meth)acrylates as done in here. Further the presented methodology also allows to refine data for monomers with existing experimental data, since the LOOCV method allows for averaging over the entire monomer space compared to 'only' fitting data for each single monomer by itself.

Regardless of the predictivity of the regressions, this work marks an important point for full correlation of complex kinetic rate coefficients with chemical structures and their basic physical properties. Machine-learning, even in its simple form of sets of regressions as used in here, has tremendous potential for simple, and readily available predictions of kinetic data. It should be noted hereby that the performed predictions occur within seconds, and can be easily implemented in kinetic modelling codes in the future.

The code used in this work is made available *via*: **https://github.com/PRDMonash/kp_predictor.**

Author contributions

EvdR performed most of the research, developed the used software, took care of data curation, revision of the manuscript and methodology development. NM contributed significantly to earlier software versions and data curation. JS gave guidance, aided in methodology and edited the manuscript. MB was involved in supervision, methodology development and editing the manuscript. TJ came up with the initial concept, provided project administration and supervision, wrote the original draft and edited the final version.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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