

Peer Review File

Manuscript Title: Electron-catalysed molecular recognition

Referee #1

- This manuscript by Stoddart and coworkers demonstrates, for the first time, that electrons can be used to catalyse non-covalent reactions. This is a fundamentally new type of catalysis, and the idea is novel enough to justify publication in Nature. The logic behind the research is very clearly presented and the mechanism of catalysis is beautifully elucidated by considering a catenane as a model for the analogous rotaxane. It is particularly interesting that the catalysis can be achieved using a wide range of reducing agents (CoCp₂, TDAE, Mg, Al, Zn, Fe) in substoichiometric amounts, and also that the rate of the non-covalent reaction can be controlled electrochemically.

Reply

- We appreciate the positive evaluation on our manuscript from this referee — particularly his / her recognition of the novelty of the research.
- One suggestion for improving the manuscript: it would be interesting to estimate the turnover number. How many moles of product can be formed per mole of electrons?

Reply

- We thank the referee for this suggestion. Based on the kinetic data, the turnover number (TON) has been estimated to be 13 — in other words, each mole of electrons is able to catalyse the formation of 13 moles of trisradical complexes. Notably, during the kinetic measurements, we cannot prevent completely ambient O₂ from intruding and penetrating slowly into the solution. This technological shortcoming weakens and even quenches the catalytic effect of electrons, particularly in the case of the long-time molecular recognition process catalysed by a tiny amount of electrons. As a result, the theoretical value of the TON should be larger if O₂ can be completely eliminated during the spectroscopic measurements. That being said, the TON value of this process is still modest, possibly resulting from the excessive stability of the catalytic intermediate. We are currently developing more efficient electron-catalysed molecular recognition systems involving less stable intermediates, so as to increase the TON.

The estimation of the TON value, as well as pertinent discussion, has been included in the Section 4.4 (Page S24–S26) of the revised Supplemental Information, which is also reproduced below highlighted in red text.

4.4 Estimation of the Turnover Number

Based on the kinetic data obtained by UV/Vis/NIR spectroscopy, we calculated the turnover number (TON) of the electron-catalysed molecular recognition between $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$. During the kinetic measurements, O_2 was found to penetrate slowly into the solution and oxidize the BIPY⁽⁰⁾ units. As a result, the catalytic effect of electrons is gradually weakened and even quenched as time goes on. This happening, which is non-negligible for long-time molecular recognition processes catalysed by a small number of electrons, renders it difficult to determine accurately the TON value. Therefore, a lower limit of TON was estimated using the yield of the $[\mathbf{D}\mathbf{C}\mathbf{R}]^{+3(\bullet+)}$ triradical complex after a moderate time (70 min), according to the following formula:

$$\text{TON} = \frac{c(\text{Com})}{c(e^-)} = \frac{A_{1080,70\text{min}}}{\epsilon_{1080} \cdot l \cdot c(e^-)}$$

wherein $c(\text{Com})$ is the concentration of the $[\mathbf{D}\mathbf{C}\mathbf{R}]^{+3(\bullet+)}$ triradical complex at 70 min and can be determined from the absorbance of the solution at 1080 nm, while $c(e^-)$, the molar concentration of injected electrons, is approximately equal to that of CoCp₂. The estimated TON values under different conditions are summarized in **Supplementary Table 3**.

Supplementary Table 3 | The estimated values of the turnover number (TON) for the electron-catalysed molecular recognition processes under different conditions

Conditions	$c(\text{Com}) / \mu\text{M}$	$c(e^-) / \mu\text{M}$	TON
1 mol% CoCp ₂	19.5	1.5	13
2 mol% CoCp ₂	33.5	3.0	11
4 mol% CoCp ₂	56.1	6.0	9
8 mol% CoCp ₂	54.9	12	5

In the case of 4 and 8 mol% CoCp₂, the TON values are relatively small, because the yield of the [DcR]^{+3(•+)} triradical complex is limited by the thermodynamic equilibrium between substrates and complexes. In the case of 1 mol% CoCp₂, the TON was estimated to be 13, i.e., each mole of electrons is able to catalyse the formation of *at least* 13 moles of the [DcR]^{+3(•+)} triradical complex. The modest value of TON, not only reflects the quenching effect by O₂, but also results from the excessive stability of the catalytic intermediate, i.e., the [DcR]^{+2(•+)} bisradical complex, which inhibits the completion of catalytic cycles. Further efforts need to be made in order to develop more efficient electron-catalysed molecular recognition systems involving less stable intermediates, so as to increase the TON value.

- On the whole, the manuscript is very well written, but the authors should avoid using the term “chemical reaction” to mean exclusively “covalent transformation”. Non-covalent reactions are “chemical reactions” too. This comment applies to the last line on page 1, line 19 on page 3 and the text in Figure 1. (Also, on page 2, line 18, change “difficult to be obtained” to “difficult to obtain”.)

Reply

- We thank the referee for raising this particular issue. We have changed the term “chemical reaction” to “covalent reaction” in both the main text and in Fig. 1 (now it is the **Extended Data Fig. 1**). In addition, the sentence on Page 2, Line 18 (now Line 15) has also been modified according to the advice from the referee.

Referee #2

- Summary of key results

The authors demonstrate that single electron transfer agents can be used to catalyze molecular recognition in the case of bipyridine radical cations. They also show that in an open electrochemical cell the same process takes place and that this can be used to modulate the mixture formed. The mechanism of the process is probed in detail, much of which is in the extensive supporting information, including a model catenane that

allows the authors to observe key proposed species without the complication of dissociation.

Originality and significance

The use of catalysts to accelerate self-assembly, at least systems that are explicitly identified, is rare. The authors cite a few examples, of which I don't think ref 16 is relevant. Ref 20 (in which protonation is observed to catalyze assembly) might be far more common than is currently recognized but perhaps that's one of the key things about this work – supramolecular chemists are typically focused on the equilibrium but pay less attention to the pathway and kinetics. This is becoming more important in supramolecular polymerization etc and “pathway complexity” is becoming more commonly recognized and investigated but it is still very neglected and I'm not aware of any work that is as detailed and elegant as that presented here. The concepts and methods presented have the potential to make a big impact in the field, particularly as applied in materials chemistry and systems chemistry. I think this is a very important contribution to the field, particularly given the simplicity of electron catalysis.

Data and methodology

The data is well discussed in the manuscript and is backed up by an extensive and detailed ESI. The methodology is robust and the conclusions sound. The level of detail presented is excellent.

Conclusions

The conclusions of the work are 100% supported by the data, particularly given the extensive experimental details provided, which are exemplary.

Reply

- We thank the referee for the positive evaluation of the manuscript, particularly his / her recognition of the significance of this research.

- Suggested improvements

In terms of the work presented, I have no suggested improvements. The only suggestion I have (which might be more appropriate for a follow up paper) would be to conduct the assembly experiment under irradiation with a suitable photocatalyst. This would not in itself add to the results (the photocatalyst is just another way of providing an electron source) but it would extend the utility of the concept.

Reply

- We thank the referee for this suggestion. During this piece of research, we attempted to execute the electron catalysis in a photochemical manner. The radical species in the system, both $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$, however, decomposed upon the irradiation with 450 nm light. Our ongoing research aims to extend the strategy of electron catalysis to a photostable host–guest system, so that the assembly can be conducted using chemical, electrochemical and photochemical means.

- References

The references seem complete and appropriate, apart from 16, which I'm not convinced is an example of catalysis in self-assembly (unless we are counting all memory effect type systems, in which case there will be many others to consider).

Reply

- We thank the referee for raising this issue. The Reference 16 has been removed.

Referee #3

- In the present manuscript, a new approach toward catalysis of supramolecular recognition is presented, wherein catalytic amounts of electrons, provided by chemical reductants or a cathode, are used to prepare supramolecular host-guest complexes. Macrocycles and molecular dumbbells, which are provided with one and two viologen units, respectively, serve as starting materials here. Due to the possibility to switch

between different redox states, the activation barrier for the entry of the dumbbell into the macrocycle can be lowered by adding electrons, resulting in the formation of the host-guest complex. Non-covalent interactions between host and guest are the driving forces for this process, which at the same time ensure that electrons can be spontaneously transferred from the host-guest intermediate to the reactants, thus enabling a chain mechanism.

Even though the concept was only demonstrated using a single example, a wide range of applications is conceivable and a broad impact can therefore be expected. The advantages of the approach are obvious. On the one hand, the method is not limited to a specific reducing agent, but can be carried out with a variety of different reagents. Second, electrochemical reduction can eliminate the need for reagents altogether, also providing the ability to control the concentration distribution of the components in the solution over time. The elegant concept has thus been explored using both various reducing agents and electrochemistry, with extensive mechanistic studies based on UV-Vis-NIR / EPR spectroscopy, control experiments, cyclic voltammetry, and DFT calculations supporting the hypotheses. The manuscript (illustrations, wording, etc.) is in very good condition and enjoyable to read. I therefore recommend publication in Nature after the following issues have been addressed.

Reply

- We thank this referee for recommending the publication of our manuscript and for providing insightful comments on it.

- 1) P4, 115-17: Which type of preliminary investigations have been carried out? Please specify or use a reference.

Reply

- We thank the referee for pointing out this source of confusion. The so-called “preliminary investigations” refer to the kinetic data in Fig. 3a (now **Fig. 2a**). Specifically, the molecular recognition between $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$ in the absence of CoCp_2

is almost kinetically forbidden. We have quoted **Fig. 2a** at the relevant position (Page 4, Line 1) in the revised manuscript.

- 2) P6, 16-9: On which basis has the absorption band at 1080 nm been assigned to the triradical complex? Please specify or use a reference.

Reply

- We thank the referee for checking carefully our manuscript and pointing out this omission. The assignment of the absorption band at 1080 nm is based on Reference 22 (*Nat. Chem.* **2010**, 3, 34–37). We have cited this reference at an appropriate position (Page 5, Line 12) in the revised manuscript.

- 3) Figure 3d and corresponding discussion: Can the conversion be shown instead of the absorbance?

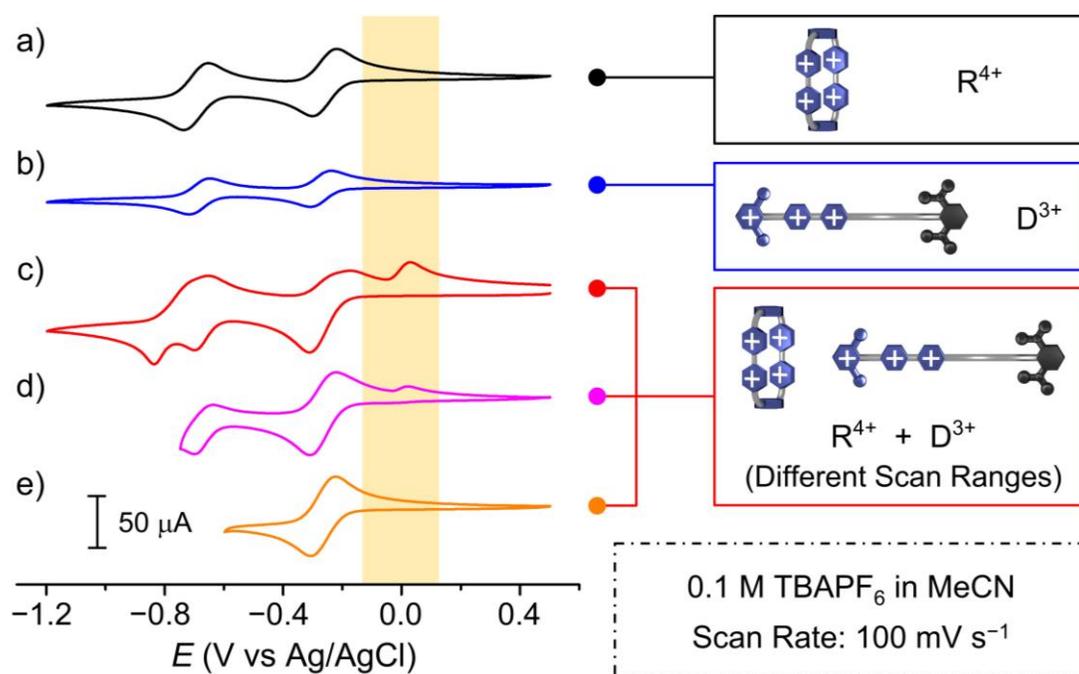
Reply

- We thank the referee for this suggestion. The Y-axis in Fig. 3d (now **Fig. 2d**) has been changed from “Absorbance at 1080 nm” to “Yield of the complex / %”. The corresponding discussions have also been modified accordingly in the revised manuscript.

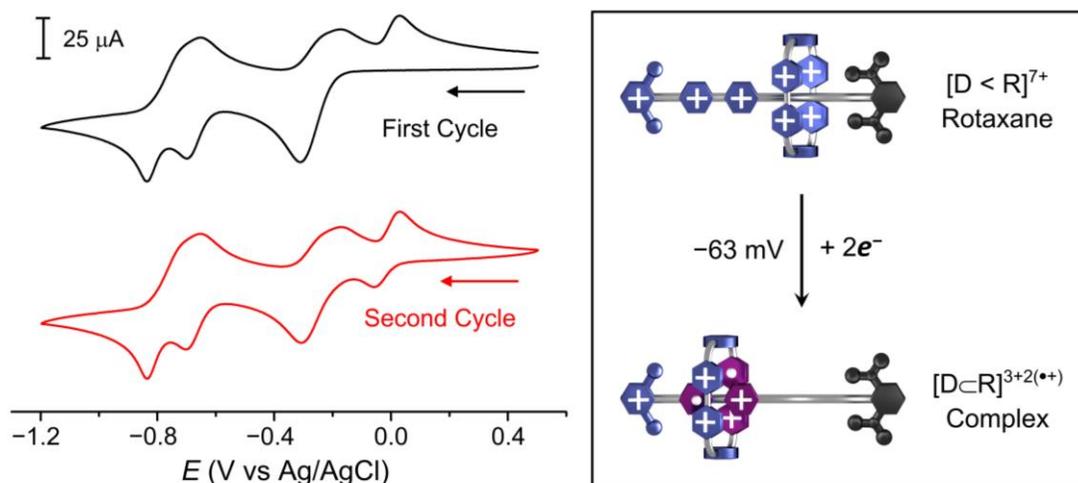
- 4) The results of the CV study are shown and discussed in the Supporting Information (Figure S13) while in the paper, it is only stated that the experiments confirm the electron-catalyzed mechanism. However, there are several issues with the CV results:
 - a) It should be indicated which cycle of the measurement is shown. This is important, since the initial reduction peak at -63 mV in Figure 13c cannot appear during the first cycle.

Reply

- We thank the referee for this piece of advice. We have added a new figure (**Supplementary Fig. 15**) on Page S35 of the revised Supplementary Information to show the difference between the first and second cycles of the CV measurements. Indeed, the reduction peak at -63 mV appears only in the second cycle, because some of the starting materials, \mathbf{R}^{4+} and \mathbf{D}^{3+} , have been transformed to a rotaxane after the first-cycle CV scan. Moreover, all the data in the revised **Supplementary Fig. 13** (Page S27) has been uniformly taken from the first cycle of CV scans, and this information has also been stated in the caption. We have included the updated **Supplementary Figs. 13** and **15** below in red for your reference.



Supplementary Fig. 13 | CV data for a) \mathbf{R}^{4+} , b) \mathbf{D}^{3+} and c–e) the equimolar mixture of \mathbf{R}^{4+} and \mathbf{D}^{3+} with different scan ranges: from $+0.5$ to -1.2 V (c), from $+0.5$ to -0.75 V (d) or from $+0.5$ to -0.6 V (e). The data were recorded at room temperature and the concentrations of all the samples were set to 1.0 mM. Each measurement includes three cycles of scan and the figure shows the first cycle.



Supplementary Fig. 15 | The first and second cycles of the CV scan on the equimolar mixture of \mathbf{R}^{4+} and \mathbf{D}^{3+} , as well as the graphical representation for the first reduction peak (-63 mV) in the second cycle. The concentrations of both compounds were 1.0 mM in MeCN solution. The scan rate was set to 100 mV s^{-1} .

- b) It would be useful to add the analyte concentrations to the caption.

Reply

- We thank the referee for this suggestion. The concentrations of all the samples used for CV measurements have been added to the figure captions.

- c) Figure S13a/b: Since the concentrations of R and D were the same (1 mM), it is unclear why their peak current densities are so similar. After all, the peaks were assigned to a 2 electron process for R and to a 1 electron process for D.

Reply

- We appreciate the detailed checking of our manuscript by the referee. We have repeated the CV measurements on \mathbf{R}^{4+} and \mathbf{D}^{3+} solutions, both at the concentration of 1 mM. Indeed, the current of \mathbf{R}^{4+} was found to be around twice that of \mathbf{D}^{3+} . Therefore, we have corrected the data in **Supplementary Fig. 13a and 13b** (Page S27 of the revised Supplementary Information), which can also be found in the reply to Comment #4a in this response letter.

- d) A discussion of the influence of electron catalysis on the voltammetry is missing. An assignment of a process to the fourth reduction peak at approx. -0.85 V that arises from the mixture of D and R should be made. Is it the reduction of the bis- or trisradical host-guest complex? Why is the peak irreversible? Release of the guest? It should be taken into account that once formed at -0.8 V, the bisradical intermediate would be capable of returning an electron to the electrode (ECEb mechanism: see ref. 35) or to D⁺ radical cation / R bisradical dication. Further experiments, e.g. scan rate variations, may be useful.

Reply

- We thank the referee for these comments and observations. As suggested, CV measurements on the mixture of **R**⁴⁺ and **D**³⁺ have been performed in variable scan rates. The redox behaviour of the system reveals a high dependence on the scan rate. We have made the assignment of each redox peak in the CV traces and presented a detailed illustration of all the events occurring over a full redox cycle. The additional experiments and related discussions have been included in the Section 5 (Page S28–S35) of the revised Supplementary Information.

In particular, in answer to the referee's question, the fourth reduction peak corresponds to the reduction from the bisradical complex to neutral species. The R and D in their neutral states have no interactions with each other, leading to the disassembly of the complex, that is to say, the release of guest molecule. Although the reduction is irreversible in the CV scan at 100 mV/s rate, we have found it to be reversible in very slow CV scans (e.g., 10 mV/s). This result indicates that the reverse process to the reduction, i.e., the reoxidation from the neutral R and D to the bisradical complex, can be only observed at very slow scan rates. This observation is reasonable, given the fact that a sufficient amount of time is required to overcome the energy barrier for the assembly of the bisradical complex from its components.

- e) A fifth measurement with a negative vertex potential at -0.8 V is recommended to exclude the possibility of the redox couple at -63 mV being linked to the process at -0.85 V.

Reply

- We thank the referee for this suggestion. An additional CV measurement scanning from +0.5 to -0.75 V has been performed, and the data is included as the **Supplementary Fig. 13e** (Page S27 of the revised Supplementary Information), which can also be found in the reply to Comment #4a in this response letter. In this case, we still observe the positively shifted peak characteristic of the trisradical complex, albeit with decreased intensity. This control experiment has excluded the possibility that the formation of the trisradical complex originates from the reduction process at -835 mV.
- 5) P7, 110 and 16: It would be useful to mention the colors of the spectra of Fig. 4b which are referred to in the text.

Reply

- We thank the referee for this suggestion. In the revised manuscript (Page 6, Lines 13 and 18), we have specified the colours of the lines when discussing the data in Fig. 4b (now **Fig. 3b**).
- 6) P11, 11-10 and Figures S37 - 39: What I miss in the treatment of possible mechanisms is back electron transfer from the bisradical host-guest intermediate to the electrode (ECEb mechanism, see comment #4d).

Reply

- We thank the referee for this reminder. We agree that the back electron transfer from the bisradical intermediate to the anode, generating the trisradical product, is also a possible way of termination during the electrolysis in an undivided cell. Therefore, a BET (back electron transfer) pathway has been added in the **Fig. 4** and **Supplementary Figs. 40–43**. The corresponding descriptions have also been included in the revised manuscript.

- 7) P11, c10-18: Here, I recommend a modification of the discussion. Although rapid diffusion increases the rate of chain termination processes, it is also necessary to promote formation of the guest complex and the chain process. Not the diffusion rate but rather unhindered convection between anodic and cathodic half-cell is problematic here, as it enables mixing of bisradical host-guest intermediates with anodically formed oxidants (and direct anodic oxidation of bisradicals, respectively). This is also illustrated by Fig. 5c. Using a divided cell would thus be an effective means to increase the (macroscopic) rate of the electron-catalyzed molecular recognition process.

Reply

- We thank the referee for this important suggestion. We completely agree with the referee that the unhindered convection will promote both termination and complexation. Based on the results we obtained when varying the stirring rate from 200 to 400 rpm during the electrolysis in an undivided cell, we can draw the conclusion that the promoting effect of fast convection on termination outweighs that on complexation. The purpose of using an undivided cell set-up is realizing the simultaneous injection and removal of electrons so as to achieve temporal control in molecular recognition.

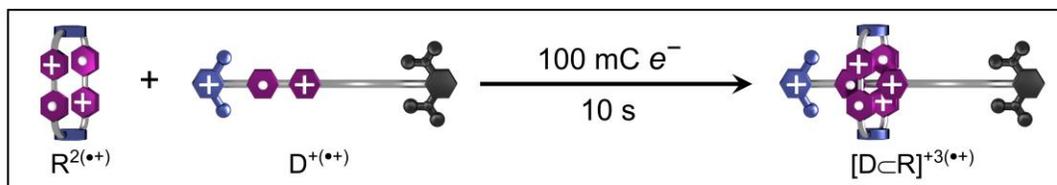
Since the solution is stirred magnetically during the electrolysis in an undivided cell, convection should provide the major means to promote mass transport and play an important role in regulating the lifetime of the bisradical intermediate. We have modified the related discussions in the revised manuscript. In detail, we have changed the word “diffusion” to “convection” to eliminate this source of confusion.

In addition, as the referee suggested, we have performed the electrolysis on the mixture of $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$ in a divided cell. This approach, which enables the permanent injection of catalytic amounts of electrons, displays a similar catalytic effect for promoting molecular recognition when compared to the experimental results by introducing chemical initiators (e.g., CoCp_2). To be specific, the injection of 100 mC (14 mol%) of electrons allows the molecular recognition between $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$ to be completed almost instantaneously. In contrast, by injecting 26 mC (3.5 mol%) of

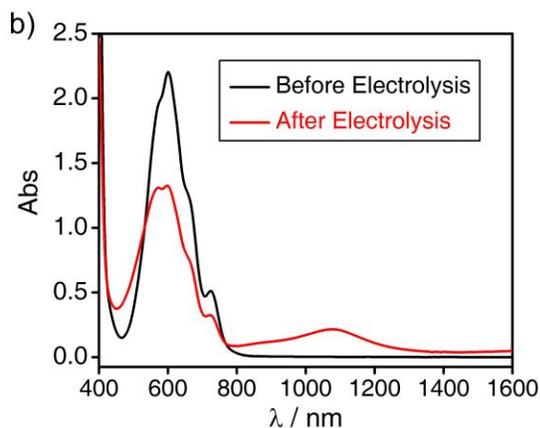
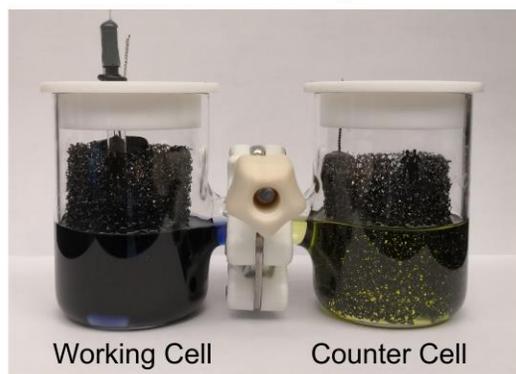
electrons and then switching off the electricity, the molecular recognition proceeds at a relatively slow rate, so that the process can be monitored by UV/Vis/NIR spectroscopy. These additional experiments and corresponding discussions have been included in the Section 8.1 (Page S63–S65) of the revised Supplementary Information, which are also reproduced below highlighted in red text.

8.1 Electrochemically Initiated Molecular Recognition in a Divided Cell

Electrochemically initiated molecular recognition between $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$ was performed in a N_2 -filled glovebox using a *divided* cell. A three-electrode system was employed, which included a reticular vitreous carbon (RVC) working electrode, an RVC counter electrode and an Ag/AgCl reference electrode. The working cell (**Supplementary Fig. 38a**, left) was filled with a MeCN solution (50 mL) containing $\mathbf{R}^{2(\bullet+)}$ (150 μM), $\mathbf{D}^{+(\bullet+)}$ (150 μM) and TBAPF₆ (0.05 M), while the counter cell (**Supplementary Fig. 38a**, right) was filled with a MeCN solution (50 mL) of excess of (trimethylammonium methyl)ferrocene hexafluorophosphate, which serves as the sacrificial electron donor. The two cells were separated by an ionic exchange membrane and held together by a clamp. The whole apparatus was connected to a Gamry multipurpose instrument (Reference 600) interfaced to a PC. The experimental parameters were instructed using the software of Gamry Framework Version 6.30 under the chronocoulometry mode. In order to inject a certain number (catalytic amount) of electrons into the host–guest system, the solutions were electrolysed under stirring at a constant potential of -0.65 V for only a few seconds before switching off the electricity.

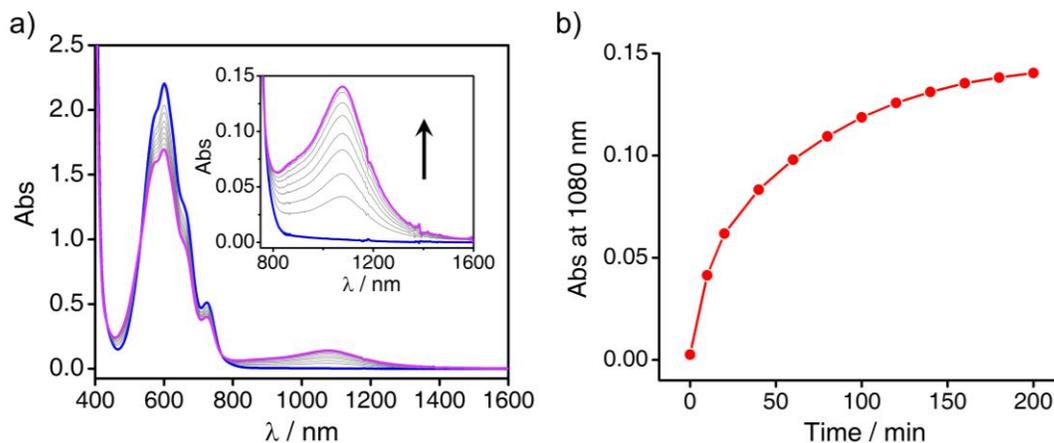
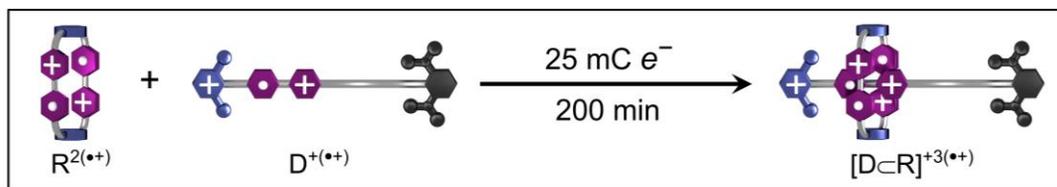


a) Three-Electrode System



Supplementary Fig. 38 | a) The photograph of a divided electrochemical cell used for initiating electron-catalysed molecular recognition. b) The UV/Vis/NIR spectra before and after the injection of 100 mC of electrons into the equimolar mixture of $R^{2(\bullet+)}$ and $D^{+(\bullet+)}$.

This approach of using divided-cell electrolysis has displayed a similar catalytic effect to that involving the introduction of chemical initiators. The injection of 100 mC (14 mol%) of electrons allows (**Supplementary Fig. 38b**) the molecular recognition between $R^{2(\bullet+)}$ and $D^{+(\bullet+)}$ to be completed instantaneously (within 10 s). In contrast, by injecting 25 mC (3.5 mol%) of electrons and then switching off the electricity, the molecular recognition proceeds (**Supplementary Fig. 39**) at a relatively slow rate, allowing the process to be monitored by UV/Vis/NIR spectroscopy.



Supplementary Fig. 39 | a) The evolution of UV/Vis/NIR spectra within 200 min after injecting 25 mC of electrons into the equimolar mixture of $\mathbf{R}^{2(\bullet+)}$ and $\mathbf{D}^{+(\bullet+)}$. b) The kinetic trace of the process.

- 8) It would be interesting to learn about conversions and Faradaic efficiencies (or better, the TONe value, see ref. 35) of the electrolyses.

Reply

- We thank the referee for raising this question. We have estimated the conversions and Faradic efficiencies of electrochemically controlled molecular recognition, and the summary of these results, as well as related discussion, have been included in the Section 8.2 (Page S72–S74) of the revised Supplementary Information, which are also reproduced below highlighted in red text.

The conversions and Faradic efficiencies of electrochemically controlled molecular recognition are estimated and summarized in **Supplementary Tables 7 and 8**. As expected, the conversion can be improved with the increased current intensity and is lowered with the increased stirring rate. In the case of 1.0 mA, 200 rpm, the conversion after 9 min electrolysis is 31.3%, a value close to the conversion at the thermodynamic equilibrium (37.4%).

Supplementary Table 7 | The calculated conversions of electrochemically controlled molecular recognition under different conditions

Conditions		Conversion / %		
		3 min	6 min	9 min
300 rpm	0.5 mA	0.6	1.4	3.2
	1.0 mA	3.5	6.9	11.2
	2.0 mA	10.8	18.0	24.0
1.0 mA	200 rpm	18.6	29.1	31.3
	300 rpm	3.5	6.9	11.2
	400 rpm	1.0	3.6	4.5

Supplementary Table 8 | The estimated values of Faradic efficiencies of electrochemically controlled molecular recognition under different conditions

Conditions		Faradic Efficiency / %		
		3 min	6 min	9 min
300 rpm	0.5 mA	0.9	1.0	1.6
	1.0 mA	2.5	2.5	2.7
	2.0 mA	3.9	3.3	2.9
1.0 mA	200 rpm	13.5	10.5	7.5
	300 rpm	2.5	2.5	2.7
	400 rpm	0.7	1.3	1.1

In order to understand the values of Faradic efficiency, we probed the electrolysis process in the undivided cell. When a BIPY^{•+} radical cation, whether in **R^{2(•+)}** or **D^{+(•+)}**, picks up an electron from the cathode to form a BIPY⁽⁰⁾ unit, there can be three possible subsequent pathways:

- In Pathway 1, the species bearing the BIPY⁽⁰⁾ unit moves quickly to the anode and returns an electron, or encounters the BIPY²⁺ unit generated from the anodic oxidation. As a result, BIPY^{•+} is restored before molecular recognition has happened. The Faradic efficiency is 0.
- In Pathway 2, a [DcR]^{+2(•+)} bisradical complex is generated, which deposits an electron at the anode or undergo single electron transfer with a BIPY²⁺ unit to generate the final product, i.e., the [DcR]^{+3(•+)} trisradical complex. As a result, the transfer of one electron from cathode to anode contributes to one round of molecular recognition. This process is a stoichiometric one, and the Faradic efficiency is 100%.
- In Pathway 3, a [DcR]^{+2(•+)} bisradical complex is generated, which transfers an electron to BIPY^{•+}, thereby affording a [DcR]^{+3(•+)} trisradical complex and a BIPY⁽⁰⁾ unit. Subsequently, this newly formed BIPY⁽⁰⁾ can propagate molecular recognition in a “chain reaction” manner. As a result, one electron can induce more than one round of molecular recognition. This process is justified as catalysis, and the Faradic efficiency is larger than 100%.

In a practical setting, the electrolysis experiments result in a combination of these three pathways. The distributions of them rely on the mass transport of chemical species. Since the solution is stirred during the process, convection should be the major form of mass transport and play an important role in regulating the lifetime of catalytic intermediates. Pathway 1 is the major one when convection is very fast, so that the lifetime of BIPY⁽⁰⁾ is not long enough to induce molecular recognition before returning to BIPY^{•+}. In contrast, Pathway 3 is dominant when convection is very slow, so that BIPY⁽⁰⁾ has sufficient time to sustain many cycles of molecular recognition. Pathway 2 is somewhere in between.

All the values of Faradic efficiencies (**Supplementary Table 8**) are lower than 100%, an observation which indicates that Pathway 1 plays a dominant role under the conditions that we have employed. The Faradic efficiency could be improved by lowering the stirring rate.

Considering the values of Faradic efficiency, the electrolysis in an undivided cell contains only partially the characteristics of catalysis. Therefore, we have described this process as “electrochemically controlled molecular recognition” and avoided using the term related to “catalysis” in both the manuscript and Supplementary Information.

- 9) P12, 17-10 and summary: The authors state that the use of electrochemistry provides a temporal control over the kinetics of complex formation. However, it remains unclear in which way this is conceptually different to constant or portion-wise addition of a chemical reductant in defined time intervals. Extension of the discussion is recommended. A major difference between the electrochemical process and the addition of chemical reductant is the constant delivery of anodically formed oxidant that curbs the chain process and quenches the reaction after switching off the current. From this point of view, a reaction in a divided cell would resemble a process that is catalyzed by chemical reductants.

Reply

- We thank the referee for these observations. As suggested, we have conducted the electrolysis experiments using a *divided* cell (see the reply to Comment #7 in this response letter), which indeed results in a molecular recognition process resembling the one initiated by chemical reductants. Both approaches, featuring the permanent injection of catalytic amounts of electrons, are conceptually different from the electrolysis in an *undivided* cell, in which electrons are simultaneously injected into and withdrawn from the solution. As a result, the overall system maintains redox neutrality during the electrolysis in the undivided cell, and this approach allows temporal control in the molecular recognition process by switching on/off the current. In order to clarify this point, additional discussion has been introduced in both the revised manuscript (Page 10, Lines 16–20) and Supplementary Information (the first paragraph in Page S63).

- 10) General method for electrochemically catalyzed molecular recognition: The used electrode materials should be provided.

Reply

- We thank the referee for this suggestion. Both the cathode and anode used for electrochemically controlled molecular recognition are reticular vitreous carbon electrodes. This information has been included in the Methods section (Page 14) of the revised manuscript.
-