A computational analysis of intramolecularity in proton transfer reactions

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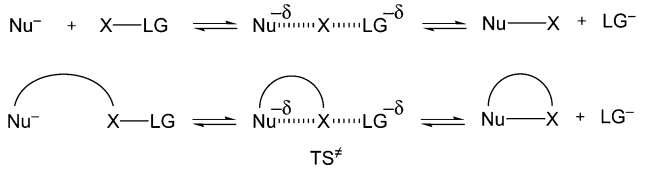
Hydrogen bonds along which most proton transfers take place are analyzed regarding their contribution to the efficiency of intramolecular processes through the assessment of effective molarities by DFT calculations on rigid intra-molecular model systems in comparison with their intermolecular counterparts. A few cyclic systems in which there is no possibility of hydrogen bonding between reactants neither in the ground state nor in the product are identified by theoretical calculations as leading to important rate increases in intramolecular general-base catalysis constituting a new exception to the rule of low effective molarities (EMs) for proton transfers. The recovery of high efficiency in these systems is attributed to the absence of special features facilitating the corresponding intermolecular reactions. This work confirms that any explanation of EMs found in intramolecular systems also requires a careful analysis of the corresponding bimolecular systems.

Introduction

The high rates of intramolecular reactions are fascinating for chemists because they are reminiscent of the efficiency of enzyme catalysis and it is widely believed that a common source is, at least for a significant part, responsible both effects[1–8] Rate enhancements are usually expressed by the effective molarity (EM = k_{intra}/k_{inter}), having the dimension of a concentration and defined as the ratio of the intramolecular rate constant (k_{intra}, unimolecular and expressed in s^{-1}) to that of the corresponding bimolecular process (k_{inter}, in $s^{-1}M^{-1}$). When the geometries of both the transition state (TS) and the product are favourable, EM values reaching or exceeding 10^8 M have been reported for pathways involving the reactions of nucleophiles (Scheme 1).[5]



Scheme 1 Intermolecular *vs.* intramolecular nucleophilic reactions. In geometrically favourable systems values of EM of *ca.* 10^8 can be reached,[3] and even exceeded when strain is released at the TS.[4]

Understanding the origins of these high EM values may be facilitated by separating the reaction process into different reactions phases.[9] Through this description, two different classes of contribution to high EMs can be identified. The first one can be observed from conveniently positioning reacting groups for reaction (distance, orientation). This means that reaching the state in which reagents can enter the phase of the reaction in which chemical changes occur does not require the expense in free energy needed by approach and preparation phases[9] at the difference of intermolecular systems (Scheme 1).[2] The second class of contribution affect the transition state phase of the reaction itself, for example when strain is released as reaction proceeds simply because most intramolecular reactions involve the formation of cycles (Scheme 1) and then geometry changes involving parts of the reacting system possibly distant from the reaction center are likely to influence the free energy at the transition state. This second category may also include assistance by changes in bonding interactions involving neighbouring groups. Although these distinctions are useful to grasp the system, it is usually difficult to precisely assess their respective contributions in experimental systems, but they are in principle sufficient to explain the magnitude of the high EM values found in many intramolecular nucleophilic reactions.

Conversely, intramolecular proton transfers associated to general acid or base catalyses (IGAC-IGBC) usually lead to low EM values.[5] An usual explanation for these low EM values is connected with the loose character of the TS that does not require a full loss of motion of reacting groups relative to each other in order to allow for proton transfer.[5] Then, bringing reacting groups together at the convenient position for an intramolecular reaction would not be a significant improvement since a complete loss of motion is not required for a loose TS.[5] Specific features associated with the low mass of proton[10] (tunneling) could also be invoked to account for the usual low EM of intramolecular proton transfers or IGAC-IGBC. However, although hydride is not significantly different in weight, its transfer has been reported to be associated with high EMs in a rigid system,[11] but this conclusion has then be considered as open to discussion since a contribution of strain may lessen its value.[12] One of us[13] proposed that low EMs observed for intramolecular proton transfers actually lie in the specificity of proton exchanges that proceed along pre-formed hydrogen bonds between electronegative atoms at high rates in the thermodynamically favorable direction (Scheme 2).[14] In this view, most bimolecular proton transfers constitute examples of *induced intramolecularity*[2,13,15] since they can be considered as taking place within a molecular complex. The advantage of further making the reaction truly intramolecular by covalently connecting

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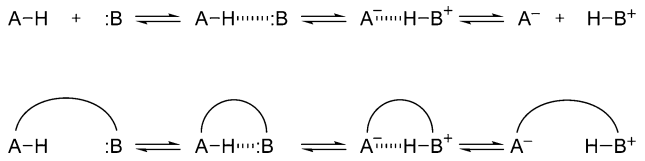
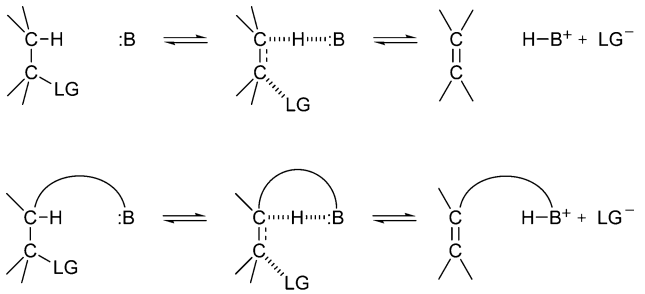


Scheme 2 Intermolecular *vs.* intramolecular proton transfers between electronegative atoms. According to the hypothesis of ref. 13, the existence of more or less stable hydrogen-bonded adducts in the "intermolecular" systems prevents the covalently bound system of taking advantage of the usual efficiency of intramolecular reactions.

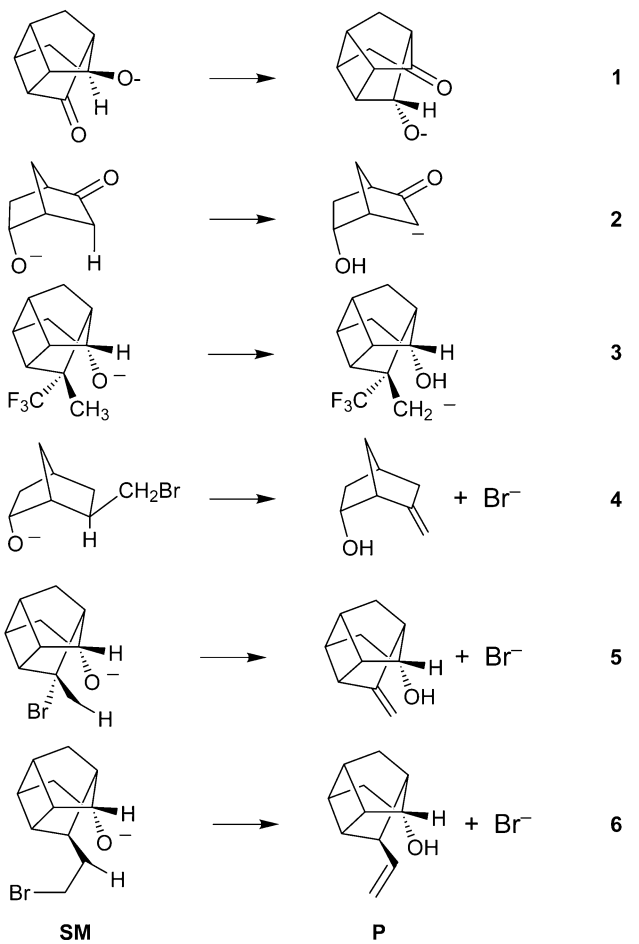


Scheme 3 Intermolecular *vs.* intramolecular proton transfers at carbon with no possibility of stabilization of reacting intermediates by hydrogen bonding. According to the rationalization of ref. 13, these systems are predicted to give rise to high EM in favourable cases.

reacting groups is then limited since most possibilities of motion of one group with respect to the other one are already lost in the hydrogen-bonded complex, *i.e.* EMs cannot be increased through convenient positioning as a result of the first category of contributions mentioned above. This explanation of the low EMs for most intramolecular proton transfers based on the existence of hydrogen-bonded complexes has been challenged by Kirby who alleged that hydrogen bonding with the solvent is predominating over that with the catalyst in the reactant state.[16] But effective molarities are determined in the *standard state* (1 M reactant concentration) and not at the experimental concentration of reactants (usually much lower). Making the conservative hypothesis that hydrogen bonds with the general acid or base (1 M) are likely to be at least as strong as those with water (55 M) for catalysis to be detectable, it follows that the upper limit for the factor accounting for the predominance of the solvent in the intermolecular reaction is assigned to a value of *ca.* 55 in water.[13] A value below 55 M for EM can still be considered as low by comparison with values approaching 10^8 M, in the absence of strain, for the first class of contribution assigned by Page and Jencks[3,4] to entropy. However, high efficiencies have been observed for enzyme reactions involving proton transfer so that the identification of processes allowing to recover high EM in intramolecular proton transfers is valuable. In fact, several intramolecular systems have been studied in which the development of a strong intramolecular hydrogen bond at the transition state[17] contributes to increase the rate by transition state stabilization (the second class of contribution described above). Since the first class is more intrinsically linked to the specificity of intramolecular reactions, we embarked on studies dedicated to identify intramolecular systems in which convenient positioning is responsible for high EMs in reactions involving proton transfer. We report here the results of a theoretical investigation performed on several model systems dedicating an important role to the occurrence of hydrogen-bonded complexes in determining the efficiency of proton transfer processes. Systems in which reacting centers are neither hydrogen-bonded in the ground state or in the final state are identified as those allowing to recover the *usual* effect of intramolecularity, which does not preclude the well-known influence of a change in the strength of any present hydrogen bond (Scheme 3).[17,18]

Results and discussion

The calculations were performed with the models displayed in Scheme 4 and the reference intermolecular systems (Scheme 5) on different reaction processes: hydride transfer, proton abstraction, and base-catalyzed bromide elimination. The optimized structures

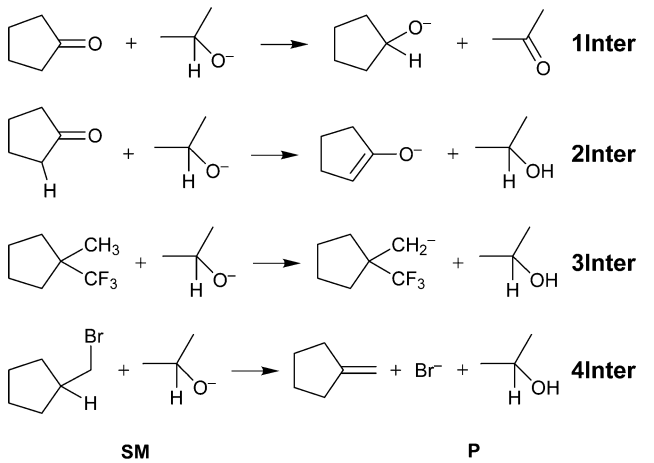


Scheme 4 Intramolecular model systems for hydride transfer (**1**), proton abstraction (**2**, **3**), or general base-catalyzed reactions (**4**, **5**, **6**).

were calculated both in vacuum and in aqueous solution and either in the absence or in the presence of one molecule of water. In all cases water was found to hydrogen bond with the carbonyl or hydroxyl groups without essentially altering the conclusions. The optimized structures in the presence of 1 molecule of H_2O were re-optimized in a cluster of water using the Onsager method (water dielectric constant = 78.39). Calculations of this kind have been successful in reproducing the tendency of changes in EM values compared to experimental values. This adequacy has been observed in intramolecular nucleophilic reactions of

Table 1 Activation energies and effective molarities computed for intramolecular systems **1–6**. For reactant systems **5** and **6** the intermolecular reaction **4Inter** was used as a reference to assess EM values

	$\Delta G^{\neq}$//kcal mol^{-1} Gas phase	EM/M	$\Delta G^{\neq}$//kcal mol^{-1}	EM/M	$\Delta G^{\neq}$//kcal mol^{-1} Water as a solvent	EM/M	$\Delta G^{\neq}$//kcal mol^{-1}	EM/M
System	Without inclusion of water		With inclusion of 1 H_2O		Without inclusion of water		With inclusion of 1 H_2O	
1	14.95	2.1×10^4	21.39	0.8×10^3	15.37	5.9×10^4	22.86	1.5×10^3
2	5.05	0.17	12.12	1.3	5.89	7.1	13.61	0.34
3	19.86	0.04	18.87	1.9×10^4	15.09	0.93	20.76	19.9
4	0.31	1.9×10^3	6.68	3.6	5.34	50	10.65	2.1
5			0.0	~2.5×10^7			0.57	~2.5×10^7
6			0.0	~6.5×10^7			0.0	~6.5×10^7



Scheme 5 Intermolecular model systems for hydride (**1Inter**), proton transfer (**2Inter**, **3Inter**), or general base-catalyzed (**4Inter**) reactions. System **4Inter** was also used as a reference intermolecular reaction for bromide eliminations starting from **5** and **6**.

substituted 3-aminoalkyl halides and substituted chlorohydrins[8] as well as in proton transfer reactions in some of Kirby's enzyme models[19] where a linear correlation between the calculated and the experimental log EM was obtained with R values in the range 0.93–0.98

The calculated EM was found to exceed 10^3 M for the hydride transfer reaction in system **1** and to be independent of the medium selected for calculation (Table 1). Though this value lies three orders of magnitude below the published experimental value (6.5×10^6 M),[11] determined with a system differing only by the presence of a methyl group on the rigid structure and the dioxane/water (50 : 50 v/v) solvent, it remains that it corresponds to the range usually observed for intramolecular reactions in favorable cases.

Proton transfer was investigated using hypothetical structures (**3**, **5**, **6**) derived from system **1** and related systems already subjected to experiment (**2**, **4**).[6] Results are different from those computed for hydride transfer, at least in solution. Independently of the mode of calculation, in system **2**, which involves the abstraction of a proton from a ketone to give an enolate, low EMs are predicted either in the gas phase or in solution with no effect of hydrogen-bonding with a molecule of water (Table 1). Any hydrogen bond in **2InterSM** would be very weak and unlikely to allow intermolecular proton transfer to proceed at rates similar to that of the intramolecular system **2SM**. But it is worth noting that in addition to the predominant conformation of **2InterP** state corresponding to a complex that is hydrogen-bonded with the enolate oxyanion (Fig. 1), an interaction with the carbon atom bearing a partial negative charge is not unlikely. This complex may facilitate proton transfer in the reverse direction according to the Eigen's mechanism,[14] and a development of the hydrogen bond may contribute to the stabilization of the transition state, which is confirmed by the *ca.* 2.75 Å C–O distance in the structure of **2InterTS** (Fig. 1), compatible with TS stabilization by hydrogen bonding. Owing to the principle of microscopic reversibility this factor is likely to facilitate the bimolecular reaction starting from **2InterSM**, whereas much less stabilization would be available from the constrained geometry of the intramolecular system, which provides an explanation to the low EM found for **2SM** system. Actually, in most intramolecular models studied here, the change in strain and the distortion of hydrogen bonds regarding linearity are likely to play an important role.[20] Although, this distortion may be less important, EM remains low in system **3**, which is consistent with the existence of a hydrogen bond between the localized carbanion and the hydroxyl group in system **3InterP**, already present in the state **3InterTS**, explaining the low EM value for system **3** in a way similar to the explanation given above for model **2**. This explanation has been confirmed by the calculated structures consistent with the formation of hydrogen bonds in the transition and product states **3InterTS** and **3InterP** (Fig. 2).

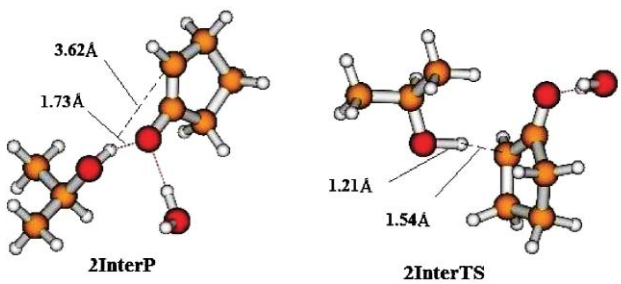


Fig. 1 Structures of the transition and product states in system **2**.

Our analysis, based on the presence of a hydrogen bond in the transition states **2InterTS** and **3InterTS** sufficient to impede the observation of high EMs, implies that a bonding interaction, missing in the **2InterSM** and **3InterSM** states is formed as the reaction proceeds and contributes to the stabilization of the TS of the intermolecular reaction whereas this effect is limited by distortion in the intramolecular one. Indeed, any hydrogen bond in systems **2** and **3** would be strained, which is consistent with the computed values of $\Delta G^{\neq}$ (Table 1).

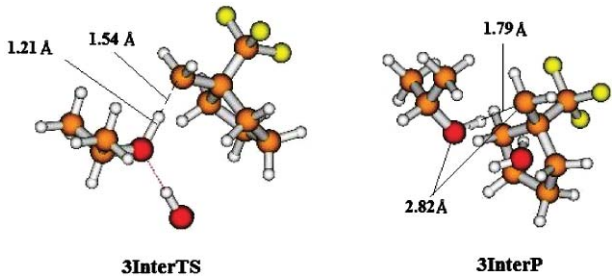


Fig. 2 Structures of the transition and product states in system **3**. The hydroxyl group in the product is at hydrogen bonding distance of the carbanion (C–O distance 2.82 Å).

The comparison of systems **2** and **3** with the model involving hydride transfer indicates that proton transfer corresponds to a specific process that does not take advantage of intramolecularity in the same way as other kinds of reactions, which is consistent with the description that intermolecular proton transfer along hydrogen bonds are already occurring intramolecularly in the hydrogen-bonded complex of the reference intermolecular system.[13] This kind of intermediate not only corresponds to the definition of an encounter complex - usually a transient species with a lifetime governed by van der Waals interactions (constrained by almost insignificant kinetic barriers in simple chemical systems) and then not considerably longer than that of a TS - but when a hydrogen bond is present, this species additionally takes advantage of a significant stabilization of the reactive configuration, which is still present at the TS and thus increases the reaction rate. It is worth noting that this analysis is independent of the explanation given to the usual high rates of intramolecular reactions and compatible, for example, with explanations based on entropy[3,4] or on the time of residence at a critical distance,[6] which have been considered as two different ways to account for the same factor.[4]

To have a decisive clue in favor of this interpretation we looked for models with no possibility of interaction between charged groups of reacting species (able to pre-organize the system for reaction) in the initial and the final states. The process of a base-catalyzed elimination of a leaving group (Scheme 3), in which proton transfer is concerted with heavy atom reorganization, is likely to correspond to this definition since there is no development of strong electrostatic interactions as the reaction proceeds. This process corresponds to base catalysis but a similar acid catalyzed pathway is conceivable in the reverse direction provided that the fast addition of a nucleophile does not leave a significant lifetime to the carbocation formed by protonation.[21] The process displayed in Scheme 3 was analyzed by theoretical methods in the case of model molecules derived from system **4** introduced initially by Menger.[6] Indeed, systems **5** and **6** turned out to display high computed values for EMs, associated with fast intramolecular rates since reactions are almost barrierless. The release of strain accompanying the reaction, not very different from the one occurring in the other systems studied here, seems unlikely by itself to account for the EM. Additionally, there is no significant reduction in the distance of oxyanion to carbon in the ground states **5SM** and **6SM** compared to **3SM** as a way to account for the change in computed rates. The lower intramolecular efficiency in model **4** is very probably the consequence of a geometry that is less favorable to proton transfer and consistent with the above mentioned importance of strain in system **2**. High EMs calculated for systems **5** and **6** can thus be considered as the result of the absence of any particular stabilization in the intermolecular counterpart **4Inter** so that the fact of conveniently positioning the reacting groups for reaction recovers high efficiency in the intramolecular processes **5** and **6** (first class of contribution). This recovery can thus be attributed to the absence of hydrogen bonding in the reaction of the intermolecular reference system **4Inter**. It strongly supports the idea that the usual observation of low EMs for intramolecular proton transfers results on the contrary from hydrogen bonding in the ground state of most proton transfer reactions that is responsible for already inducing intramolecularity in intermolecular systems and precludes any possibility of further increasing rates by conveniently positioning reacting groups.[13]

Rules for EM in Proton Transfer

From data published in the literature and from the present discussion, we suggest several rules governing the efficiency of intramolecular proton transfers based on the contribution of intramolecularity[13] and of changes in hydrogen bond strength at the TS.[17,18]

Proton transfer along a hydrogen bond. When the transfer occurs between electronegative atoms (*e.g.* N, O, S) no significant advantage is usually observed because the intermediacy of a more or less stable adduct in intermolecular processes allows the transfer to be as fast as in intramolecular systems.[13] The kinetic advantage of a proton transfer along a hydrogen bond compensates for the abundance of hydrogen-bonded complex with the solvent. This conclusion is valid provided that both processes do not involve significant changes in hydrogen bond strength. But a special mention has to be made for some systems reported to display high EMs.[17,22] These exceptions correspond to concerted reactions leading to strong intramolecular hydrogen bonds in the product. The development of these hydrogen bonds proceeds as reaction progresses and can contribute to stabilize intermediate stages including the TS with a favorable consequence on the rates.[17] Theoretical investigations that reproduce high values of EMs for salicylic acid-derived systems have been carried out with calculation tools similar to those used in this work.[19]

Proton transfer from or to carbon[23] *and more generally systems that do not give rise to hydrogen bonds*. In principle, this situation should allow intramolecular systems to display high EM. But situations in which hydrogen bonds are absent both in the reactant state and in the product are not so usual so that a wide spectrum of situations is possible. For instance, when a carbanion is formed, a hydrogen bond can be present in the product even if it is absent in the non-ionized state. In this case, a hydrogen bond is developing at the TS, which contributes to TS stabilization of the *intermolecular* process whereas its strength is dependent of the structure of the reactant undergoing the intramolecular process. Since the latter process exceptionally meets the requirement of distance and linearity for taking a full advantage of hydrogen bonding EM usually remains limited. Regarding this contribution, enzymes do not have such limitations to adapt active site geometry to the TS because it is determined by their overall tertiary structure and not only by the arrangement of the neighbouring chemical bonds. They evolved towards adapted structures able to take advantage of the full extent of stabilization by hydrogen bonding, which may

account for their efficiency in proton transfer catalysis. However we demonstrated here that a few chemical systems, in which there is no electrostatic interaction both in the reactant and product states, can allow intramolecular proton transfers to display high EMs as shown by theoretical prediction on systems **5** and **6**.

Conclusions

The fact that calculations reproduce the different behaviors of proton and hydride transfer with respect to intramolecularity shows that the question of the origin of low EMs for proton transfer is in principle accessible to theoretical investigations with no need for specific assumptions. Understanding the effect of intramolecularity on proton transfers requires having a full description of interaction changes occurring on going from the ground state to the transition state of both the intramolecular and the intermolecular processes. The present investigation on model systems may serve as a basis for future experimental studies aimed at finding high EMs for proton transfer based on alternative assumptions. It demonstrates that precisely positioning reacting groups, in addition to the development of strong hydrogen bonds or the release of strain at the transition state, must be considered as a tool to obtain high EMs in IGAC/IGBC for the systems in which the intermolecular counterpart does not involve the formation of hydrogen-bonded complexes. Moreover, it contributes to explain why enzymes, the evolution of which has optimized the geometry of the active site, can fully benefit of both intramolecularity and of the favorable contribution of hydrogen bonding at the transition state, whereas intramolecular systems hardly match the distance and orientation required for having full hydrogen bonding and linear geometries. The importance of pre-formed hydrogen bonds, emphasized here, is an example of the general need of preorganizing the reacting groups of the system before the transition sate[9,24] to reach high catalytic efficiencies. It reproduces important features of enzymatic reactions and indications have been provided that these enzymatic preorganization and chemical steps occur on very different timescales.[25]

Calculation methods

The DFT at B3LYP/6-31G(d,p) calculations were carried out using the quantum chemical package Gaussian-98.[26] The starting geometries of all the molecules presented in this study were obtained using the Argus Lab program[27] and were initially optimized at the AM1 level of theory.[26] An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant.[28] The "reaction coordinate method"[29] was used to calculate the activation energy in systems **1–6** and **1Inter-4Inter**. Verification of the desired reactants and products was accomplished using the "intrinsic coordinate method".[27] The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing any constrains imposed while executing the energy profile. The activation energies obtained from DFT and HF levels of theory for **1–6** and **1Inter-4Inter** were calculated with and without the inclusion of solvent (water). The calculations with the incorporation of a solvent were performed using the Onsager model.[30]

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