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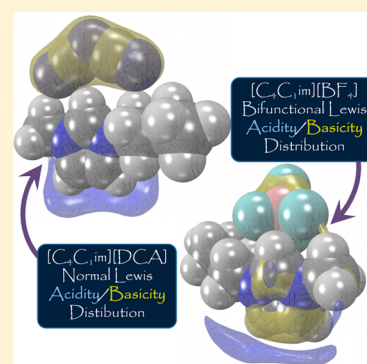
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## Regional Electrophilic and Nucleophilic Fukui Functions Efficiently Highlight the Lewis Acidic/Basic Regions in Ionic Liquids

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## S Supporting Information

**ABSTRACT:** The origin of catalysis and selectivity induced by room temperature ionic liquids in several organic reactions has putatively been associated with the concept of *cation effect* (hydrogen bond donor ability of the ionic liquids) or *anion effect* (hydrogen bond accepting ability of the ionic liquids). We show that there may be cases where this a priori classification may not be correctly assigned. Cations may concentrate both Lewis acidity and basicity functions in one fragment of the ionic liquid: an effect we tentatively call bifunctional distribution of the molecular Lewis acidity/basicity. Bifunctionality on the cation is however anion dependent through electronic polarization effects. The molecular distribution of the Lewis acidity/basicity may simply be assessed by evaluating the regional Fukui function within a reference ion pair structure. The model is tested for a set of nine ionic liquids based on the 1-butyl-3-methylimidazolium cation commonly used as solvent to run organic reactions.



## ■ INTRODUCTION

Room temperature ionic liquids (RTILs) have been the object of increasing interest due to a wide variety of interesting properties which make them have a large number of applications in chemistry.<sup>1–3</sup> Undoubtedly the most significant property of these ionic solvents is the large number of cations and anions that can potentially be combined to form new RTILs with specific properties. This last property has opened the possibility to obtain a significant range of solvents with very different properties, converting them into “designer solvents”, whose properties can be specified to suite the requirements of a particular reaction.<sup>4–6</sup> The design and choice of ionic liquids commonly focuses on physical properties, such as water miscibility, viscosity, conductivity, polarity, and solubility. The microscopic chemical structure of a RTIL is thought to dramatically affect the reactivity, selectivity, and reaction rates of a significant number of chemical reactions.<sup>1,2,7</sup> However, most of the chemical (solvent and catalytic) effects of RTILs on organic chemical reactions are still poorly understood. This is the case, for instance, of the relative molecular acidity and basicity of ionic liquids. These properties may drive the specific or dual performance of RTIL as reaction media or as catalyst. Along this line, the concepts of Lewis acidity/basicity become a key aspect, because the solvent effects promoted by RTIL are currently associated with their potential ability to bound the dissolved substrates via hydrogen bond interactions. Bronsted acidity/basicity is less general for the purpose of understanding the different molecular solute–solvent interactions at a

microscopic level, where proton transfer processes from or to the solvent have been less studied.

Because Lewis acid and base properties of RTILs have not yet well been understood, it is the primary purpose of this work to shed some useful insight onto the electronic characterization of these properties at the most fundamental level of the electronic structure of matter. One of the relevant problems in the design of new task specific RTILs is related to the optimization of their potential as hydrogen bond donor or acceptor species. Lewis acidity/basicity has normally been defined as the capacity of a given species to accept or to release an electron pair from the surrounding chemical environment, respectively.<sup>1,8,9</sup> The literature devoted to the study of RTILs has been associated with the hydrogen bond donor and acceptor concepts to the cation (*cation effect*) and to the anion (*anion effect*) forming the RTIL, respectively.<sup>10–15</sup>

For instance, RTILs bearing metal halide anions are expected to display Lewis acidity, especially those based upon chloroaluminate anions. However these RTILs have been progressively less studied.<sup>1,8,9</sup> For this reason, the development of water-stable acidic ionic liquids is highly desirable. One approach to design acidic ionic liquids was to introduce the (Lewis) acidity in the anion moiety of the RTIL, such as, for instance,  $\text{HSO}_4^-$  and  $\text{H}_2\text{PO}_4^-$ .<sup>15–17</sup> Another efficient approach for designing water-stable acidic ionic liquids was to introduce

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**Table 1.** Electrophilic ( $N_{\Omega}^+$ ) and Nucleophilic ( $N_{\Omega}^-$ ) Fukui Function Values Condensed over the Cations and the Anions of the RTILs  $[C_4C_{1im}][X]$  Considered at the B3LYP/6-311++G(d,p) (BS1) and B3LYP/AUG-cc-pVTZ (BS2) Levels of Theory

X	cation				anion				HBA/HBB distribution <sup>a</sup>
	$N_{\Omega}^{+}$		$N_{\Omega}^{-}$		$N_{\Omega}^{+}$		$N_{\Omega}^{-}$		
	BS1	BS2	BS1	BS2	BS1	BS2	BS1	BS2	
BF <sub>4</sub> <sup>−</sup>	0.97	0.97	0.73	0.72	0.03	0.03	0.26	0.28	bifunctional
CF <sub>3</sub> CO <sub>2</sub> <sup>−</sup>	0.98	0.97	0.25	0.24	0.02	0.03	0.75	0.76	borderline
Cl <sup>−</sup>	0.97	0.97	0.26	0.25	0.03	0.03	0.74	0.75	borderline
DCA <sup>−</sup>	0.95	0.97	0.15	0.17	0.05	0.05	0.85	0.83	normal
CH <sub>3</sub> SO <sub>3</sub> <sup>−</sup>	0.96	0.96	0.18	0.19	0.04	0.04	0.82	0.81	normal
NTf <sub>2</sub> <sup>−</sup>	0.94	0.94	0.23	0.22	0.06	0.06	0.77	0.78	borderline
OAc <sup>−</sup>	0.97	0.97	0.18	0.19	0.03	0.03	0.82	0.81	normal
OTf <sup>−</sup>	0.96	0.96	0.38	0.34	0.04	0.04	0.62	0.66	borderline
PF <sub>6</sub> <sup>−</sup>	0.97	0.97	0.79	0.73	0.03	0.03	0.21	0.26	bifunctional

<sup>a</sup>Lewis acidity and basicity distribution. See text for details about the labeling.

Bronsted acidic groups on the cation moiety.<sup>18</sup> We have already shown that the presence of Bronsted acidic fragments on the cations has a clear effect of activating the Lewis acidity on another site, normally that identified with the hydrogen bond acceptor property (which we shall emphasize here, is a local or regional, not a global property, of the RTIL).<sup>19</sup> On the other hand, RTILs classified as Lewis bases have a number of interesting and useful properties.<sup>1,9,14</sup> MacFarlane et al.<sup>20,21</sup> have shown that ionic liquids containing Lewis base anions can exhibit base catalysis activity. An interesting question about this problem is the following: Which is the site responsible for catalysis in this type of task specific RTILs? We shall demonstrate herein that the following points are relevant to assign the Lewis acidity/basicity in RTIL: (i) Lewis acidity/basicity concepts are more pertinent than those referred to as Bronsted acidity/basicity, because if we assume that solvation and catalysis is mostly driven by hydrogen bond interactions, the Bronsted acidity/basicity scale is not really useful because it refers to a different chemical process where the acidic/basic hydrogen atom is completely transferred or accepted in the form of a proton. (ii) The molecular Lewis acidity/basicity is essentially a regional property of the RTIL, not a global one. This point, not new,<sup>19,22</sup> is of great importance because there may be some cases where acidity/basicity could be located in one of the fragments forming the RTIL, and not necessarily associated with a cation or anion effect a priori. The two points defined above are relevant to achieve a sound classification of Lewis acidity/basicity in RTIL and have the following problem of implementation: the cation or anion properties must be defined for each one in the presence of the corresponding counterion, because the ability of the Lewis acidic center to accept a fraction of electronic charge from the hydrogen bond acceptor in the substrate dissolved in the RTIL must be attenuated to a different extent by the presence of the anion. The same is true for defining an effective Lewis basicity. Consider further the mutual electronic polarization that can result in electrophilic/nucleophilic activation, an effect tightly related to hydrogen bond acidity (HBA) or hydrogen bond basicity (HBB) enhancement. This problem may however be overcome if we use, as a reference state for both, the cation and the anion forming a hypothetical ion pair structure, taken as a virtual thermodynamic state.<sup>23</sup>

## THEORETICAL METHODS

Whatever the global property of HBA or HBB being used (electrophilicity, nucleophilicity, or charge capacity), the Fukui function (FF) is the quantity that projects the molecular property onto regions of the model RTIL ion pair. Therefore, this function is the key quantity that can define the Lewis acidity/basicity distribution on a fundamental electronic basis. We propose the condensed to atom electrophilic FF  $f_k^+$  to be the natural distributor of Lewis molecular acidity and the nucleophilic FF  $f_k^-$  to be the corresponding distributor of Lewis molecular basicity. In this sense, the model becomes extremely simple, as the condensed-to atom molecular FF may be readily obtained by using the definitions<sup>24–26</sup>

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \quad (1)$$

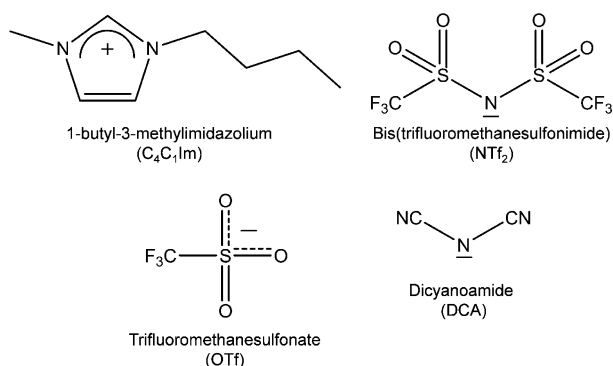
$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \quad (2)$$

and integrating over the corresponding basins  $\Omega_k^\pm$ , achieving the condensed to basins FF given by<sup>25</sup>

$$N_{\Omega}^\pm = \int_{\Omega_k^\pm} \rho(\vec{r}) d\vec{r} = \sum_{k \in \Omega^\pm} f_k^\pm \quad (3)$$

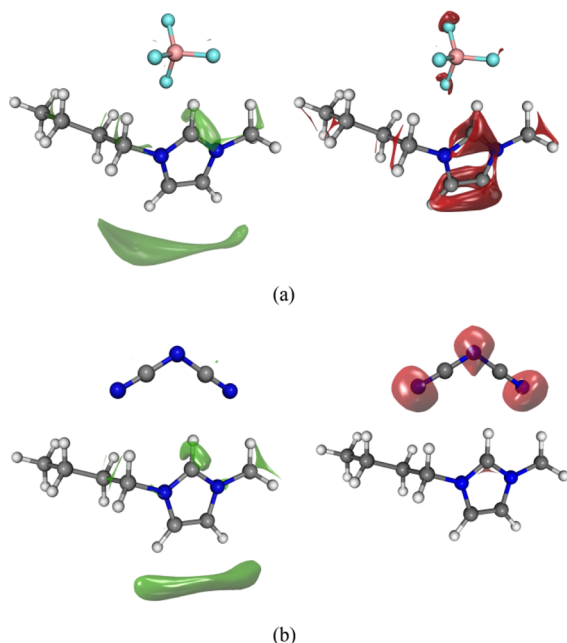
The basins  $\Omega_k^\pm$  represent here molecular regions where the electrophilic Fukui function ( $\Omega_k^+$ ) and nucleophilic Fukui function ( $\Omega_k^-$ ) have a maximum, respectively.<sup>25</sup> Both regions are reliable models for regional Lewis acidity/basicity that can be used to model the HBA and HBB properties of a given RTIL. Therefore, the chemical interpretation will be as follows: the region with the greater  $N_{\Omega}^+$  will be the most susceptible site to accept electronic charge (or donate a hydrogen bond). On the other hand, the moiety with the greater  $N_{\Omega}^-$  will be the region with the major ability to donate electronic charge (or accept a hydrogen bond).

The geometry optimization and the FF were obtained using the B3LYP functional and two basis sets, namely 6-311++G(d,p) and AUG-cc-pVTZ, with the Gaussian 09 package.<sup>27</sup> The two different methods were used to prove that all the calculations are basis set independent. Table 1 summarizes the regional electrophilic/nucleophilic FF condensed over the cation and the anion moieties, for a set of 9 RTIL based on the 1-butyl-3-methylimidazolium cation commonly used as reaction media in organic chemistry. The general structures of the cation and several anions considered in this study are shown in Scheme 1.

**Scheme 1. Structures of  $C_4C_1im$  and Several Anions Used in the Present Study**

## RESULTS AND DISCUSSION

We introduce the concept of “normal distribution”, for those cases where the Lewis molecular acidity ( $N_\Omega^+$ ) is mainly centered at the cation fragment, whereas the Lewis molecular basicity is centered at the corresponding anion (i.e.,  $N_\Omega^- > 0.8$  eV). On the other hand, the “bifunctional distribution” labeling is used when both the Lewis acidity and basicity are located at the same region of the RTIL (the cation in the present case and  $N_\Omega^- < 0.3$  eV). First of all, a general view of Table 1 reveals that, for the anions  $BF_4^-$  and  $PF_6^-$ , a bifunctional distribution is obtained, thereby suggesting that both the Lewis acidity and basicity can be located at the cation moiety. The RTILs with the anions  $CF_3CO_2^-$ ,  $Cl^-$ ,  $NTf_2^-$ , and  $OTf^-$  are borderline, while the other ones ( $DCA^-$ ,  $CH_3SO_3^-$ , and  $OAc^-$ ) may be labeled as normal distributions. Figure 1 shows as representative the extreme cases for the calculated  $f^+(\vec{r})$  and  $f^-(\vec{r})$  FF, for the RTILs  $[C_4C_1im][BF_4^-]$  and  $[C_4C_1im][DCA^-]$ . It is important to point out that both basis sets lead to almost the

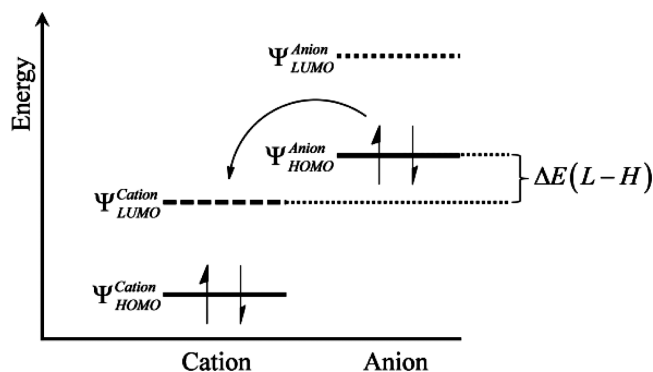


**Figure 1.** Electrophilic (green) and nucleophilic (red) Fukui functions for (a)  $[C_4C_1im][BF_4^-]$  and (b)  $[C_4C_1im][DCA^-]$  RTILs. The results presented correspond to those calculated at the B3LYP/AUG-cc-pVTZ level of theory.

same results, thereby suggesting that this property is basis set independent (see Table 1).

It seems that some anions induce electronic polarization on the cation that results in nucleophilic activation in some specific regions. In this way, the anions  $BF_4^-$ ,  $PF_6^-$ ,  $CF_3CO_2^-$ ,  $Cl^-$ ,  $NTf_2^-$ , and  $OTf^-$  may confer an *amphoteric* character to the cation forming the RTIL. However, whether or not the Lewis basicity or Lewis acidity or both will determine the kinetics of the reaction will also depend on the nature of the molecules dissolved in it.<sup>1,2</sup> The anion polarization effects have already been reported,<sup>28</sup> in the interaction of  $BF_4^-$ ,  $PF_6^-$ , and  $NTf_2^-$  with the transition structure of a Diels–Alder reaction.<sup>29</sup> The polarization effect may be assessed using the softness gap, as previously discussed.<sup>30</sup>

In the process of formation of an ionic pair, an electron is transferred from the *HOMO* of the anion to the *LUMO* of the cation (see Scheme 2); therefore, the energy released or

**Scheme 2. Schematic Representation of the Electron Transfer Process for the Formation of an Ionic Pair**

required ( $\Delta E(L-H)$ ) to carry out this process may be a simple model to predict whether a given RTIL will have a normal or a bifunctional response.

The  $\Delta E(L-H)$  energy gap may be simplified considering that the cation is always the same, and therefore,  $\Delta E(L-H) = \epsilon_{LUMO}^{cation} - \epsilon_{HOMO}^{anion} \propto -\epsilon_{HOMO}^{anion}$ , since  $\epsilon_{LUMO}^{cation}$  is a constant reference in all cases. In density functional theory, the *HOMO* energy is the ionization potential.<sup>31</sup> The regional ionization potential ( $IP_k$ ) can then be given by<sup>32–34</sup>

$$IP_R = -\epsilon_H N_\Omega^- \quad (4)$$

This index is related to the local ionization potential proposed by Politzer to describe physical properties of organic molecules.<sup>32,33</sup> The Lewis acidity and basicity may correctly be assessed by the regional ionization potential ( $IP_R$ ). The regional IP values are summarized in Table 2 for the set of RTIL under study.

The regional ionization potential is used here as a descriptor that naturally describes the (electronic polarization) effect induced by the anion in interaction with a cation of general structure  $C_4C_1im$ . With the aid of this index, it is possible to reclassify the borderline RTILs: high ionization potential ( $IP_R > 1.5$  eV) leads to normal distributions, and low ionization potential ( $IP_R < 1.5$  eV) leads to bifunctional RTILs.<sup>32,33</sup> In this context, the chemical meaning of a higher or lower regional ionization potential is that in the first case both the anion and cation may participate in any HB to the substrate, whereas in the latter the cation dominates HBA and HBB processes.



**Table 2. Frontier Molecular Orbital Energies and Their Differences<sup>a</sup>**

ion	HOMO	LUMO	$IP_R$	HBA/HBB distribution <sup>b</sup>
$C_4C_1im^+$	-11.8	-5.1		
$BF_4^-$	-4.5	3.9	0.2	bifunctional
$CF_3CO_2^-$	-2.2	3.6	2.2	normal
$Cl^-$	-0.8	6.2	3.2	normal
$DCA^-$	-1.8	3.5	2.8	normal
$CH_3SO_3^-$	-2.0	2.7	2.6	normal
$NTf_2^-$	-4.1	2.8	0.8	bifunctional
$OAc^-$	-1.0	2.8	3.4	normal
$OTf^-$	-2.9	3.4	1.4	bifunctional
$PF_6^-$	-5.3	4.1	0.0	bifunctional

<sup>a</sup>All values were calculated at the B3LYP/AUG-cc-pVTZ level of theory and are expressed in electronvolts. <sup>b</sup>Lewis acidity and basicity distribution. See text for details about the labeling.

In order to illustrate the reliability of this proposal, two model reactions have been chosen. Welton et al. studied the nucleophilic aromatic substitution ( $S_NAr$ ) between 1-fluoro-4-nitrobenzene and *p*-anisidine in several ionic liquids.<sup>4</sup> The best solvents in terms of higher yields are the ionic liquids bearing  $CF_3CO_2^-$  and  $CH_3SO_3^-$  anions (yields >70%). On the other hand, when the reaction is run in  $[C_4C_1im][BF_4]$ ,  $[C_4C_1im][NTf_2]$ ,  $[C_4C_1im][OTf]$ , and  $[C_4C_1im][PF_6]$ , the yields are below 5%. The authors proposed that the best ionic liquids for this reaction must contain an anion with high values of  $\Delta G$  of deprotonation of the conjugate acid of the anion. These anions must be stable species, and therefore, the capability to accept a hydrogen bond (from the reactants) will be expressed at the anion moiety of the RTIL. Those RTILs bearing anions with enhanced Lewis basicity are reported to be the best candidates for this  $S_NAr$  reaction. High Lewis basicity or regional ionization potential implies that the capability to accept a hydrogen bond is increased. Therefore, the anions  $CF_3CO_2^-$ ,  $Cl^-$ ,  $DCA^-$ ,  $CH_3SO_3^-$ , and  $OAc^-$  may safely be considered as potential counterions for the  $C_4C_1im$  based ionic liquids as reaction media for a  $S_NAr$  process. An important question that immediately appears is whether an ionic liquid satisfying this condition may interfere as potential nucleophile in this type of reaction. We recently demonstrated that  $S_NAr$  reactions need protonated nucleophiles to promote the leaving group detachment.<sup>35,36</sup> Since ionic liquids with normal distribution are formed by stable bases from strong conjugated acids, these anions are not good nucleophiles for the  $S_NAr$  process in any way. Consequently, the results reported by Welton et al. are in good agreement with those predicted with the regional ionization potential model defined in eq 4.

On the other hand, Welton,<sup>29</sup> Seddon,<sup>37</sup> and many other authors<sup>38–40</sup> have studied the Diels–Alder reaction between cyclopentadiene and the dienophiles acrolein, methyl acrylate, and acrylonitrile in several RTILs. The best results (yields and reaction rates) have been reported for the RTILs  $[C_4C_1im][BF_4]$ ,  $[C_4C_1im][NTf_2]$ ,  $[C_4C_1im][OTf]$ , and  $[C_4C_1im][PF_6]$ . On the other hand, the lower yields (reaction rate data are scarce in literature) were obtained with ionic liquids containing the anions  $Br^-$  and  $CF_3CO_2^-$ . Although the RTIL  $[C_4C_1im][Br]$  has not been studied in these works, the  $[C_4C_1im][Cl]$  pair is a reasonable choice to model this cycloaddition in ionic solvents. In this case, the best performance as reaction media is related to RTILs with a bifunctional Lewis acidity/basicity distribution. Note that, as proposed by Welton and Chiappe,<sup>29</sup>

solvation and catalysis are better achieved for RTILs bearing weak Lewis basic anions. The proposed mechanism of catalysis involves a hydrogen bond interaction between the cation and a heteroatom in the dienophile. According to these authors, a successful interaction is achieved when the anion behaves as a spectator counterion that facilitates the polarization of the cation, not competing for a hydrogen bond to the cation. This observation reveals the importance of the anion on the HBA of cation: in this case, the role of the anion is to modulate the electronic charge reorganization at the cation that facilitates the hydrogen bond interaction toward the reaction center. These results are again in good agreement with the model presented herein. Additionally, the same analysis may be accomplished for other reactions where bifunctionally distributed ionic liquids may become better choices as reaction media. Just to name a few examples, consider for instance, Kemp eliminations,<sup>41,42</sup> electrophilic additions,<sup>43–45</sup> and some Knoevenagel condensations.<sup>46,47</sup>

## CONCLUSIONS

In summary, we propose that the denomination “cation or anion effects” may be not a priori related to HBA or HBB abilities of RTILs, in the sense that at least in imidazolium based ionic liquids these properties may be not intrinsic properties of the ions. It appears that the normal or bifunctional Lewis acidity/basicity of a RTIL does depend on the pair of ions that form it, with the anion not being a priori a region for accepting hydrogen bonding. This result has been already addressed by Welton et al. and other authors on an experimental basis.<sup>1,2</sup> The main results presented herein are expected to be of relevance because they may be used (i) to correctly assign the Lewis acidic and basic centers in the interpretation of specific solvation or catalysis experimentally observed and (ii) to guide the theoretical study of solvation effects by quantum chemical methods using the supermolecule approach, and (iii) the condensed to atom Fukui function model may be used for the design of new RTILs, where the Lewis acidity or Lewis basicity is being optimized for a specific reaction (task specific RTILs). The model has been contrasted against experimental results for two organic reactions. The separation between normal and bifunctional ionic liquids introduces a borderline zone that cannot be assessed with a desired resolution. We expect that the classification of ionic liquids presenting normal, bifunctional, or borderline hydrogen bonding acidity/basicity can be more precisely established as more experimental data will be available in the future. Future work is in process in our group to generalize these ideas for a more complete set of RTILs, incorporating other series of cations and anions.

## ASSOCIATED CONTENT

### Supporting Information

Complete reference 27 and Cartesian coordinates, total energy, and number of imaginary frequencies of the ionic pairs calculated. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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