

## Influence of the Correlation, Aggregation, and Solvation on *ab initio* Computed Li–C, Li–N, and Li–Li NMR Coupling Constants

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The  $^1J$  and  $^3J(\text{C-Li})$ ,  $^1J(\text{N-Li})$ , and  $^2J(\text{Li-Li})$  NMR coupling constants have been calculated for various homogeneous and heterogeneous aggregates of methyllithium and lithium dimethylamide at the HF and MP2 levels of calculation. Ethereal solvation has also been taken into account either through a continuum model or through the explicit introduction of  $\text{Me}_2\text{O}$  molecules. The results obtained are in good general agreement with the experimental data available for methyllithium itself or model alkylolithiums and supports the empirical rule proposed by Bauer, Winchester, and Schleyer to evaluate  $^1J(\text{C-Li})$  provided that calculations include solvent and/or aggregation effects.

### Introduction

The organolithium compounds are among the most widely used reagents in organic chemistry.<sup>1</sup> Their nucleophilic and basic properties explain why these species play a unique role in synthesis. Their tendency to aggregation in solution is well-known, and the consequences of this feature on their reactivity are the object of continuous studies. The recent increase of high-field NMR performances and the optimization of new pulse sequences have made this spectroscopy the best current tool for the study of the solution state of such reagents.<sup>2</sup> Still, determining the aggregation level of an organolithium is a difficult task. Bauer, Winchester, and Schleyer have compared the  $^1J(\text{C-Li})$  constants for a series of alkylolithiums under various oligomeric forms.<sup>3</sup> They have deduced from this survey an empirical rule (called hereafter the BWS rule)  $^1J(^{13}\text{C}-^6\text{Li}) = (17 \pm 2)/n$  (where  $n$  is the number of lithium nuclei surrounding the carbon considered). Thus, a standard  $^{13}\text{C}$  spectrum can give relatively direct access, through the  $^1J(^{13}\text{C}-^6\text{Li})$  and multiplicity determinations, to an evaluation of the aggregation state of  $^6\text{Li}$ -labeled organolithium reagents provided they are engaged in a so-called static aggregate. Because they rarely bring crucial information on the molecular conformations (except, of course, for the

$^3J(\text{H-H})$  ones, using Karplus' type relationships), coupling constants are not often computed.<sup>4</sup> Nevertheless, the BWS rule has been theoretically validated for  $^1J(^{13}\text{C}-^7\text{Li})$  and even extended to the  $^1J(^{15}\text{N}-^6\text{Li})$  couplings thanks to the pioneering work of Kikuchi et al.<sup>5</sup> carried out at the Hartree–Fock level. The comparison of the experimental  $^1J(\text{C-Li})$  or  $^1J(\text{N-Li})$  values to the computed ones thus became very helpful to determine the aggregation state or the geometrical arrangement around the lithium through a combined NMR-quantum mechanics approach. However, the highly accurate treatment of spin–spin coupling using correlated approaches is known to be computer-demanding.<sup>4b</sup> This limits such calculations to relatively small species, which often hardly model the sophisticated systems experimentally studied, or to DFT-based methods with the uncertainties linked, in the case of coupling constants,<sup>6</sup> to the choice of the functional. However, because simplifications are needed, it appeared interesting to evaluate their respective impact on the quality and the accuracy of the results. Three different alleviation modes have been considered, that is the number of atoms in the aggregates, the solvent, and the correlation contribution. To our knowledge, the influence of this last term on the nuclear spin–spin  $^1J(\text{N-Li})$  coupling constants had not been taken into account yet. We chose to focus on simple representative model compounds, e.g., methyllithium and lithium dimethylamide,

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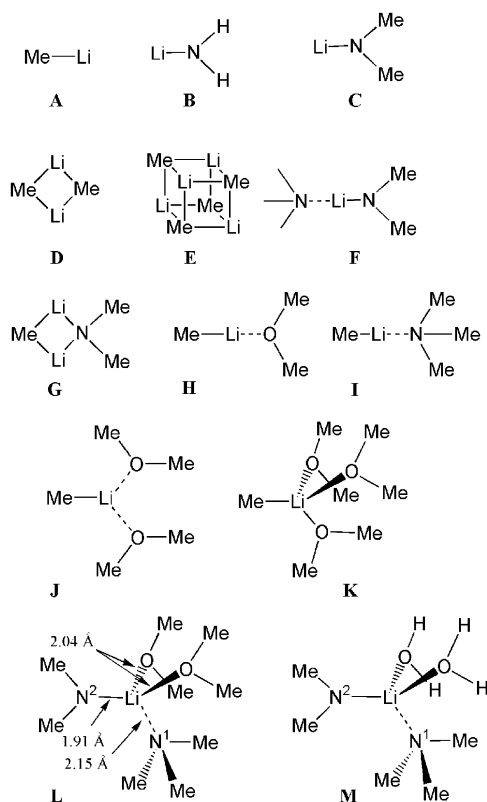


FIGURE 1. Organolithium systems considered in this work.

and to examine various homo/heterogeneous aggregates of these molecules for their isolated as well as solvated state (Figure 1).

The  $^{13}\text{C}$ - $^6\text{Li}$  and  $^{15}\text{N}$ - $^6\text{Li}$  coupling constants have been calculated at the HF and MP2 levels for all these systems. The  $^2J(\text{Li-Li})$  coupling constants have also been taken into account, despite their small values, because of the importance of these data for the structure determination of multinuclear complexes and their experimental availability through  $^6\text{Li}$ - $^6\text{Li}$  INADEQUATE or COSY type experiments.<sup>3,7</sup>

## Results and Discussion

**Computational Details.** Except when notified in the text, all calculations have been performed using the usual 6-31G\*\* basis set. Geometries have been optimized in a preliminary step, within the Density Functional Theory framework using the B3P86 functional for consistency with previous works,<sup>8</sup> as implemented in the JAGUAR 3.5 software.<sup>9</sup> Influence of the solvent on the organolithium compounds conformation has been accounted for according to two different approaches: a continuous model (DELPHI)<sup>10</sup> and a discrete one in which up to three dimethyl ether molecules (taken as model of THF) have been complexed to the lithium species.

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In a second step the coupling constants have been determined at the HF and MP2 levels of calculation using the DALTON program.<sup>11</sup> All components, namely the diamagnetic and paramagnetic spin-orbit (DSO and PSO), spin-dipole (SD) couplings, and Fermi contact have been evaluated for the smallest compounds. As the DSO, PSO, and SD contributions were found negligible in all these cases, they will not be reported here. For the larger species, these three quantities have been completely neglected in order to accommodate computational limits. The specific influence of the solvent on these constants has also been taken into account, either within the SCRf (Self-Consistent-Reaction-Field)<sup>12,13</sup> scheme as implemented in DALTON<sup>14</sup> and using a continuum model for THF or explicitly as in the H–L structures (Figure 1). Only the  $^6\text{Li}$  data are reported here since the coupling constants for the 6 and 7 isotopes are simply proportional with one another.

**(MeLi)<sub>n</sub> Aggregates (n = 1, 2, and 4).** Table 1 shows that the coupling constants computed for the MeLi monomer (Figure 1A) are, whatever the approach used, in very poor agreement with the 17 Hz value expected from the BWS rule. All attempts to improve these results either by using a larger basis set or by estimating vibrational effects failed. Although strongly reducing the coupling constants, correlation effects, accounted for at the MP2 level of calculations, are also unable to lead to a reasonable coupling constant value. This suggests that another effect, such as solvation, should be considered. It will be done in details in the next section. The situation is, however, different for the dimer (Figure 1D) and the “static”<sup>2a</sup> tetramer (Figure 1E) of MeLi. As seen from Table 1, even at the HF level, computed coupling constants are in fair agreement with the BWS rule and measured values. For the dimer, MP2 corrections (<2 Hz) improve slightly the values and lead, for a gas-phase isolated species, to 9.9 vs  $8.5 \pm 1$  Hz from the BWS rule. The same quality of result is obtained for the tetramer: 7.0 Hz (theoretical) vs  $5.7 \pm 0.7$  from the BWS rule (each lithium being surrounded by three carbon nuclei). We will see in the following section that this statement still holds for the solvated dimer and tetramer. This good agreement suggests that  $^1J(\text{C-Li})$  coupling constants can be predicted at the MP2 level for such aggregates. Moreover, for larger analogous systems, the size of which would preclude MP2 evaluations, it is expected that a simple HF approach will still provide relatively reliable con-

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**TABLE 1. Coupling Constants (Hz) for Aggregates of Methyllithium<sup>a</sup>**

species	gas-phase geometry				solvated geometry			
	coupling constant	$d^b$ (Å)	$J(\text{HF})$	$J(\text{MP2})$	$d^b$ (Å)	$J(\text{HF})$	$J(\text{SCRF})$	$J(\text{MP2})$
MeLi [A]	$^1J(^{13}\text{C}-^6\text{Li})$	1.97	41.0	25.9	2.03	44.1	30.4	27.5
(MeLi) <sub>2</sub> [D]	$^1J(^{13}\text{C}-^6\text{Li})$	2.11	11.7	9.9	2.13	11.3	11.0	9.5
	$^2J(^6\text{Li}-^6\text{Li})$	2.18	3.9	4.2	2.25	3.1	2.9	3.4
(MeLi) <sub>4</sub> [E]	$^1J(^{13}\text{C}-^6\text{Li})^c$	2.19	7.0		2.22	6.7	6.7	6.0
	$^3J(^{13}\text{C}-^6\text{Li})$	3.66	0.4		3.68	0.4	0.4	0.4
	$^2J(^6\text{Li}-^6\text{Li})$	2.40	-0.7		2.44	-0.7	-0.7	-0.6

<sup>a</sup> The bond lengths were obtained at the B3P86 level, either in the gas phase or using a continuous model of solvation (see the text).

<sup>b</sup> Distance between coupled atoms. <sup>c</sup> Experimental value = 5.5 Hz in THF.<sup>2a,15</sup>

stants since the correlation contribution reduces upon the increasing size of the aggregate.

The Li–Li coupling constant can be calculated, even in the case of symmetrical species in which it cannot be measured directly. For the staggered conformer of (MeLi)<sub>2</sub>, it amounts to 4.2 Hz (Table 1).

**Solvation Effects on (MeLi)<sub>n</sub> Aggregates (n = 1, 2, and 4).** Table 1 also reports the values of the coupling constants obtained using optimized solvated geometries (B3P86 + DELPHI–THF), at the HF, SCRF, and MP2 levels of calculation.

For the dimer and the tetramer, using these geometries in which the C–Li bond length is slightly increased with respect to that in the gas phase, the agreement with the BWS value is improved. MP2 corrections are quite small for both aggregates. At this level of calculations, the theoretical value for (MeLi)<sub>4</sub> is 6.0 vs 5.5 Hz (measured in THF) or  $5.7 \pm 0.7$  (BWS rule). In the tetramer, the long-range  $^3J(^{13}\text{C}-^6\text{Li})$  equals 0.4 Hz and is insensitive to correlation effects. For the Li–Li coupling constants, our best estimate amounts to 3.4 Hz for (MeLi)<sub>2</sub>, a value drastically reduced to -0.6 Hz for the “static” tetramer. This tiny value is compatible with the INADEQUATE results obtained recently by Eppers et al.,<sup>7</sup> with those presented by McKeever et al.<sup>15</sup> in their pioneering work on that subject or with those by Brown et al.,<sup>16</sup> who concluded to the very smallness of this constant.

The set of data reported in Table 1 shows that SCRF calculations of the coupling constants are not significantly improved with respect to the HF values. For the monomer, the situation remains dramatic: the coupling constant amounts still to 27.5 Hz at the MP2 level, to be compared to  $17 \pm 2$  Hz (BWS rule). It has unfortunately not been possible to repeat the computation at the SCRF/MP2 level, which would have combined both solvent and correlation effects.

This prompted us to model the solvent as a cluster of Me<sub>2</sub>O and MeLi (Figure 1H and Table 2). With only one Me<sub>2</sub>O accreted, a significant improvement is observed, even at the uncorrelated HF level: 27.0 Hz, to be compared to 41 Hz (gas-phase isolated MeLi, Table 1) and to  $17 \text{ Hz} \pm 2$  Hz (BWS rule). At the MP2 level, the coupling constant is decreased to a much better value of 18.7 Hz. Adding a second Me<sub>2</sub>O species (Figure 1J), improves the agreement at the HF level: 18.9 Hz. The MP2 corrections are expected to be very small and to slightly reduce the value.

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**TABLE 2. Coupling Constant (Hz) for Solvated/Complexed Methyllithium**

species	coupling constant	$d^a$	$J(\text{HF})$	$J(\text{MP2})$
MeLi, Me <sub>2</sub> O [H]	$^1J(^{13}\text{C}-^6\text{Li})$	1.99	27.0	18.7
MeLi, 2 Me <sub>2</sub> O [J]	$^1J(^{13}\text{C}-^6\text{Li})$	2.03	18.9	
MeLi, 3 Me <sub>2</sub> O [K]	$^1J(^{13}\text{C}-^6\text{Li})$	2.07	14.6	
MeLi, NMe <sub>3</sub> [I]	$^1J(^{13}\text{C}-^6\text{Li})$	1.99	26.5	18.5
	$^1J(^{15}\text{N}-^6\text{Li})$	2.08	-3.1	-2.7

<sup>a</sup> Distance between coupled atoms.

If, finally, a third Me<sub>2</sub>O molecule is aggregated (Figure 1K), HF calculations give a value of 14.6 Hz, which is slightly underestimated with respect to that given by the extrapolation to  $n = 1$  in the BWS rule of thumb. We here recall that there is no sure experimental measure for MeLi monomer. There are however evidences for the existence of *sec*-BuLi monomers in THF, with a coupling constant amounting to 14.0 Hz,<sup>3</sup> close to our computed value, and departing slightly from the BWS rule. Experimental values for monomeric *t*-BuLi amounts to a still lower value of 11.9 Hz.<sup>2,3</sup>

These results suggest that correlation effects are not the dominant factors to get computationally correct coupling constants. Actually solvation and/or complexation, especially in the very close vicinity of the lithium atom, are/is the essential contribution(s) since a similar improved agreement between calculated and measured values takes place upon methyllithium aggregation (vide supra). This seems to explain the poor  $^1J(^6\text{Li}-^{13}\text{C})$  coupling constant, when compared to experiments, obtained by Ruud et al.<sup>17</sup> in their highly correlated calculations on the vinyl lithium species in the gas phase. Moreover, because of the increasing quality of the results with the number of solvent molecules surrounding the lithium atom, a feature not taking place in the SCRF treatment, it appears that the use of a continuous description of the solvent is precluded.

**Lithium Amides.** The importance of these reagents in organic synthesis incited us to consider simple model monomers as well as amine-amide complexes and one mixed aggregate between lithium dimethyl amide and methyllithium. The strong interaction observed between amines and amides in solution<sup>18</sup> as well as the interest recently raised by noncovalent complexes between chiral

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**TABLE 3. Coupling Constants (Hz) for Various Lithium Amides<sup>a</sup>**

species	coupling constant	$d^a$ (Å)	$J(\text{HF})$	$J(\text{MP2})$
H <sub>2</sub> NLi [B]	$^1J(^{15}\text{N}-^6\text{Li})$	1.74	-11.8	-11.0
Me <sub>2</sub> NLi [C]	$^1J(^{15}\text{N}-^6\text{Li})$	1.76	-13.1	-12.2
Me <sub>2</sub> NLi, NMe <sub>3</sub> [F]	$^1J(^{15}\text{N}-^6\text{Li})$	1.79	-9.9	-9.2
	$^1J(^{15}\text{N}-^6\text{Li})$	2.08	-2.8	-2.4
Me <sub>2</sub> NLi, MeLi [G]	$^1J(^{15}\text{N}-^6\text{Li})$	1.90	-8.3	-7.7
	$^1J(^{15}\text{N}-^6\text{Li})$	2.01	-4.4	-3.6
	$^2J(^6\text{Li}-^6\text{Li})$	2.21	2.0	2.3
	$^1J(^{13}\text{C}-^6\text{Li})$	2.10	12.7	10.9
	$^1J(^{13}\text{C}-^6\text{Li})$	2.12	13.4	11.0

<sup>a</sup> The bond lengths were obtained at the B3P86 level. <sup>b</sup> Distance between coupled atoms.

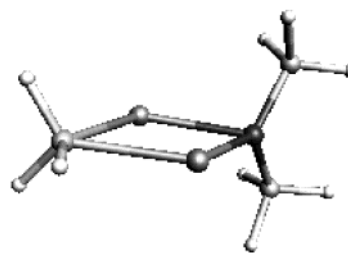
amides and alkyllithiums<sup>19</sup> explain these choices.  $^1J(^{15}\text{N}-^6\text{Li})$  constants are reported in Table 3 for H<sub>2</sub>NLi (Figure 1B) and Me<sub>2</sub>NLi (Figure 1C). Correlation effects are clearly less important than for MeLi, a feature also observed for (MeLi, NMe<sub>3</sub>) (Figure 1I) as can be seen from Table 2. This observation explains the good agreement between experimental data and Koizumi's results on  $^1J(^{15}\text{N}-^6\text{Li})$  constants obtained at the uncorrelated HF level of calculation using a MIDI-4\* basis set.<sup>5b</sup>

To our knowledge, no experimental data are available for H<sub>2</sub>NLi, but lithium dialkylamide monomers are known to exhibit  $|^1J(^{15}\text{N}-^6\text{Li})|$  absolute constant values between 7.5 and 10 Hz in solution.<sup>20</sup> Since the solvation is expected to reduce the computed gas-phase values, as found in the previous sections and by comparing  $J(\text{N}-\text{Li})$  in Me<sub>2</sub>NLi to that in the complex (Me<sub>2</sub>NLi, NMe<sub>3</sub>) (Figure 1F), our computed values, reported in Table 3, seem to be reasonable. Moreover, our calculations on this complex suggest that a small, but still measurable,  $^1J(\text{N}-\text{Li})$  coupling constant between the lithium of an amide and the nitrogen of a complexing amine could be observed in some cases. As for structure F, <sup>6</sup>Li NMR spectrum of the symmetrical G structure (Figures 1G and 2), one of the smallest possible mixed aggregates of lithium amide and alkyllithium, is expected to be a singlet. However, most static conformations of such a complex are disymmetrical and will thus exhibit two different N–Li bonds (see Table 3) and therefore distinct  $^1J(^{15}\text{N}-^6\text{Li})$  coupling constants (the longer the bond, the smaller the coupling constant). The situation is different for the  $^1J(^6\text{Li}-^{13}\text{C})$  coupling constants: the two C–Li bond lengths are found to be almost identical. Therefore, at the correlated level of calculations, the two  $^1J(^6\text{Li}-^{13}\text{C})$  constants differ by less than 0.1 Hz for the conformer displayed in Figure 2. Finally, the  $^2J(^6\text{Li}-^6\text{Li})$  coupling constant amounts to 2.0 Hz at the SCF level; the correlation contribution is positive and increases this value up to 2.3 Hz.

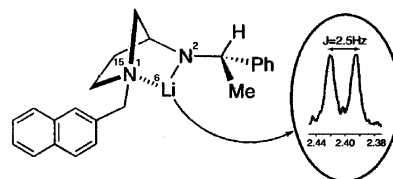
**An Illustrative Application: The (Me<sub>2</sub>NLi, 2Me<sub>2</sub>O, NMe<sub>3</sub>) Aggregate.** The previous sections suggest that

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**FIGURE 2.** Geometrical arrangement of complex G (MeLi–LiNMe<sub>2</sub>) used in the calculation.



**3-AP**

**FIGURE 3.** <sup>6</sup>Li spectrum of a <sup>6</sup>Li–<sup>15</sup>N doubly labeled 3-aminopyrrolidine (3-AP) lithium amide.

reliable coupling constants can be obtained at the HF level of calculation provided that the solvation of the lithium atom is correctly described. We have applied this approach to a solvated model of the <sup>6</sup>Li–<sup>15</sup>N doubly labeled lithium amide depicted in Figure 3.

This 3-aminopyrrolidine (3-AP) lithium amide is a chiral ligand, forming noncovalent complexes with alkyllithium compounds. Because they react with aldehydes, yielding alcohols with relatively high enantiomeric excesses, these complexes have been the objects of detailed NMR investigations.<sup>21</sup> This solvated amide is unfortunately much too large to be computed as such. It has thus been modeled by the complex Me<sub>2</sub>NLi–2Me<sub>2</sub>O–NMe<sub>3</sub> (Figure 1L) in which NMe<sub>3</sub> mimics the intramolecular N<sup>1</sup>–Li bond and the two Me<sub>2</sub>O molecules have been added to complete the first coordination shell of the lithium atom. The full optimization of this complex (B3P86/6-31G\*\*) led to the characteristic distances reported in Figure 1 (Li–O = 2.04 Å, Li–N<sup>2</sup> = 1.91 Å and Li–N<sup>1</sup> = 2.15 Å). These values were found to be in fine accord with typical crystal structure data for 1:1 lithium amide-amine mixed complexes<sup>22</sup> (Li–N = 2.04 and 2.14 Å).<sup>22b</sup> In a second step and because of computational limitations, the calculation of the coupling constants has been performed on the simpler (Me<sub>2</sub>NLi–2H<sub>2</sub>O–NMe<sub>3</sub>) aggregate (Figure 1M), derived from the optimized structure of Figure 1L by replacing the oxygen methyl radicals by hydrogen atoms, with standard OH bond lengths (0.96 Å), and using the 6-31G\* basis set. Our calculation predicts the  $^1J(^{15}\text{N}^1-^6\text{Li})$  coupling constant between the lithium and the amine nitrogen to amount to –2.2 Hz, close to the experimental value of 2.5 Hz.

(21) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267.

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The similarity between this  $^1J(\text{N-Li})$  value and that calculated for  $\text{MeLi-NMe}_3$  ( $-2.7$  Hz; Table 2, entry 4) suggests that this coupling constant is in the range expected for a lithium cation–tertiary amine coordination. This piece of data supports the folding of 3-AP lithium amide into a norbornyl-like structure as well as the existence of measurable through-space Li/N couplings. Incidentally, this value also agrees with the  $2.7$  Hz coupling measured for  $\alpha$ -aminoorganolithium compounds recently studied by Low and Gawley, in which a coordination between the lithium and the  $\alpha$ -nitrogen atom takes place.<sup>23</sup> Finally, the  $^1J(\text{N-Li})$  coupling constant between Li and  $\text{N}^2$  is computed to be equal to  $-7.5$  Hz. Albeit no measured value is available for this very amide, experimental  $^1J(\text{N-Li})$  couplings in lithium amides are found in the same range.<sup>20</sup>

### Conclusion

The results presented in this paper indicate that calculated values of  $^1J(^{13}\text{C-}^6\text{Li})$  and  $^1J(^{15}\text{N-}^6\text{Li})$  coupling

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constants can be in fine agreement with corresponding experimental data provided that the aggregation and/or the solvation of the organolithium species considered is taken in account. It appears also that the refinement of the computational level (size of the basis set, introduction of electron correlation) is of a significantly lesser importance than intermolecular interactions in the determination of these one-bond spin–spin coupling constants. Finally, the good agreement found between the  $^1J(\text{N-Li})$  calculated on a model system and that measured on a 3-aminopyrrolidine lithium amide comes as a supplementary evidence to the norbornyl folding of these structures, deduced from nonempirical theoretical calculations,<sup>24</sup> as well as NOESY and HOESY NMR spectra.<sup>19c</sup> It is worth mentioning that this type of conformational arrangement has also been characterized by X-ray crystallography for platinum and vanadium complexes of 3-AP.<sup>25</sup>

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