

# Speciation of $\text{ZnMe}_2$ , $\text{ZnMeCl}$ , and $\text{ZnCl}_2$ in Tetrahydrofuran (THF), and Its Influence on Mechanism Calculations of Catalytic Processes

Juan del Pozo,<sup>†,∇</sup> María Pérez-Iglesias,<sup>†</sup> Rosana Álvarez,<sup>§</sup> Agustí Lledós,<sup>\*,‡,Ⓜ</sup> Juan A. Casares,<sup>\*,†</sup> and Pablo Espinet<sup>\*,†,Ⓜ</sup>

<sup>†</sup>IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47011 Valladolid, Spain

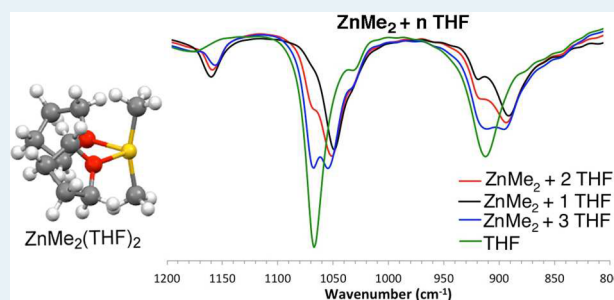
<sup>‡</sup>Departament de Química, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Spain

<sup>§</sup>Departamento de Química Orgánica, Facultad de Química (CINBIO), Universidade de Vigo, Campus As Lagoas-Marcosende, 36310 Vigo, Spain

## S Supporting Information

**ABSTRACT:** This paper examines the speciation of  $\text{ZnMe}_2$ ,  $\text{ZnMeCl}$ , and  $\text{ZnCl}_2$  in tetrahydrofuran (THF) solution, and provides experimental (infrared (IR) and calorimetric experiments) and density functional theory (DFT) data to conclude that the species in THF solution are, beyond a doubt,  $\text{ZnMe}_2(\text{THF})_2$ ,  $\text{ZnMeCl}(\text{THF})_2$ , and  $\text{ZnCl}_2(\text{THF})_2$ . Consequently, coordinated THF should be used in DFT mechanistic calculations (e.g., Negishi reactions in THF). Naked or single THF coordinated molecules are virtually nonexistent in THF solutions. A cluster-continuum model for the solvent is recommended to obtain a more-correct representation. The presence or absence of THF produces a marked effect on the thermodynamics of the Negishi catalysis and a lesser effect on the kinetics of the transmetalation.

**KEYWORDS:** Negishi, THF solutions,  $\text{ZnX}_2$  speciation, DFT and experimental, cluster continuum model, transmetalation, calorimetry



## INTRODUCTION

Many transition-metal-catalyzed reactions are carried out in noncoordinating solvents; however, more frequently, the solvents used have some—from modest to high—coordinating ability. This is seldom a problem for experimental kinetic studies of reaction mechanisms: the data measured in the experiment simply impose their own physical value, regardless of the prejudices of the experimentalist about the possible implication of the solvent to produce these values. In a theoretical calculation, however, it is the decision of the theoretician to keep open the opportunity for the solvent to participate in the mechanism, or deny it by not including explicit solvent molecules as potentially coordinating ligands.<sup>1,2</sup> This choice influences the entire evolution of the computational study.

Modeling organic solvents as a polarizable continuum medium characterized by its dielectric constant (implicit solvent model) is mandatory in density functional theory (DFT) calculations of organometallic reactions;<sup>3</sup> however, this correction cannot spare the need of explicit solvent molecules as potential ligands that can interact coordinate to acid metal centers, with the corresponding enthalpic and entropic consequences. A recent example has shown that the direct Ar–benzyl coupling of  $\text{ZnPh}_2$  with benzyl halides occurs very fast and efficiently in benzene, but becomes very slow and inefficient if tetrahydrofuran (THF) is added to the benzene

solution.<sup>4</sup> This experimental observation was interpreted considering that THF coordination to  $\text{ZnPh}_2$  is stronger than the interaction of the  $\text{ZnPh}_2$  with the benzyl halide reagent. Since the latter is needed for the direct coupling, the addition of THF quenches the coupling. This behavior was also found by theoretical calculations, only when THF molecules were explicitly included. The case could have never been explained with neglect of the solvent molecules.

Calculations not adding solvent molecules as coordinated ligands often create *in silico* species that cannot be conceived to exist in the presence of a coordinating solvent (the reader will excuse us for not mentioning specific examples here). For the case of good coordinating solvents (e.g., acetonitrile (MeCN), dimethylformamide (DMF), hexamethylphosphoramide (HMPA), pyridine (py), dimethyl sulfoxide (DMSO), etc.), a chemically judicious prior guess in favor of their participation can be made. This adds complexity to the mechanism and, very importantly, brings about the problem of how to address entropy.<sup>1,5,6</sup> Moreover, in cases of small enthalpy values, the accompanying entropic contribution is very significant, and overestimation of the entropy might introduce high percentages of error in  $\Delta G$ , perhaps leading to mistaken interpretations.<sup>7</sup>

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Thus, in these cases, the decision to use (or not use) explicit participation of solvent molecules can be controversial, and disregarding the possible participation of poorly coordinating solvents is a reasonable temptation. Papers with both practices can be found. Skipping references to other authors, in some of our papers on the mechanism of the Negishi reaction, we have used  $\text{ZnMe}_2(\text{THF})_2$ ; in others, we have used just  $\text{ZnMe}_2$ , depending on the preference of the theoreticians contributing to the paper.<sup>8</sup> In both circumstances, our calculations have satisfactorily reproduced the experimental  $\Delta G^\ddagger$  data available. For this reason, we are still in doubt regarding whether  $\text{ZnMe}_2(\text{THF})_2$  and not just  $\text{ZnMe}_2$  must be considered. Since the Negishi reaction is gaining importance, particularly for difficult coupling reactions involving  $\text{C}(\text{sp}^3)$ , and since THF is the usual solvent for these reactions (but also for many others!), we have decided to investigate experimentally the speciation of  $\text{ZnMe}_2$ ,  $\text{ZnClMe}$ , and  $\text{ZnCl}_2$  in THF.

What is known today about  $\text{ZnMe}_2$  and  $\text{ZnMe}_2(\text{THF})_2$ ? Back in 1859, Sir Edward Frankland reported the synthesis of  $\text{ZnMe}_2$ .<sup>9,10</sup> He noticed that its separation from the solvent ( $\text{OEt}_2$ ) was almost impossible.  $\text{ZnMe}_2$  is a liquid at room temperature, which was structurally characterized as a symmetric linear molecule ( $\text{sp}$  hybridization for Zn) in the gas phase in 2003,<sup>11</sup> and in the solid state ( $d_{\text{C-Zn}} = 1.927(6)$  Å) in 2011.<sup>12</sup> Quantum mechanical calculations indicate considerable polarization of the two identical Zn–Me bonds toward the C atoms.<sup>13</sup> Surprisingly, there are no recent experimental studies on the formation of complexes of  $\text{ZnMe}_2$  with ethers (often used as reaction solvents), but remarkable studies by Thiele in 1962 showed that cyclic ethers  $\text{O}(\text{CH}_2)_n$  ( $n = 2-5$ ; this includes the case of THF) form 1:2 complexes with  $\text{ZnMe}_2$ .<sup>14</sup> Although this study lacks modern structural characterization, the stoichiometry  $\text{ZnMe}_2(\text{THF})_2$  was ascertained by full elemental analysis. Determination of its apparent molecular weight by cryoscopy, in benzene or in cyclohexane, afforded values lower or much lower than expected for the 1:2 adduct, meaning that  $\text{ZnMe}_2(\text{THF})_2$  undergoes partial THF dissociation in these solvents (somewhat higher in benzene than in cyclohexane).<sup>14,15</sup> Another indication that the binding of THF to  $\text{ZnMe}_2$  is not strong was the observation of a large dissociation of  $\text{ZnMe}_2(\text{THF})_2$  in its vapor.<sup>14</sup> To the best of our knowledge, a structural characterization of  $\text{ZnMe}_2(\text{THF})_2$  in the solid state is still lacking. The available X-ray structure of  $[\text{Zn}(\text{C}_6\text{F}_5)_2(\text{THF})_2]$  displays a highly distorted tetrahedral geometry,<sup>16</sup> with two angles ( $\text{C-Zn-C} = 132.1^\circ$  and  $\text{O-Zn-O} = 92.4^\circ$ ) very different from the  $109.47^\circ$  in an ideal tetrahedron.<sup>17</sup> The related  $[\text{ZnCl}_2(\text{THF})_2]$  also displays a distorted tetrahedral geometry with  $\text{Cl-Zn-Cl} = 127.24^\circ$  and  $\text{O-Zn-O} = 97.52^\circ$ , and the two slightly differently arranged THF molecules produce different Zn–Cl (2.176 and 2.184 Å) and Zn–O (2.009 and 2.016 Å) bonds.<sup>18</sup>  $\text{ZnEtCl}$  exists in the solid state as a coordination polymer with three-coordinated Zn.<sup>19</sup> As for the Schlenk-type equilibria between  $\text{ZnR}_2$  and  $\text{ZnX}_2$  ( $\text{R} = \text{Me, Et}$ ;  $\text{X} = \text{Cl, I}$ ), it is well established by infrared (IR) spectroscopy that they are strongly shifted toward the formation of  $\text{ZnRX}$  in THF and in  $\text{OEt}_2$ .<sup>20</sup>

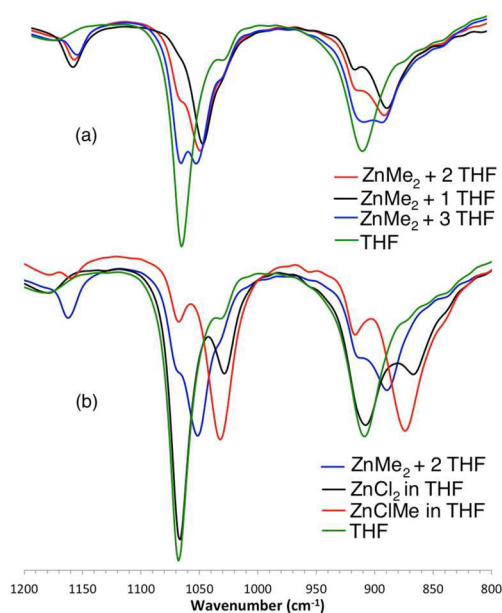
Notwithstanding the reported facility of  $\text{ZnMe}_2(\text{THF})_2$  to dissociate THF in other circumstances,<sup>14</sup> it seems reasonable to us that, in solutions of  $\text{ZnMe}_2$  in THF, the coordinating nature of THF and the enormous concentration of THF in itself, acting as a solvent,<sup>21</sup> should largely push any associative equilibrium of THF with  $\text{ZnMe}_2$  toward the tetracoordinated compound. Here, we are searching for objective data, both from

experiment and from calculations, on the speciation of Zn derivatives in THF solution.

## RESULTS AND DISCUSSION

**Nuclear Magnetic Resonance (NMR) Studies.** Variable-temperature nuclear magnetic resonance (NMR) is the technique that usually allows for precise experimental studies in solution, but our experiments on  $\text{ZnMe}_2/\text{THF}$  mixtures failed to provide useful information. The  $^1\text{H}$  or  $^{13}\text{C}$  spectra of a 1:2 molar  $\text{ZnMe}_2:\text{THF}$  mixture at  $-60^\circ\text{C}$  showed only one Me signal. Additions of THF did not produce any significant drift. This is compatible with THF dissociation being negligible in THF or, more likely, with NMR not being appropriate for this problem.

**Infrared (IR) Spectroscopy Studies.** Solutions made by mixing THF and the corresponding Zn compound ( $\text{ZnMe}_2$ ,  $\text{ZnMeCl}$ , or  $\text{ZnCl}_2$ ) under nitrogen, were examined by infrared (IR) spectroscopy. Neat THF (no Zn present) displays two C–O intra-ring stretching bands at  $\sim 1067\text{ cm}^{-1}$  ( $\nu_{\text{asym}}$ ) and  $\sim 908\text{ cm}^{-1}$  ( $\nu_{\text{sym}}$ ).<sup>22</sup> Since, in the Zn complexes, these vibrational modes also involve participation of the O–Zn bond, the two absorptions are useful to evaluate the THF/Zn interactions. Figure 1a shows the IR spectra in the range of  $800-1200\text{ cm}^{-1}$



**Figure 1.** (a) IR spectra of mixtures of  $\text{ZnMe}_2$  and THF in ratios of 1:1 (black), 1:2 (red), and 1:3 (blue); (b) IR spectra of mixtures of  $\text{ZnMe}_2$  (blue),  $\text{ZnMeCl}$  (red) or  $\text{ZnCl}_2$ , and THF. The bands of uncoordinated THF ( $1067$  and  $908\text{ cm}^{-1}$ ) are observed in all of the spectra.

for the different solutions of  $\text{ZnMe}_2$  in THF, mixing the two reagents in 1:1, 1:2, and 1:3 ratios in order to allow for the formation of the potential complexes  $\text{ZnMe}_2(\text{THF})$ ,  $\text{ZnMe}_2(\text{THF})_2$ , or higher coordination numbers. The wavelengths corresponding to the main species observed in Figure 1 are listed in Table 1.

In the 1:1 mixture of THF and  $\text{ZnMe}_2$ , the  $1067\text{ cm}^{-1}$   $\nu(\text{C-O})_{\text{asym}}$  band of THF shifts down to  $1048\text{ cm}^{-1}$ . An analogous effect (shift from  $908$  to  $888\text{ cm}^{-1}$ ) is found for the symmetric stretching band (Figure 1a and Table 1, entry 1), suggesting weakening of the C–O bond upon THF coordination.

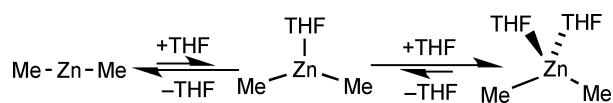
**Table 1.** IR Wavenumbers for C–O Stretching of THF

entry	compound	$\nu(\text{C-O})_{\text{sym}}; \nu(\text{C-O})_{\text{asym}}$ ( $\text{cm}^{-1}$ )	$\Delta\nu(\text{C-O})_{\text{asym}}; \Delta\nu(\text{C-O})_{\text{sym}}$ ( $\text{cm}^{-1}$ ) <sup>a</sup>
1	neat THF	1067; 908	
2	ZnMe <sub>2</sub> + 1 equiv THF	1048; <sup>b</sup> 888 <sup>b</sup>	19; 20 <sup>b</sup>
3	ZnMe <sub>2</sub> (THF) <sub>2</sub>	1051; 890	16; 18
4	ZnClMe(THF) <sub>2</sub>	1033; 874	34; 34
5	ZnCl <sub>2</sub> (THF) <sub>2</sub>	1028; 866	39; 42

<sup>a</sup> $\Delta\nu(\text{C-O}) = \nu(\text{C-O})_{\text{neat}} - \nu(\text{C-O})_{\text{coord}}$ . <sup>b</sup>*Deceptive!!*

The addition of further THF is done first to reach the stoichiometric proportion ZnMe<sub>2</sub>:THF = 1:2, and then to provide a large excess of THF (1:3 ratio), giving rise to an apparent shift of the minimum of the band assigned to coordinated THF, from 1048 cm<sup>-1</sup> to 1051 cm<sup>-1</sup> and then to 1055 cm<sup>-1</sup>. A principal component analysis of the spectra (Figures S2 and S3 in the Supporting Information (SI)) shows that this shift is a deceptive appearance that is due to the overlap of  $\nu(\text{C-O})_{\text{asym}}$  for ZnMe<sub>2</sub>(THF)<sub>2</sub> (1048 cm<sup>-1</sup>) and free THF (1067 cm<sup>-1</sup>) in different proportions. The same deceptive effect is observed for  $\nu(\text{C-O})_{\text{sym}}$ . Interestingly, in the ZnMe<sub>2</sub>:THF = 1:2 mixture, the  $\nu(\text{C-O})_{\text{asym}}$  band shows a shoulder at 1067 cm<sup>-1</sup>, revealing that ZnMe<sub>2</sub>(THF)<sub>2</sub> undergoes some dissociation.<sup>23</sup>

In conclusion, all the IR spectra observed detect only ZnMe<sub>2</sub>(THF)<sub>2</sub> and free THF, regardless of the ZnMe:THF ratio. Unobservable ZnMe<sub>2</sub> must exist for THF/Zn ratios lower than 2:1. The existence of small amounts (below the limits of observation) of ZnMe<sub>2</sub>(THF) in equilibrium cannot be fully disproved; however, overall, the coordination of a second THF molecule to an initial species ZnMe<sub>2</sub>(THF) is clearly preferred to the coordination of a first THF molecule to ZnMe<sub>2</sub>. In other words, as suggested in Scheme 1, the existence of three-coordinated ZnMe<sub>2</sub>(THF) seems very unfavorable versus its rearrangement to a mixture of ZnMe<sub>2</sub> and ZnMe<sub>2</sub>(THF)<sub>2</sub>.

**Scheme 1.** THF Coordination Equilibria, As Suggested by IR Observations

The changes in  $\nu(\text{C-O})$  upon coordination to ZnMe<sub>2</sub> are small (Table 1,  $\Delta\nu(\text{C-O}) = 20 \text{ cm}^{-1}$ ), suggesting that the O–Zn dative bond in ZnMe<sub>2</sub>(THF)<sub>2</sub> is weak. The O–Zn bonds are expected to be stronger for more acidic ZnXY fragments. In effect, the differences  $\Delta\nu(\text{C-O})$  rise to 34/34 cm<sup>-1</sup> and 39/42 cm<sup>-1</sup>, respectively, for the symmetric/asymmetric vibrations in ZnClMe(THF)<sub>2</sub> and ZnCl<sub>2</sub>(THF)<sub>2</sub> (Figure 1b).<sup>24</sup>

IR evidence is fairly conclusive, supporting that, in THF, the three Zn derivatives ZnMe<sub>2</sub>, ZnMeCl, and ZnCl<sub>2</sub> are only observed as their ZnXY(THF)<sub>2</sub> complexes. However, dissociation equilibria with very small  $\Delta G^0$  values (e.g., 2 kcal mol<sup>-1</sup>) could make the concentration of other species, such as ZnXY(THF), unobservable. Furthermore, IR observation cannot detect uncoordinated ZnXY molecules, such as ZnMe<sub>2</sub>. Consequently, below, we examine further evidence via other methods.

**Calorimetric Studies.** The heat of reaction of liquid ZnMe<sub>2</sub> with THF was measured in a microcalorimeter by adding THF

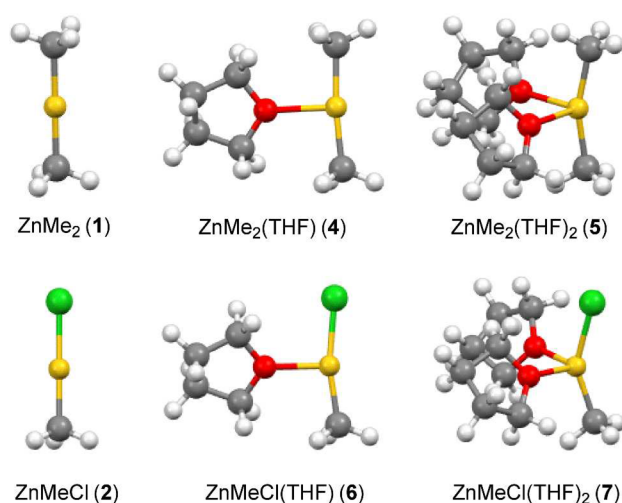
to neat ZnMe<sub>2</sub>. First, two moles of THF per mole of ZnMe<sub>2</sub> were added to reach the stoichiometric ratio of ZnMe<sub>2</sub>:THF = 1:2. Then, an excess of THF was injected. The first addition of THF produced  $\Delta H = -6.3 \text{ kcal mol}^{-1}$ . The second injection produced only a modest additional heat release ( $\Delta H = -1.6 \text{ kcal mol}^{-1}$ ). These results support that coordination had not been fully completed after the addition of stoichiometric THF and required an excess of solvent in order to further shift the coordination equilibrium toward ZnMe<sub>2</sub>(THF)<sub>2</sub>. This tendency of ZnMe<sub>2</sub>(THF)<sub>2</sub> to establish some dissociation equilibrium in THF is in agreement with the IR observations, and it means that part of the heat released in the second addition comes from fulfilling the tetracoordination of ZnMe<sub>2</sub> and is not due to the dilution enthalpy of ZnMe<sub>2</sub>(THF)<sub>2</sub> (1) in THF (1) (so-called *excess enthalpy*). The overall heat released after the addition of an excess of THF ( $-7.9 \pm 0.2 \text{ kcal mol}^{-1}$ ) accounts for the enthalpy of coordination of THF to ZnMe<sub>2</sub> to form ZnMe<sub>2</sub>(THF)<sub>2</sub> plus the excess enthalpy, but the two contributions cannot be measured independently. Excess enthalpy values reported in the literature suggest that this contribution should be small, compared with the bond energies. Reported values of excess enthalpy, corresponding to the dilution of nonprotic solvents (that we take as models of ZnMe<sub>2</sub>) in THF, span from about +0.19 kcal mol<sup>-1</sup> for *n*-hexane (maximum value for a molar fraction of  $\chi = 0.5$ ),<sup>25</sup> to +0.026 kcal mol<sup>-1</sup> for acetonitrile (maximum value for  $\chi = 0.35$ ).<sup>26</sup> Also reported, the heat of dilution of MgEt<sub>2</sub>(THF)<sub>2</sub> from 0.2 M to 0.043 M in THF is  $-0.2 \text{ kcal mol}^{-1}$ .<sup>27</sup> Taking these data as reference, a reasonable error estimation if ignoring the heat of dilution in our measured figures may be approximately  $\pm 0.2 \text{ kcal mol}^{-1}$ , leading to  $\Delta H_{\text{soln}}^0 = -7.9 \pm 0.4 \text{ kcal mol}^{-1}$  for the bonding enthalpy of two THF molecules to ZnMe<sub>2</sub> ( $\sim 4 \text{ kcal mol}^{-1}$  for one bond). This is a remarkably small value for an overall coordination enthalpy involving two ligands. Comparing with related structures, it is only about one-third of the calculated bonding enthalpy of two molecules of THF to MgMe<sub>2</sub>.<sup>28</sup>

Experimental calorimetric data could not be obtained under similar conditions for ZnMeCl or for ZnCl<sub>2</sub>,<sup>29</sup> but the THF coordination energy is expected to be stronger for more-electronegative substituents on Zn (ZnMe<sub>2</sub> < ZnMeCl < ZnCl<sub>2</sub>). This is supported by the calculations discussed below.

**DFT Studies: Structural Results.** DFT optimization of the structures of [Zn(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>(THF)<sub>2</sub>] were made with different functionals and compared with its X-ray determined structure.<sup>16</sup> The best agreement was found with the M06 functional (see the SI), which was selected to calculate the structures of the Zn compounds and their possible complexes with one or two THF molecules (Figure 2). Table 2 lists informative computed distances and angles of these structures.

The set of structures and their geometrical parameters show remarkable features (more marked for ZnMe<sub>2</sub>). Since the donor–acceptor Zn–THF bond distances are long, compared to the sum of covalent radii for Zn and O, these bonds must be weak, because of smaller orbital overlap, and have a relatively significant electrostatic contribution. There are precedents for this analysis. In fact, the highly distorted tetrahedral structure calculated for ZnMe<sub>2</sub>(THF)<sub>2</sub>, with small O–Zn–O and large Me–Zn–Me angles, finds similar structural features in isoelectronic Mg(alkyl)<sub>2</sub>(THF)<sub>2</sub> compounds.<sup>30</sup> For these Mg complexes, an analysis of the chemical bonding with generalized valence bond (GVB) wave functions has concluded that the THF molecules and the Mg atom are held together





**Figure 2.** Representation of the DFT computed structures. [Legend: red, O; yellow, Zn; gray, C; and green, Cl.]

only by classical electrostatic forces.<sup>31</sup> Although somewhat higher covalent participation can be expected for Zn, with a smaller covalent radius than Mg ( $r_{\text{cov}}(\text{Zn}) = 1.22 \text{ \AA}$ ,  $r_{\text{cov}}(\text{Mg}) = 1.41 \text{ \AA}$ ),<sup>32</sup> there are no steric hindrance reasons to be argued for the long Zn–O calculated distances (up to 2.211 Å;  $\sim 1.90 \text{ \AA}$  is expected for a covalent single bond).<sup>33</sup> We find it plausible that the p-orbitals in  $\text{ZnMe}_2(\text{THF})_2$  are less prone to participate in covalent interactions, especially in donor–acceptor interactions, because of notable nuclear shielding on Zn by the strongly donor Me substituents, which makes the p-orbitals high in energy and, consequently, bad acceptors. Increasing the covalence for the Zn–O bonds can be expected when more-electronegative substituents replace Me groups, increasing the electrophilicity of Zn. This is reflected in a shortening of the Zn–O bond lengths (from 2.211 Å for entry 5 in Table 2 to

2.009 Å for entry 9 in Table 2). In the same sense, the C–Zn–X bond closes (from 161° for entry 5 in Table 2 to 127.2° for entry 9 in Table 2) and the O–Zn–O angle opens, less steeply (from 82.7° for entry 5 in Table 2 to 97.2° for entry 9 in Table 2).

$\text{ZnMe}_2$  (1) and  $\text{ZnMeCl}$  (2) have perfectly linear calculated structures, as expected for sp orbitals for Zn. The changes upon coordination are discussed first for  $\text{ZnMe}_2$ . Upon coordination of one THF molecule, the linear bonding arrangement in 1 undergoes a moderate deformation of the Me–Zn–Me angle, giving a T-shaped structure for the putative  $\text{ZnMe}_2(\text{THF})$  (4), not detected experimentally. Coordination of a second THF molecule forms tetracoordinated 5, with a very large Me–Zn–X angle and a very small O–Zn–O angle, relative to identical 109.47° angles in a regular tetrahedron (Table 2). Assuming that the Zn–O interactions are significantly electrostatic, as in  $\text{Mg}(\text{alkyl})_2(\text{THF})_2$ , the THF ligands should be placed where the nuclear charge is less shielded (that is, in the plane bisecting the Me–Zn–Me bond). It is there where the THF ligands are found in 4 and 5. The O–Zn–O angle, close to 90° in 5, is due to the directional covalent donor–acceptor contribution to this bond, which will make more efficient overlapping in the direction of the empty Zn orbitals. In simple terms, we could say that, for the Me–Zn–Me bonds, the Zn atom is contributing two approximately  $\text{sp}_z$  orbitals (with somewhat less s and more p in the contribution, in order to bend the angle from 180°) and, approximately, the empty  $\text{p}_x, \text{p}_y$  orbitals (with less p and some s contribution) determining the O–Zn–O angle.

The trend for Zn to produce angles getting closer to tetrahedral (getting closer to  $\text{sp}^3$  hybridization) when the electronegativity of the substituents increases reflects the stabilization and increasing covalent participation of the p orbitals. The progressive shortening of the O–Zn distances (2.21 Å in  $\text{ZnMe}_2(\text{THF})_2$ , 2.052 Å in  $\text{ZnMeCl}(\text{THF})_2$ , 2.009 Å in  $\text{ZnCl}_2(\text{THF})_2$ ) supports an increasingly covalent (donor–

**Table 2.** DFT Computed Distances and Angles of Zn Derivatives<sup>a</sup>

entry	compound	Angles (deg)		Distances (Å)			
		O–Zn–O	C–Zn–X	Zn–O	O–C	Zn–C	Zn–Cl
1	$\text{ZnMe}_2$ (1)		180			1.932	
2	$\text{ZnMeCl}$ (2)		179.9			1.920	2.175
3	THF (3)				1.426, 1.426		
4	$\text{ZnMe}_2(\text{THF})$ (4)		174.2	2.208	1.437, 1.437	1.944, 1.944	
5	$\text{ZnMe}_2(\text{THF})_2$ (5)	82.7	161.2	2.211 2.211	1.429, 1.432 1.429, 1.432	1.967, 1.967	
6	$\text{ZnMeCl}(\text{THF})$ (6)		166.9	2.092	1.443, 1.444	1.932	2.190
7	$\text{ZnMeCl}(\text{THF})_2$ (7)	89.8	147.3	2.052 2.052	1.439, 1.437 1.442, 1.437	1.965	2.258
8	$\text{Zn}(\text{C}_6\text{F}_5)_2(\text{THF})_2$ (8)	92.4(1)	132.1(2)	2.093 2.113		1.999, 2.012	
9	$\text{ZnCl}_2(\text{THF})_2$ (9)	97.5(2)	127.2(1)	2.009, 2.016			2.176, 2.184

<sup>a</sup>Data for 8 and 9 have been taken from their X-ray structures.

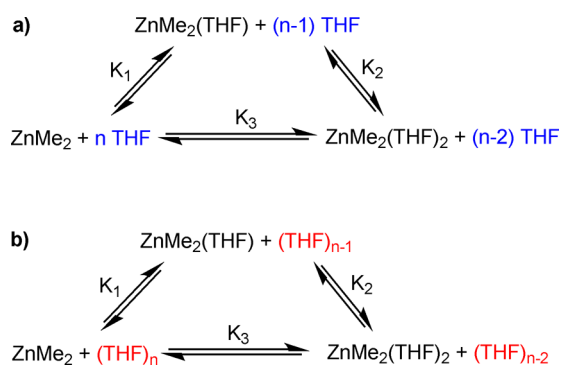
acceptor) participation in the O–Zn bond. The variation of O–Zn distances is in agreement with the observed trend of vibrational frequencies in the IR region.

The possible existence of five-coordinated species with three-coordinated THF molecules was investigated.<sup>34</sup> All attempts to optimize  $\text{ZnMe}_2(\text{THF})_3$ , starting with three solvent molecules coordinated to zinc always ended producing  $\text{ZnMe}_2(\text{THF})_2$  and one THF molecule expelled from the metal. This suggests that such an adduct with three solvent molecules is not stable.

**DFT Studies: Thermodynamic Results.** Inclusion of solvent molecules in the coordination sphere of a metal is a particular case of association–dissociation process in a condensed phase. The accurate description of such processes by conventional DFT methodology is fraught with difficulties, among them, those related with entropy changes in solution,<sup>35</sup> which can be circumvented by *ab initio* molecular dynamics (AIMD) simulations, in which the solute is placed in a box containing hundreds of solvent molecules (not only the two coordinating molecules).<sup>36,37</sup> However, AIMD calculations are extremely time-intensive.<sup>38</sup> For this reason, two simpler approximations to address solvent coordination effects were applied here to calculate the  $\Delta G^0$  of the THF-bonded zinc species in solution.

The simplest approximation, which is frequently used in published works, introduces explicitly only two THF molecules per Zn, in consonance with our experimental results (Scheme 2a).<sup>39</sup> The solvent molecules that will eventually get involved in

**Scheme 2. Coordination Equilibria of THF Plus  $\text{ZnMe}_2$ : (a) Considering the Solvent as Individual Molecules and (b) Considering the Solvent as a Cluster of  $n$  Molecules ( $n = 2-4$ )**



coordination appear as individual noninteracting independent particles, and the total number of particles in the equilibrium decreases when THF molecules coordinate to Zn, from  $n + 1$  to  $n$ , and then to  $n - 1$ . This is a major unfavorable entropic contribution to the Gibbs energy of coordination. This model may be correct for reactions in gas phase, but it overestimates the entropy contribution for reactions in condensed phase, where the solvent molecules are interacting with each other, and are not free molecules.

In our case, because of the small magnitude of the enthalpic contributions measured by calorimetry for  $\text{ZnMe}_2(\text{THF})_2$ , a very likely overestimation of entropy might be particularly misleading for the calculated  $\Delta G^0$  values. One way to adjust this oversimplified description and attenuate the entropic contribution of THF is to consider the uncoordinated solvent molecules not as free individuals, but as being involved in intermolecular dipolar links with other solvent molecules. This

new perspective can be modeled considering a certain number ( $n$ ) of solvent molecules as constituting a cluster:  $(\text{THF})_2$ ,  $(\text{THF})_3$ ,  $(\text{THF})_4$ , etc., from which the coordinating molecules will proceed. This means that, for  $n \geq 3$ , the total number of particles remains constant (two particles) throughout the equilibria of formation of the two  $\text{ZnMe}_2$  complexes (4 and 5) with one ( $K_1$ ) or, respectively, two ( $K_3$ ) THF molecules, as shown in Scheme 2, eliminating a major contribution to entropy changes upon coordination. This cluster-continuum model has been successfully applied to the calculation of  $\text{p}K_a$  values,<sup>40</sup> and it has been extended to the calculation of Gibbs energy changes in solution.<sup>41</sup>

The calculated Gibbs energy values ( $\Delta G^0$ ) for the equilibria in Schemes 2a (only for the case of  $\text{ZnMe}_2$  and two individual THF molecules) and 2b (for  $\text{ZnMe}_2$  with 2–5 THF clusters; for  $\text{ZnClMe}$  and  $\text{ZnCl}_2$  with 4 THF cluster molecules) are gathered in Table 3.

**Table 3. DFT Calculated  $\Delta G^0$  Values (at 0 °C) for the Equilibria in Scheme 2**

entry	$n$ (model)	$\Delta G^0$ (kcal mol <sup>-1</sup> )		
		for $K_1$	for $K_2$	for $K_3$
1 ( $\text{ZnMe}_2$ )	$n = 1 + 1$ (2a)	0.1	-6.1	-6.0
2 ( $\text{ZnMe}_2$ )	$n = 2$ (2b)	-3.9	-6.1	-10.0
3 ( $\text{ZnMe}_2$ )	$n = 3$ (2b)	-4.6	-10.1	-14.7
4 ( $\text{ZnMe}_2$ )	$n = 4$ (2b)	-3.7	-10.8	-14.5
5 ( $\text{ZnMe}_2$ )	$n = 5$ (2b)	-3.2	-9.8	-13.0
6 ( $\text{ZnClMe}$ )	$n = 4$ (2b)	-8.3	-15.7	-24.0
7 ( $\text{ZnCl}_2$ )	$n = 4$ (2b)	-17.3	-23.4	-40.7

Regardless of the approximation chosen and the size of the cluster, all of the entries in Table 3 share the characteristic that the coordination of the second THF molecule is more exergonic than the first coordination. This is particularly marked for  $\text{ZnMe}_2$ . The differences between these values for  $K_1$  and  $K_2$  are so high that the concentration of  $\text{ZnMe}_2(\text{THF})$  in equilibrium with  $\text{ZnMe}_2(\text{THF})_2$  should be negligible. This is consistent with our nonobservation of the three-coordinated species.

Usually, the incorporation of a second covalently coordinated ligand to a metal center, in reactions that proceed via the substitution of weak ligands for stronger ligands, is less favorable than incorporation of the first one, because after the first coordination, the metal center exhibits less acceptor nature toward the second one. The opposite observation here indicates that the higher stabilization of the molecule in the incorporation of the second ligand is not due to only the bond energy of the new Zn–THF bond that is formed. As a matter of fact, the two Zn–O bonds are slightly longer (recall Table 2) and, hence, are presumably weaker in  $\text{ZnMe}_2(\text{THF})_2$  than in  $\text{ZnMe}_2(\text{THF})$ , and the same applies to the two Zn–Me bonds. Structural changes can induce other effects that can be decisive to the overall stability of a molecule. We suggest that part of the molecular stabilization of  $\text{ZnMe}_2(\text{THF})_2$  is due to the structural change produced upon coordination of the second THF molecule, closing the Me–Zn–Me angle (this angle varies only very little upon coordination of the first THF molecule). Extrapolating from the well-known trans-influence in square-planar complexes, where highly donor ligands try to avoid mutually trans positions, the destabilizing contribution associated with two powerful bond dipolar moments oriented opposite to each other in  $\text{ZnMe}_2$  ( $180^\circ$ ) is lowered

progressively when the angle between these dipoles closes, as in  $\text{ZnMe}_2(\text{THF})_2$  ( $161^\circ$ ).<sup>42</sup> Overlooking these structural effects on the  $\Delta G^0$  values upon coordination might lead to the deceptive conclusion that the Zn–O bond energies in  $\text{ZnMe}_2(\text{THF})_2$  are higher than for the same bond in  $\text{ZnMe}_2(\text{THF})$ . As indicated previously, the bond distances in Table 2 support exactly the opposite.

The calculations with only one coordinating THF (Table 3, entry 1) suggest that the formation of  $\text{ZnMe}_2(\text{THF})$  ( $K_1$ ) should be slightly unfavorable (positive  $\Delta G^0$ ). Anyone trusting a prior exploration with this calculation would be misled to decide not to include coordinating THF. All the data in our study prove that it is compulsory to introduce two coordinating THF molecules for correct calculations. The misleading result of entry 1 in Table 3 for  $K_1$  is a warning of the danger of trusting partial results.

Although it is not possible to separate enthalpic and entropic contributions in calculations with a continuum model,<sup>43</sup> some observations can be made by combining the calculated  $\Delta G^0$  results with the experimentally determined  $\Delta H_{\text{solv}}^0$ . Looking at the most relevant data in Table 3 (those in column  $K_3$  in Table 3) and taking into account the experimental enthalpy value ( $\Delta H_{\text{solv}}^0 = -7.9 \text{ kcal mol}^{-1}$  for the coordination of two THF), the  $\Delta G^0$  values show that

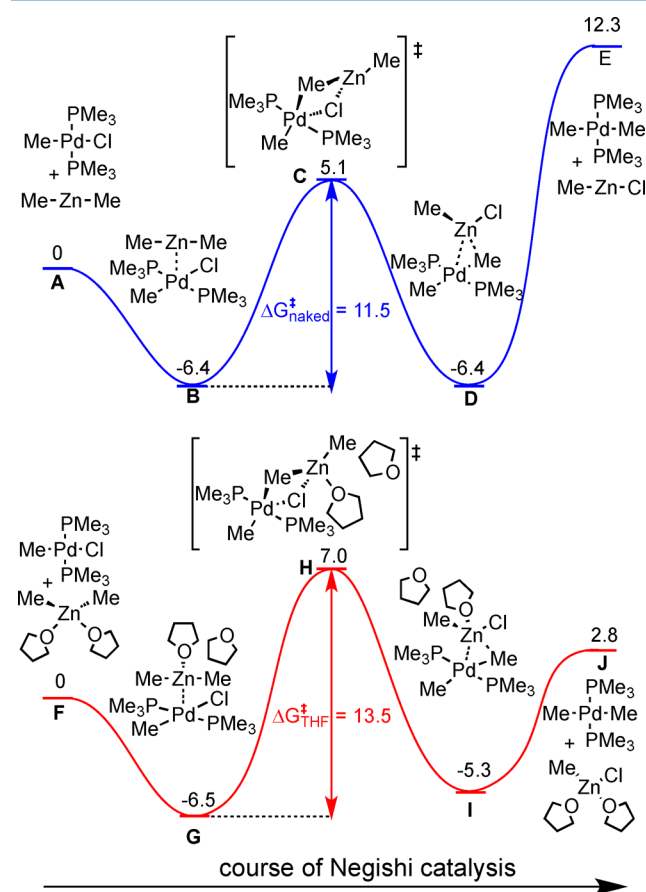
- moving from method 2a (entry 1) to method 2b (entry 2) produces an immediate change from unfavorable entropy contribution when the solvent is considered as independent molecules ( $T\Delta S^0 = -1.9$ , since  $\Delta G^0 = -6.0$  is less negative than  $\Delta H_{\text{solv}}^0$ ), to favorable entropy contribution ( $T\Delta S^0 = +2.1$ , since  $\Delta G^0 = -10.0$  is more negative than  $\Delta H_{\text{solv}}^0$ ) when the solvent is handled as a cluster; and
- this effect improves when the equilibrium in Scheme 2 keeps the number of particles during the coordination reaction constant and equal to 2 (for  $n > 2$ , entries 3–5), and becomes approximately steady in the range of  $n = 3$ –5.

We suggest cluster  $(\text{THF})_4$  as a less expensive but sufficiently good representation of the solvent. Clearly, all the calculations predict that the coordination of two THF molecules to  $\text{ZnMe}_2$  is significantly exergonic, in agreement with the THF coordination equilibria proposed in the experiment (Scheme 1).  $\Delta G^0$  calculations for  $\text{ZnMeCl}$  or  $\text{ZnCl}_2$  (entries 6 and 7 in Table 3) show, as expected, more exergonic processes than  $\text{ZnMe}_2$ .

**DFT Studies: Relevance to the Transmetalation Step in the Negishi Coupling Using  $\text{ZnMe}_2$ .** These  $\Delta G^0$  values have direct translation to the thermodynamics of the transmetalation steps of Me to a metal (often corresponding to Me for Cl exchanges), producing much larger differences in the transmetalation equilibria when coordinating THF is considered. Using the values in Table 3, we note that, in the  $(\text{THF})_4$  cluster model, releasing the two THF molecules to obtain the corresponding naked  $\text{ZnX}_2$  compound would cost  $14.5 \text{ kcal mol}^{-1}$  from  $\text{ZnMe}_2(\text{THF})_2$  (entry 4),  $24.0 \text{ kcal mol}^{-1}$  from  $\text{ZnMeCl}(\text{THF})_2$  (entry 6), and  $40.7 \text{ kcal mol}^{-1}$  from  $\text{ZnCl}_2(\text{THF})_2$  (entry 7). Consequently, the contribution of the presence of coordinating THF to the formation of  $\text{ZnMeCl}(\text{THF})_2$  from  $\text{ZnMe}_2(\text{THF})_2$ , calculated from the data in Table 3, is  $9.5 \text{ kcal mol}^{-1}$ .<sup>44</sup> In other words, in a Negishi coupling, this transmetalation will be favored by  $9.5 \text{ kcal mol}^{-1}$  in THF, compared to a noncoordinating solvent. Similarly, if the Zn

reagent was  $\text{ZnMeCl}$  and the transmetalation product was  $\text{ZnCl}_2$ , the thermodynamic benefit for transmetalation in THF will be, compared to a noncoordinating solvent,  $16.7 \text{ kcal mol}^{-1}$ . Thus, the Zn organometallics are more powerful transmetalating reagents in THF, and calculations omitting explicit THF give a largely inexact image of these transmetalation equilibria. The influence of the coordinating solvent on the values of the activation energy of the transmetalation, and, consequently, on the kinetic behavior with or without THF, is not as easy to analyze.

In order to examine this question in more detail, we have carried out a comparative DFT study of the transmetalation profiles on the model complex  $\text{PdMeCl}(\text{PMe}_3)_2 + \text{ZnMe}_2$ , using or excluding coordinating THF (see Figure 3).<sup>45,46</sup>



**Figure 3.** Gibbs energy profile of the Negishi transmetalation step ( $\text{kcal mol}^{-1}$ ): (top) without explicit THF and (bottom) with two coordinating THF molecules (M06 optimizations in THF described by the SMD continuum model).

The two calculated  $\Delta G^\ddagger$  values for the model studied are very similar ( $\Delta G_{\text{THF}}^\ddagger = 13.5 \text{ kcal mol}^{-1}$ ;  $\Delta G_{\text{naked}}^\ddagger = 11.5 \text{ kcal mol}^{-1}$ ) with a difference of only  $1.9 \text{ kcal mol}^{-1}$ . Such a small difference suggests that the two methods could match equally well (or equally poorly) an experimental value for the activation energy (for instance,  $12 \text{ kcal mol}^{-1}$ ) if accepted approximations were applied. Things are very different, with regard to the  $\Delta G^0$  values. Both profiles predict an unfavorable (endergonic) transmetalation,<sup>47</sup> but  $\Delta G^0$  is very much affected by THF coordination ( $\Delta G_{\text{THF}}^0 - \Delta G_{\text{naked}}^0 = -9.5 \text{ kcal mol}^{-1}$ ), as deduced from the data in Table 3 (entries 4 and 6). If  $\Delta G_{\text{THF}}^0$  matches an experimental value reasonably well,  $\Delta G_{\text{naked}}^0$  will



largely fail. Moreover, since the naked profile predicts that the formation of the dimethyl palladium complex would cost 18.7 kcal mol<sup>-1</sup>, E becomes higher in energy than the transmetalation transition state C. In these circumstances, the transmetalation activation energy (associated with C) would become kinetically irrelevant if the process had to continue to produce the coupling product. However, in the profile with coordinated THF, the transition state H, being higher than J, would still be relevant and potentially rate-determining (depending on the activation barriers of other steps in the cycle).

In experimental studies, the  $\Delta G_{\text{exper}}^{\ddagger}$  values can be determined with good precision, usually by nuclear magnetic resonance (NMR), measuring the reaction rates of a transmetalation process isolated from the catalytic cycle. In contrast, quantification of  $\Delta G^0$  requires the observation and integration of the products at both sides of the equilibrium, which is only occasionally accessible.<sup>48</sup> For this reason, often, the only experimental datum determined is  $\Delta G_{\text{exper}}^{\ddagger}$ .<sup>8</sup> Consequently, a satisfactory experiment–calculation match only requires a good reproduction of  $\Delta G_{\text{exper}}^{\ddagger}$ , which is equally achieved in both profiles of Figure 3. Possible mismatches in other points of a more-complex profile, or in  $\Delta G^0$  in the simple profile of Figure 3, can remain hidden or be overlooked when  $\Delta G_{\text{exper}}^{\ddagger}$  values are not available.<sup>49</sup>

Figure 3 illustrates well that both calculations can afford reasonably good values of  $\Delta G^{\ddagger}$  but, for a reaction in THF of the most frequent case of Negishi catalysis, which involves alkyl/Cl exchange, the one without THF will strongly fail in  $\Delta G^0$ . However, it is convenient to note that other exchanges in Negishi catalysis have less marked electronegativity differences of the groups exchanged, which will lead to lower  $\Delta G_{\text{THF}}^0 - \Delta G_{\text{naked}}^0$  calculated differences for them. As a matter of fact, in our own previous studies without coordinated THF, the results for  $\Delta G^0$  were not warning us of the problem studied here, because they never involved the primary Me/Cl exchange,<sup>50</sup> but only Me/Me exchanges in ZnMe<sub>2</sub>-catalyzed Pd isomerization processes ( $\Delta G^0 = 0$ ),<sup>8c</sup> or Me/Ph exchanges in the study of so-called “secondary transmetalations” ( $\Delta G^0$  moderately affected by THF coordination).<sup>8d</sup> Finally, it is also clear that solvents more strongly coordinating than THF will produce larger  $\Delta G_{\text{solvent}}^0 - \Delta G_{\text{naked}}^0$  differences.

## CONCLUSIONS

All the experimental and calculated data support, beyond any doubt, that, in THF solution, the species ZnMe<sub>2</sub>, ZnMeCl, and ZnCl<sub>2</sub> are coordinated with two THF molecules. The bonding forces for this coordination have a high electrostatic content for ZnMe<sub>2</sub>(THF)<sub>2</sub> and become increasingly covalent for more electronegative substituents on Zn, which increase the electrophilicity of the Zn center. The structural effect is that the high distortion from an ideal tetrahedron, found in ZnMe<sub>2</sub>(THF)<sub>2</sub> moves toward less-distorted structures and smaller Y–Zn–X angles in the same sense. Particularly for ZnMe<sub>2</sub>, the structural change upon closing the Me–Zn–Me angle is probably a significant contribution to the stabilization of the complex, whereas, for species with more electronegative Y and/or Z substituents, the formation of two extra and stronger Zn–THF bonds is more relevant.

Any theoretical study in THF should consider the species ZnMe<sub>2</sub>(THF)<sub>2</sub>, ZnMeCl(THF)<sub>2</sub>, and ZnCl<sub>2</sub>(THF)<sub>2</sub> as the ones participating in reactivity. Calculations in the literature for reactions in THF (or other coordinating solvents) without

these two coordinating molecules may be considered useful models for reactions carried out in noncoordinating solvents (obviously needing a rectification of the implicit solvent model correction), but do not represent what happens in a coordinating solvent. Structural proposals featuring intermolecular or intramolecular interactions to Zn should be examined with caution. They are probably inconsistent with the speciation in a real solution, where stronger Zn–THF interactions will be formed instead.<sup>51</sup>

Studies carried out with two explicit molecules of THF to coordinate Zn are, in principle, fully correct. The use of a cluster model for the solvent is recommended as a nonarbitrary procedure to improve the estimated  $\Delta G^{\ddagger}$  and  $\Delta G^0$  values.

In the model case studied here, the lack of two molecules of coordinated THF produces only a moderate difference in  $\Delta G^{\ddagger}$ , but the difference in  $\Delta G^0$  for Me/Cl transmetalation is very large, showing that the information on the transmetalation equilibrium in THF is very unrealistic if obtained in calculations without coordinated THF. It can be more acceptable for exchanges of groups of similar electronegativity.

A practical consequence of this study is that the transmetalation equilibria ZnMe<sub>2</sub>/ZnMeCl are much more favorable in a coordinating solvent than in a noncoordinating one. Moreover, the  $\Delta G^0$  difference in a coordinating solvent is even larger for the transmetalation pair ZnMeCl/ZnCl<sub>2</sub>. Combining ZnMeCl and a coordinating solvent should provide the most favorable thermodynamics for Negishi reactions.

Although the observations in this paper concern direct studies of Negishi catalysis, whether theoretical or experimental, similar solvent dependence can be expected for other catalysis using organometallics of other electropositive metals as nucleophiles. The structural similarity of zinc and magnesium derivatives, already noted in the text, immediately connects these conclusions to the Kumada coupling.

Finally, this study is a good occasion to share our thoughts about the best way to progress in the use of experimental + computational chemistry. Although calculations are not real life, they provide invaluable content and knowledge that is otherwise inaccessible. Progress in calculations needs experimental reference values as the touchstone of developments in theoretical methods. It is a hard task to get these experimental data. The accuracy of the experimental values is dependent on the precision and correctness of the experiments, not on whether they match the calculations better or worse. The accuracy of the computations is dependent on the ability to describe many molecular factors mathematically, and improved methods must be in continuous development. Common sense must be exercised to get the best of both worlds with a reasonable effort.

For experimental works that include calculations, less-exact calculations can provide sufficient mechanistic information. Often, the very valuable structural and mechanistic information that calculations provide will not change with the choice of functional or with the size of model used. In fact, methodological changes such as the choice of functional can produce large changes in the calculated thermodynamic parameters without significant changes in the mechanistic and structural information.<sup>52</sup> Experimental papers should not be charged, without a good reason, with excessive demands to perform heavy adjustment of their accompanying DFT calculations. They cannot be punished for having experimentally determined the value that is pursued with an improved calculation.

On the other hand, for theoretical papers aimed at developing methodology, tuning a more perfect match of calculation to an experimental value is the natural way to check their quality. However, papers containing only calculations with mechanistic proposals should, sometimes, be required to provide some experimental support, or at least be asked for bibliographic support of plausibility in real conditions of their mechanistic proposals. Theoretical projects should be aware, when setting the theoretical contour conditions of the calculation, that the absence of just one species present in the flask but not in the computer can make the results unrealistic. This can be, in our opinion, more important than pursuing higher accuracy.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03636.

Experimental methods and data, computational methods and data, and associated references (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: agusti@klinton.uab.es (A. Lledós).

\*E-mail: casares@qi.uva.es (J. Casares).

\*E-mail: espinet@qi.uva.es (P. Espinet).

### ORCID

Agustí Lledós: 0000-0001-7909-422X

Pablo Espinet: 0000-0001-8649-239X

### Present Address

<sup>†</sup>Presently at Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467, USA.

### Author Contributions

All authors contributed equally.

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(23) Note that, in the spectrum with a lower concentration of THF (the black trace in Figure 1a), the bands corresponding to some noncoordinated THF are still observable, as a shoulder for the asymmetric stretching, and as a clear band at 908  $cm^{-1}$  for the  $\nu(C-O)_{sym}$ . Thus the composition of this mixture contains some noncoordinated THF, tetrahedral  $ZnMe_2(THF)_2$  and, necessarily, the remaining Zn as non-observable linear  $ZnMe_2$ . The same applies to the dissociation observed for  $ZnMe_2(THF)_2$  (the red trace in Figure 1a).

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(39) The two approximations shown in Scheme 2 include the correction for THF as bulk solvent with a polarizable continuum medium with dielectric constant  $\epsilon = 7.4257$  (SMD model), but differ in the number and state of the explicit THF molecules that participate in the equilibrium.

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(41) (a) Bryantsev, V. S.; Diallo, M. S.; Goddard, W. A., III. *J. Phys. Chem. B* **2008**, *112*, 9709–9719. (b) Ho, J.; Ertem, M. Z. *J. Phys. Chem. B* **2016**, *120*, 1319–1329.

(42) We are aware that, in transition metals, the trans effect is reasoned, taking into account that trans ligands are sharing common d-orbitals, whereas in Zn, the 3d orbital is full, highly stabilized, and does not participate in bonding. However, the ultimate destabilizing reason of these trans phenomena is that electron densities prefer to avoid, as much as they can, high electronic repulsions when sharing a common space and this preference holds also as discussed for ZnMe<sub>2</sub>.

(43) The continuum model only provides Gibbs energy of solvation, not enthalpies or entropies. Despite the frequent mistake of taking the energy in solution to be equivalent to enthalpy, comparison of this parameter with experimental  $\Delta H$  values cannot be done. See ref 3, ref 6b and: (a) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647–3658.

(44) Since the Pd complex does not change by the presence of THF, the Gibbs energy differences come only from the Zn molecules considered.

(45) As a matter of fact, this exact reaction has never been measured experimentally, but there are closely related calculations available in the papers in ref 8 and in the following: (a) Ribagnac, P.; Blug, M.; Villa-Urbe, J.; Le Goff, X.-F.; Gosmini, C.; Mézailles, N. *Chem.—Eur. J.* **2011**, *17*, 14389–14393. (b) Nicolas, E.; Ohleier, A.; D'Accriscio, F.; Pécharman, A.-F.; Demange, M.; Ribagnac, P.; Ballester, J.; Gosmini, C.; Mézailles, N. *Chem.—Eur. J.* **2015**, *21*, 7690–7694.

(46) Since the purpose of the study is to compare the results with or without explicit solvent molecules, the  $\Delta G^\ddagger$  or  $\Delta G^0$  values shown in

Figure 3 do not contain any procedure to modify them by using commonly accepted approximations.

(47) It is very common that PdR<sub>2</sub>L<sub>2</sub> + [M]–Cl will be less stable than PdRCL<sub>2</sub> + [M]–R. In catalysis, the subsequent irreversible C–C coupling will pull forward the transmetalation, in the counter-thermodynamic sense.

(48) For instance, for an equilibrium of A + B = C + D, a value of  $\Delta G^0 = 2 \text{ kcal mol}^{-1}$  is associated with an ~100:1 concentration ratio of the components at the two sides, which practically precludes NMR observation of one of the sides of that uneven equilibrium.

(49) Equilibria can alternatively be studied by calorimetric methods but these afford  $\Delta H^0$ , not  $\Delta G^0$ .

(50) These were made with two explicit molecules of coordinated THF. See refs 8a and 8b.

(51) (a) For instance, the very recently reported and X-ray characterized (phen)Ar<sub>2</sub>Pt–Zn(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub> adduct, containing a dative Pt–Zn bond can be formed in toluene and crystallized from that solution. See: Liberman-Martin, A. L.; Levine, D. S.; Ziegler, M. S.; Bergman, R. G.; Tilley, T. D. *Chem. Commun.* **2016**, *52*, 7039–7042.10.1039/C6CC02433E (b) More recently, the X-ray characterized (bhq)<sub>2</sub>Pd–Zn(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>, containing a dative Pd–Zn bond, has been captured and crystallized from CH<sub>2</sub>Cl<sub>2</sub>. The very labile Pd–Zn bond undergoes chemical exchange at –100 °C. See: Oeschger, R. J.; Chen, P. *Organometallics* in press (DOI: 201710.1021/acs.organomet.7b00113). (c) Similar intermediates [Pd]–ZnMe<sub>2</sub>, with a much less electrophilic Zn center, found *in silico* in our calculations without explicit THF (refs 8c and 8d), are plausible molecules in cyclohexane and perhaps in toluene or CH<sub>2</sub>Cl<sub>2</sub>, but not in THF, where coordination of THF would split the extremely weak Pd–ZnMe<sub>2</sub> dative bond.

(52) For an interesting example (a very simple ligand coordination reaction in Rh) of enormous differences in  $\Delta G^\ddagger$ , depending on the functional used, see: Sieffert, M.; Bühl, M. *Inorg. Chem.* **2009**, *48*, 4622–4624.