

Two-State Reactivity as a New Concept in Organometallic Chemistry[§]

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ABSTRACT

It is proposed that spin-crossing effects can dramatically affect reaction mechanisms, rate constants, branching ratios, and temperature behaviors of organometallic transformations. This phenomenon is termed two-state reactivity (TSR) and involves participation of spin inversion in the rate-determining step. While the present analysis is based on studies of transition metals under idealized conditions, several recent reports imply that TSR is by no means confined to the gas phase. In fact, participation of more than a single spin surface in the reaction pathways is proposed as a key feature in organometallic chemistry.

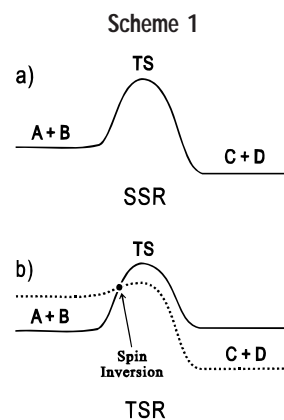
Numerous paradigms, e.g., the frontier orbital concept and orbital symmetry rules, helped to pattern and understand organic and inorganic reactions. These descriptions of chemical reactivity are, however, based on the paradigm of spin conservation, namely that the rate-determining step(s) proceed on surfaces with uniform spin multiplicity (Scheme 1a). These reactions can be classified in terms of single-state reactivity (SSR). Even traditional photochemistry often relies on SSR in that after excitation the whole system, i.e., reactants, transition structures, and products, remains on an excited surface; relaxation to the ground state occurs only after the reaction of interest is completed.¹

Recently, we proposed that the SSR paradigm has an important congener in organometallic chemistry, namely, two-state reactivity (TSR). Here, more than one spin surface connects reactants and products (Scheme 1b).² We accordingly define the following: *A thermal reaction which*

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involves spin crossover along the reaction coordinate from reactants to products needs to be described in terms of two-state reactivity, if product formation arises from an interplay of spin inversion and the respective barrier heights on both spin surfaces.^{3,4} Thereby, TSR can provide low-energy paths for otherwise difficult processes, and the spin inversion junctions can act as rate bottlenecks as well as mechanistic distributors in product formation. While the clear-cut examples for TSR are by and large confined to coordinatively unsaturated transition-metal compounds in the gas phase, TSR is proposed as a fundamental concept in organometallic chemistry and oxidation catalysis in particular.^{2,5}

State-Selective Reactivity of Transition Metals

State-selective organometallic reactivity studies were pioneered by Armentrout and co-workers⁶ in a series of elegant experiments which inter alia demonstrated that spin conservation is quite a strict rule in the reactions of "bare" metal ions with neutrals such as molecular hydrogen and alkanes.⁴ For example, Fe⁺ (⁴F) cation is about 50 times more reactive toward H₂ than the Fe⁺ (⁶D) ground state, even if the ⁶D → ⁴F excitation energy is taken into account.⁷ It is important to note that the mere observation of state-selective reactions also disproves that spin inversion is generally very facile in reactions of organometallic species. Later results were puzzling, however, because as expected the excited states were often more reactive, but they exhibited product-branching ratios similar to those of the ground states. For example, Weisshaar and co-workers⁸ reported that Fe⁺ (⁴F) reacts about 3 times faster with propane than the Fe⁺ (⁶D) ground state, while the branching ratios for C–H and C–C bond cleavages were essentially identical for all states examined. Similar product distributions were also found for reactions of ground- and excited-state Cr⁺ with alkanes, if the relative energy contents are taken into account.⁹ Further, van Koppen et al. reported that the quintet and triplet 4s¹3d⁷ excited states of Co⁺ cation exhibit comparable reactivities toward

[§] This paper is dedicated to Albert Eschenmoser, in friendship and admiration, on the occasion of his 75th birthday.

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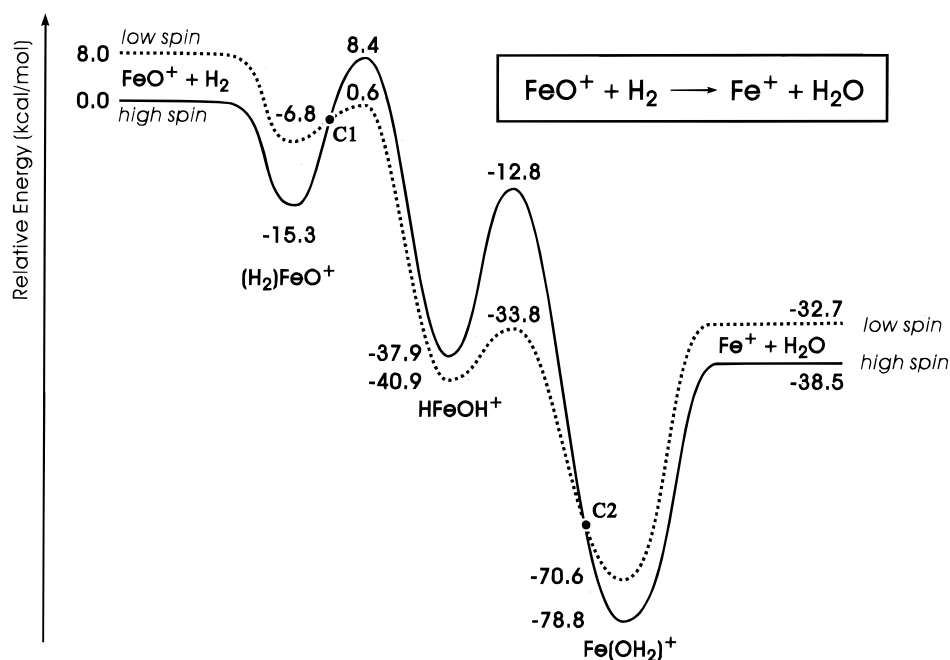
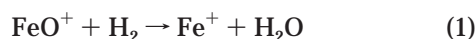


FIGURE 1. Calculated potential energy surface of the FeO^+/H_2 system; data taken from ref 20c. It is important to recognize that, without TSR, FeO^+ would not react with H_2 under thermal conditions. Further, note the double spin crossing at C1 and C2 in this particular system.

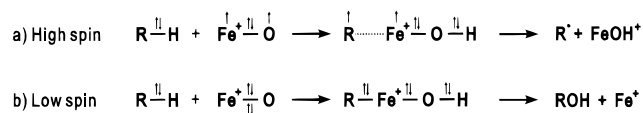
substrates such as propane although nascent from different spin surfaces; the $4s^03d^8$ ground state behaves differently in this particular system.¹⁰ While each of these results may constitute a mere coincidence, the repeated observation that differences in spin multiplicities affect rate constants but not branching ratios is inconsistent with a picture involving separated hypersurfaces for each spin state; in such a case, identical branching ratios must be an exception.

Meanwhile, theoretical approaches to gas-phase transition-metal chemistry indicated that often the reactants, possible intermediates, and products had ground states of different spin multiplicities. Examples are the reduction of water by the early transition-metal cations $\text{Sc}^+ - \text{V}^+$,¹¹ oxidations involving the cationic metal dioxides VO_2^+ and CrO_2^+ ,¹² C–H and C–C bond activations of alkanes by bare 3d metal cations,¹³ or loss of a CO ligand from $\text{HCo}(\text{CO})_4$.¹⁴ However, the spin inversion itself was often neglected, and it has even been argued that “the notion of ‘spin blocking’ of organometallic reactions in the condensed phase is inappropriate”.¹⁵ Although the necessity to explicitly consider surface hopping as a mechanistic step in organometallic chemistry was pointed out more than 10 years ago,¹⁶ the assumptions of either strict spin conservation or its complete neglect prevailed until 1994. This was in part due to difficulties in the appropriate theoretical descriptions of spin crossover in polyatomic metal compounds and, more importantly, the lack of unambiguous experimental examples for a violation of spin conservation along the reaction path, which provoked the necessity to tackle this aspect.¹⁷



An obvious example for TSR was found in two independent studies of reaction 1.¹⁸ Formally, the reaction

Scheme 2



conserves spin because the reactants and products have ground states of the same spin multiplicities, i.e., FeO^+ (${}^6\Sigma^+$) and Fe^+ (${}^6\text{D}$). However, three kinetic phenomena cannot be explained in terms of conventional mechanistic schemes.¹⁹ (i) The intermolecular kinetic isotope effects associated with the activations of H_2 , HD, and D_2 , respectively, are rather low, implying that H–H bond cleavage is not rate-determining in the activation of H_2 . (ii) At nearly thermal energies the rate of reaction 1 decreases with increasing energy, viz., reaction 1 exhibits an inverse temperature dependence. (iii) At slightly elevated energies, a second, endothermic channel leading to production of FeOH^+ competes effectively with reaction 1. Detailed experimental and theoretical analysis revealed that the thermal process involves a spin crossover en route from the sextet reactants to a low-lying transition structure (TS) located on the quartet surface (Figure 1).^{20,21}

An essential aspect for the understanding of these surfaces concerns the bonding situation of the insertion intermediate HFeOH^+ in the different spin states. As formation of an insertion intermediate requires the formation of two covalent bonds, spin coupling of the electrons must occur. However, many bare metal oxides, including FeO^+ , have high-spin ground states.² If the reactants stay on the high-spin surfaces, i.e., they exhibit SSR, only one covalent bond can be formed to conserve high spin. This, in turn, results in radical-type reactions, e.g., generation of an alkyl radical R^{\cdot} (Scheme 2a). In a TSR scenario, crossover from high-spin to low-spin allows for perfect pairing and hence the formation of the low-

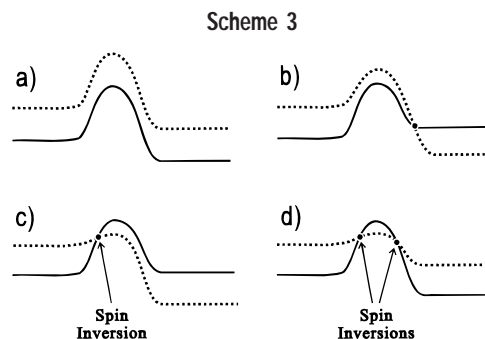
spin insertion intermediates having two covalent bonds; subsequently, the hydroxylation product ROH is formed via reductive elimination (Scheme 2b). As the reaction can occur concertedly, bond activation is energetically less demanding on the low-spin surface.²⁰ This results in a situation in which the lowest-lying reaction coordinate involves a crossover between two spin surfaces.

The origin of TSR is exemplified by referring to dioxygen.^{2,20a} Due to favorable high-spin (HS) bonding, the O₂ molecule exhibits a $^3\Sigma_u^+$ triplet ground state, for which concerted reactions are spin-forbidden. In contrast, singlet dioxygen readily reacts with several organic and inorganic compounds in a concerted manner. This difference in reactivity is due to the fact that the low-spin (LS) state O₂ ($^1\Delta_g$) has a low-lying LUMO and a high-energy HOMO, i.e., the two π^* orbitals can favorably interact with the substrate, whereas the LUMO of O₂ ($^3\Sigma_u^+$) is rather high in energy. Hence, repulsive interactions between the substrate and the half-filled orbitals of the HS species disfavor bond activations, whereas the LS states have low-lying vacant orbitals and, as such, good bonding capabilities and low barriers.

Scope of TSR

The occurrence of TSR for a given set of reactants and products has some particular requirements. The first prerequisite is a high-spin ground state of the reactants and a low-spin excited state, which are separated by a reasonably small energy gap ($\Delta E_{LS/HS}$). Such a situation is encountered in many coordinatively unsaturated organometallic and inorganic species. For example, several bare transition-metal cations have high-spin ground states with closely spaced low-spin states. Further, many metal oxides have high-spin ground states,²² e.g., the FeO⁺ cation, which has a $^6\Sigma^+$ ground state and low-lying ($\Delta E_{LS/HS} \approx 0.8$ eV) quartet states ($^4\Phi$, $^4\Pi$, and $^4\Delta$).^{20,21} Similar patterns apply for metal oxo species in biological systems such as cytochrome P-450.^{5,23} These are just a few examples which possess the TSR fixture, and some main-group compounds also obey this formalism, e.g., molecular oxygen or carbenes. The origin of the HS/LS situation may vary for TSR reagents. In some cases it arises from unsaturation in the bonding of the central atom (e.g., Fe⁺ or CH₂), while in others the HS ground states simply reflect the preferred bonding situations, irrespective of whether the central atoms are saturated (e.g., O₂, FeO⁺, (porphyrin)FeO⁺).^{2,20a,23}

Other prerequisites for the occurrence of TSR are (i) that the rate-determining transition structure (TS) arises from a spin multiplicity other than the reactant ground states²⁴ and (ii) that the interplay of two spin surfaces determines the product distribution. In part, this requires a low $\Delta E_{LS/HS}$ of the reactants, but we should ask ourselves why the energetic order of TSs of the two spin surfaces changes? If the mechanisms and overall reaction enthalpies are similar on both surfaces, the Hammond postulate suggests that the excited surface remains above that of the reactant ground states throughout the entire reaction path (Scheme 3a). If the mechanisms are similar, but the



reaction enthalpy of the excited surface is larger than that of the reactant ground states, crossing is likely to occur after passage of the TS (Scheme 3b). Both situations can consistently be described as SSR. Constraints caused by spin inversion of the products in Scheme 3b can be covered by the preexponential factor of an Arrhenius-type description, unless the crossing in Scheme 3b is attended also by different products. If mechanisms differ, in that the excited-state surface is much flatter on the reactant side, then crossing could occur along the reaction path from the reactants to the TS (Scheme 3c); this a typical TSR scenario. In the most subtle case, reactants and products arise from the same spin surface, while the lowest-lying TS comes from another one (Scheme 3d).

According to the arguments discussed for the FeO⁺/H₂ system, “inverse” TSR, i.e., a rate-determining spin inversion from a low-spin to a high-spin surface, appears less likely—though not impossible—because the lowest-lying transition structure for bond activation is expected to arise from the low-spin manifold. Hence, crossing from LS to HS is expected to occur after passage of the TS, ending up in a situation similar to that depicted in Scheme 3b, and hence an SSR picture, unless the product distribution is determined by the interplay of the two states.

An essential SSR/TSR parameter to be considered is the intersection between the surfaces via spin-orbit coupling.^{20b} If the coupling is virtually zero, the probability of spin inversion (p_{SI}) is negligible, and SSR predominates, irrespective of the shape of the potential energy curves in Scheme 3a–d; this situation seems to apply for the Fe⁺/H₂ system mentioned above.⁷ Likewise, if coupling between the spin surfaces has unit efficiency, i.e., $p_{SI} = 1$, the crossing is completely avoided, resulting again in an adiabatic surface which can be described by SSR.³ Only if the potential energy surfaces fit Scheme 3c or d and p_{SI} is moderate can TSR play a role. Given that spin-orbit coupling is large for heavy elements, TSR is primarily expected for 3d transition metals, and perhaps also for the 4d block; for 4f, 5d, and 5f elements $p_{SI} \approx 1$ is assumed, however. While this line of reasoning is qualitative so far, it can be probed experimentally by examining whether heavy transition metals exhibit state-specific chemistry.

To many theoreticians and spectroscopists, violation of spin conservation is an obvious and not at all new pattern in reaction dynamics.^{1,25} The key element in our presentation of TSR is, however, that it provides a new kinetic scenario for reactions which proceed at thermal energies and is thereby valuable for all branches of

Table 1. Selected Examples of Gas-Phase Reactions Presumably Involving TSR

reaction ^a	$\Delta E_{\text{LS/HS}}^b$	ref
$^3\text{Sc}^+ + ^1\text{H}_2 \rightarrow ^1\text{Sc}(\text{H})_2^+$	0.3	16a
$^3\text{Sc}^+ + ^1\text{H}_2\text{O} \rightarrow ^1\text{ScO}^+ + ^1\text{H}_2$	0.3	11
$^3\text{Sc}^+ + ^1\text{CS}_2 \rightarrow ^1\text{ScS}^+ + ^1\text{CS}$	0.3	29
$^4\text{Ti}^+ + ^1\text{H}_2\text{O} \rightarrow ^2\text{TiO}^+ + ^1\text{H}_2$	0.6	11
$^4\text{Ti}^+ + ^1\text{C}_2\text{H}_6 \rightarrow ^2\text{Ti}(\text{C}_2\text{H}_4)^+ + ^1\text{H}_2$	0.6	13
$^4\text{Ti}^+ + ^1\text{CS}_2 \rightarrow ^2\text{TiS}^+ + ^1\text{CS}$	0.6	29
$^5\text{V}^+ + ^1\text{CO}_2 \rightarrow ^3\text{VO}^+ + ^1\text{CO}$	1.1	28
$^5\text{V}^+ + ^1\text{CS}_2 \rightarrow ^3\text{VS}^+ + ^1\text{CS}$	1.1 ^c	27
$^6\text{Cr}(\text{O}_2)^+ \rightarrow ^2\text{CrO}_2^+$	— ^{c,d}	12a
$^5\text{FeC}_2\text{H}_5^+ \rightarrow ^5\text{HFe}(\text{C}_2\text{H}_4)^+$	0.6 ^{e,f}	34
$^6\text{FeO}^+ + ^1\text{H}_2 \rightarrow ^6\text{Fe}^+ + ^1\text{H}_2\text{O}$	0.8 ^g	18–21
$^6\text{FeO}^+ + ^1\text{CH}_4 \rightarrow ^6\text{Fe}^+ + ^1\text{CH}_3\text{OH}$	0.8 ^g	19, 30
$^6\text{FeO}^+ + ^1\text{C}_6\text{H}_6 \rightarrow ^6\text{Fe}^+ + ^1\text{C}_6\text{H}_5\text{OH}$	0.8 ^g	31
$^6\text{FeS}^+ + ^1\text{H}_2 \rightarrow ^6\text{Fe}^+ + ^1\text{H}_2\text{S}$	0.2 ^{c,g}	29
$^5\text{CoO}^+ + ^1\text{CH}_4 \rightarrow ^3\text{Co}^+ + ^1\text{CH}_3\text{OH}$	1.0	30
$^3\text{Ni} + ^1\text{CO} \rightarrow ^1\text{NiCO}$	0.4 ^h	17
$^4\text{NiO}^+ + ^1\text{CH}_4 \rightarrow ^2\text{Ni}^+ + ^1\text{CH}_3\text{OH}$	1.3	18

^aSimplified notation of spin states, see original sources for details. ^bLS/HS gap of the isolated metal species in eV. ^cReaction occurring at hyperthermal energies. ^dTwo crossings involved. ^eUnimolecular rearrangement. ^fVia triplet TS. ^gVia quartet TS. ^hTermolecular association.

chemistry. Specifically, when spin inversion contributes to the rate equation, the reactions may not anymore obey Arrhenius-type kinetics, RRKM-type descriptions etc., because the temperature dependence of spin inversion and passage over a (classical) barrier may operate in opposite directions. Spin inversion is basically a matter of lifetime of the reactant complex, and the latter decreases upon increasing temperature. Thus, inverse temperature dependencies can be considered as typical features, though they are certainly not unique to TSR. Another essential aspect is the SSR/TSR competition arising from the fact that the SSR route involving the reactants' spin surface circumvents the spin inversion bottleneck and hence starts to compete efficiently once it is energetically achievable.

Case Studies Involving TSR

Among the examples collected in Table 1, three systems are discussed more specifically. These are elementary reactions in which the role of TSR has been established by experimental and theoretical data. In addition to these examples, TSR may affect other reactions of transition-metal compounds and is also involved in reactions of some organic molecules.^{25,26}

(a) Atom Transfer: The $\text{V}^+ + \text{CS}_2$ System. A particularly intriguing situation with respect to TSR was found for the endothermic sulfur atom transfer from CS_2 to atomic V^+ (reaction 2).^{27,28}



The energy-dependent cross section of the VS^+ product is bimodal (Figure 2). Starting from the reaction threshold at ca. 0.8 eV, the cross section peaks about 1.2 eV, and then decreases, and rises to a second maximum at ca. 4.5 eV. Unusual is that the first endothermic channel declines even though no other product channels compete; i.e., reaction efficiency decreases with increasing energy.

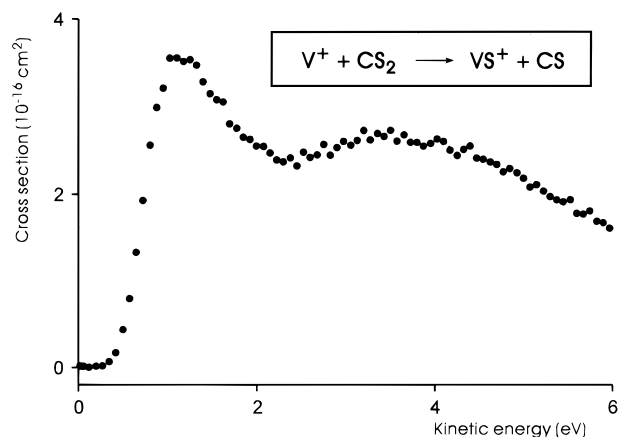


FIGURE 2. Cross section for the formation of VS^+ in the reaction of V^+ cation with gaseous CS_2 as a function of kinetic energy (center of mass frame); see ref 27 for details.

Detailed analysis^{27b} reveals that the first endothermic feature can be attributed to the spin-forbidden reaction 3 to the products' ground states; at higher energies, spin-allowed formation of excited VS^+ can occur (reaction 4).



Theory reveals a typical TSR situation for the $[\text{V}, \text{C}, \text{S}_2]^+$ system, i.e., high-spin (quintet) ground states of the reactants, low-spin (triplet) ground states of the products, and an energetically favorable low-spin TS. The necessity to change spin in reaction 3, but not in reaction 4, accounts for the observed changes in the VS^+ cross section. At lowest energies, the cross section is zero because reaction 3 is endothermic. Once the thermochemical threshold energy of reaction 3 is reached, formation of VS^+ begins to take place, but after having reached a maximum at ca. 1.2 eV, the cross section declines because the system's lifetime decreases and hence p_{SI} decreases. At about 2.2 eV, reaction 4 becomes accessible, resulting in an increase of the VS^+ cross section.

Another kinetic criterion for TSR evolves from studies of the closely related but exothermic sulfur atom transfer from COS to V^+ (reaction 5). Here, the experimentally



observed E^{-1} dependence of the VS^+ cross section is consistent with the $E^{-1/2}$ dependence of the crossing probability imposed on the regular $E^{-1/2}$ behavior of SSR reactions.^{26b} Note that reactions 2–5 demonstrate how mass spectrometric studies can provide experimental indications for the occurrence of TSR scenarios.²⁹

(b) Alkane Oxidation: Hydroxylation of Methane by FeO^+ . The C–H bond activation of methane by FeO^+ cation can be regarded as a prototype for alkane hydroxylations mediated by transition-metal oxenoids.²² Indeed, this gas-phase reaction shows distinct parallels to the features observed with alkane oxidation by metal oxo

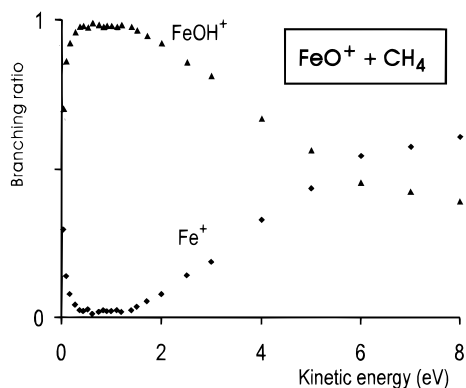
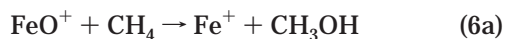


FIGURE 3. $\text{FeOH}^+/\text{Fe}^+$ branching in the reaction of FeO^+ with methane as a function of kinetic energy (center of mass frame); data taken from ref 19.

species in the condensed phase.⁵ In the gas-phase experiments, O atom transfer from the metal to methane (reaction 6a) and H-atom abstraction (reaction 6b) compete at thermal energies.¹⁸



Our analysis of reaction 6^{2,20} and subsequent explicit ab initio calculations by Yoshizawa and co-workers³⁰ predict that methane oxidation by FeO^+ cation proceeds via TSR. Here, we focus on the competition between reactions 6a and 6b and its relationship to the TSR scenario.

The branching between the Fe^+ and FeOH^+ products formed in reactions 6a and 6b shows a pronounced energy dependence (Figure 3).¹⁸ Starting from a ca. 0.4 ratio at lowest energies, the $\text{Fe}^+/\text{FeOH}^+$ ratio drops to about 0.03 between 0.5 and 1.0 eV, and then increases again, and reaches 1.0 above 5 eV. How do we explain the enormous

variation of branching of these closely related pathways in the low-energy regime? As outlined in Scheme 2, formation of methanol as the closed-shell hydroxylation product is a two-bond process and thus requires TSR.^{2,30} As surface crossing becomes less likely at shorter lifetimes of the reactant complexes, reaction 6a declines with increasing energy. Release of a CH_3^\bullet radical in reaction 6b can, however, occur via TSR *as well as* via SSR. The latter obeys an Arrhenius-type energy dependence and hence dominates at elevated energies; the increase of the Fe^+ channel at higher energies is in part due to collision-induced dissociation of FeO^+ .

The branching of the formally spin-forbidden, concerted reaction 6a and the spin-allowed atom abstraction in reaction 6b demonstrates the competition between SSR and TSR. Thus, spin inversion acts as a mechanistic distributor, as it serves as kinetic restriction of the TSR route, while SSR circumvents this bottleneck and can compete once energetically accessible. In other words, TSR is enthalpically favored but entropically hampered, whereas the opposite applies for the SSR variant. Therefore, temperature variation can dramatically influence SSR and TSR options via the crossover conditions at the spin inversion junctions.

The SSR/TSR competition has important consequences with regard to the C–H bond activation of alkanes by high-spin coupled metal oxo species. The weaker the R–H bonds to be activated, the lower are the energy demands for the radical-type HS routes; thus SSR is favored. Further, the nature of R may also affect the magnitude of p_{SI} as an additional, ill-defined parameter. Consequently, simple substrate variations may be inappropriate to probe reaction mechanisms of metal oxide-based oxidations, which are suspected of involving TSR because even minor variations can substantially affect the SSR/TSR competition.

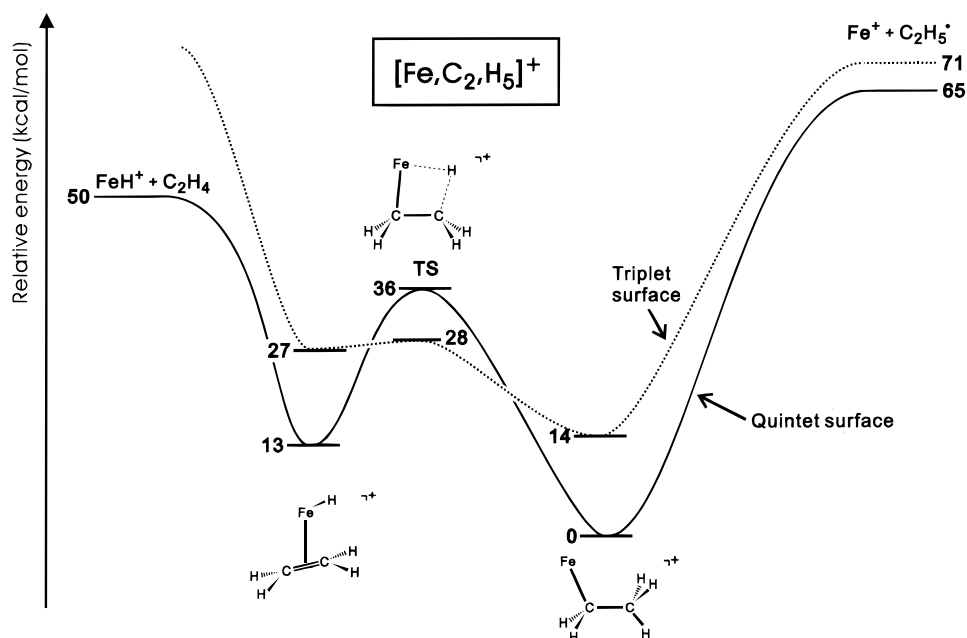


FIGURE 4. Calculated potential energy surface for β -hydrogen transfer in the $[\text{Fe},\text{C}_2,\text{H}_5]^+$ system; data taken from ref 34.

The TSR scenario in alkane hydroxylation is not at all limited to the FeO^+/CH_4 system discussed here. Thus, also the FeO^+ -mediated hydroxylations of benzene³¹ and norbornane³² as well as the oxidations of methane by neutral FeO and CoO^+ cation involve TSR.^{30,33}

(c) β -Hydrogen Transfer: The FeC_2H_5^+ Cation. A well-known problem in organometallic chemistry is associated with the fact that C–C bond formation mediated by transition-metal alkyls is often limited to those alkyl groups which lack β -hydrogen atoms, because competitive β -hydrogen transfers suppress the C–C coupling steps. A molecular prototype of this situation is the iron ethyl cation FeC_2H_5^+ and its rearrangement to $(\text{C}_2\text{H}_4)\text{FeH}^+$. Although the experimental evidence is limited in this case,³⁴ we select the $[\text{Fe}, \text{C}_2, \text{H}_5]^+$ system as an example of the extreme situation depicted in Scheme 3d.

FeC_2H_5^+ and $(\text{C}_2\text{H}_4)\text{FeH}^+$ exhibit quintet ground states, whereas the lowest-lying TS is located on the triplet surface (Figure 4). Hence, a double spin inversion en route from reactants to products is predicted. The reason for the surface intersection is that, in the low-spin TS, the movement of the atoms occurs much more in concert than on the HS surface. This is reflected by the associated imaginary modes which amount to $1050i \text{ cm}^{-1}$ on the HS compared to only $444i \text{ cm}^{-1}$ on the LS surface. The preference of the low-spin TS can be attributed to an additional stabilization of the TS by empty orbitals on the metal, which is impossible on the high-spin surface.

Relevance of the TSR Concept: Concise Mechanistic Consequences?

The TSR paradigm is essentially a mechanistic concept derived from experimental and theoretical considerations of metal ion chemistry in the gas phase. Therefore, applied chemists may consider TSR as an interesting idea, which nevertheless may be irrelevant for the description of reactions that occur in the condensed phase.^{15a} Despite the huge differences between gas-phase experiments with isolated (ionic) species and reactions in condensed matter, several obvious parallels exist,^{5,22} and it appears unjustified to dispute the role of TSR in condensed phase organometallic chemistry.^{15b,35} In particular, our analysis suggest that TSR has some profound kinetic implications, i.e., unusual kinetic isotope effects, inverse temperature dependencies, and pronounced changes in branching ratios. These kinetic parameters can, in turn, be used to support or disprove a possible TSR behavior of a particular system by appropriately designed experimental studies.

To illustrate the value of the TSR model in explaining kinetic phenomena, let us briefly mention three recent case studies related to metal-based oxidations in the condensed phase. (i) In a series of ongoing studies of alkane activation by cytochrome P-450, Newcomb and co-workers³⁶ invoked TSR as a consistent explanation for the counterintuitive ratios of rearranged and unrearranged products in the hydroxylations of methylcyclopropanes. (ii) Jin and Groves³⁷ suggested that spin crossover can explain reactivity differences between substituted metal porphyrin oxides. (iii) Linde et al.³⁸ invoked participation

of spin inversion in alkene epoxidations by salene catalysts as a rationale for the anomalies in the observed stereoselectivities. Of course, these examples cannot prove the occurrence of TSR in the condensed phase,¹⁵ yet TSR offers a conceptually attractive explanation for these experimental findings that are difficult to understand by any other existing concepts.

These case studies may thus serve to stimulate further research in this area; kinetic studies of metal-mediated oxidation reactions in the presence of external fields appear particularly promising.³⁹ As many parameters may influence net reaction kinetics, we propose to probe external field effects on relative rates in systems which show a delicate branching in the product distribution, e.g., the cytochrome P-450-mediated hydroxylation of ethylbenzene.⁴⁰ Note, however, that the details of P-450-mediated hydroxylation need to be analyzed theoretically. As postulated,⁵ it may resemble oxidations by FeO^+ ; however, the coupling of the ferryl species with the radical cation site present in the porphyrin ligand, e.g., ferromagnetic and antiferromagnetic coupling,²³ needs to be resolved.

Finally, the suggested SSR/TSR competition has important consequences for the interpretation of comparative studies on ligand/substituent effects, etc., which are often used to derive mechanistic information in condensed-phase chemistry. For example, if substitution favors the reaction under study by increasing the overall exothermicity, both SSR and TSR barriers will profit, but the SSR channel is likely to dominate because it circumvents spin inversion. These considerations can account for the seemingly contradictory findings in C–H bond activations by cytochrome P-450. Newcomb and co-workers³⁶ reported that hydroxylations of methyl cycloalkanes do not proceed via radical intermediates, thereby questioning the common rebound mechanism⁴¹ of cytochrome P-450. The opposite conclusion was reached by Dinnocenzo and co-workers,⁴² who reported that benzylic C–H bond activation by cytochrome P-450 involves radical intermediates. SSR/TSR competition in P-450 can provide a rationale for these apparently opposing interpretations of related reactions. Thus, the strong C–H bonds in methyl cycloalkanes favor concerted routes via TSR, while the weakness of benzylic C–H bonds lowers the barriers for both the LS and HS routes, and hence SSR dominates resulting in the production of radicals.

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