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Bernd Goldfuss · Maria Schumacher

Umpolung catalysts: comparative assessments on reactivities

Abstract Umpolung catalysis is studied by a sequence of model reactions (CPCM in THF, B3LYP/6-31G*) with different aldehydes and catalysts. We involved addition of the catalyst to the aldehyde and 1,2-H-migration to form a carbanionic d^1-species, which is the crucial intermediate according to the Lapworth- and Breslow-mechanisms. Cyanide, *N*-methylthiazol-2-ylidene, and a glycol-based phosphite perform as umpolung catalysts, formaldehyde, acetaldehyde, benzaldehyde, and acrolein are substrates in this study. In these aldehyde substrates, alkyl-substitution disfavors but π-conjugation favors formation of the carbanionic d^1-intermediate. The nucleophilic carbene, *N*-methylthiazol-2-ylidene, is the strongest umpolung catalyst, while the phosphite is about as active as cyanide.

Keywords Umpolung · Catalysis · Cyanide · Carbenes · Phosphites

Introduction

As early as in 1832, Wöhler and Liebig discovered the cyanide-catalyzed conversion of benzaldehyde to benzoin [1–3]. In 1903, Lapworth proposed for this reaction, a spectacular, now a well-established mechanism involving a α-hydroxyl carbanion as key intermediate (Scheme 1) [4]. Today, such carbanionic intermediates are synthetically highly appreciated as d^1-synthons [5–7]. It is not only cyanide, but also heterocyclic, nucleophilic carbenes are suitable for such "umpolung" catalyses. In vitamin B_1, a thiazol-2-ylidene decarboxylates pyruvic acid in vivo [8]. According to the Breslow [9] mechanism, thiazol-2-ylidenes and other artificial, chiral carbenes

B. Goldfuss (✉) · M. Schumacher
Institut für Organische Chemie,
Greinstrasse 4, 50939 Köln, Germany
E-mail: Goldfuss@uni-koeln.de

[10] are not only active catalysts for enantioselective benzoin-couplings [11–12] (for a computational study on enantioselective, thiazolium-catalyzed benzoin additions see: [13]) but also for Stetter-couplings [14–20]. Recently, Johnson et al. described lithiophosphites as third generation umpolung catalysts for benzoin-couplings with acylsilanes. The close analogy to Lapworth- and Breslow-mechanisms is clearly apparent (Scheme 1) [21, 24] (previous work: [22, 23]).

All three umpolung catalysts, form as central intermediate the carbanionic d^1-species in the catalytic cycle (the generation of formoin (formose) from formaldehyde via umpolung under the influence of $Ca(OH)_2$ is intensively discussed as explanation for prebiotic sugar formation: [25–31]). Here, we compute simplified model reactions to assess kinetic and thermodynamic propensities for the formation of this key intermediate with different substrates and catalysts.

Computational details

All structures were fully optimized and characterized by frequency computations using Gaussian 03 [32] with standard basis sets [33, 34] and the B3LYP [35] (implementation: [36–38]) hybrid-DFT method. Zero point energies and thermochemical analyses were scaled by 0.9806 [39]. The polar solvent THF ($\varepsilon = 7.58$) was considered for optimizations using the polarizable conductor calculation model (CPCM) [40, 41] with Pauling–Merz–Kollman atomic radii with explicit hydrogen atoms and the ofac = 0.8 and rmin = 0.5 settings.

Results and discussion

Cyanide represents the simplest of the three types of umpolung catalysts. To assess intrinsic catalyst characteristics, the formation of the crucial d^1-intermediate was computed neglecting counterions (Scheme 2) [14]. Because of the high polarity of the structures, polar

Scheme 1 Umpolung catalysts for conversions of aldehydes (Ef = H) and acylsilanes (Ef = SiR′₃) to d¹-acyl anion equivalents, which couple with aldehydes or Michael-systems to acyloin- or Stetter-adducts, respectively. Pyruvate decarboxylation (Ef = CO₂ and elimination) is in vivo initiated by thiamin (vitamin B₁)
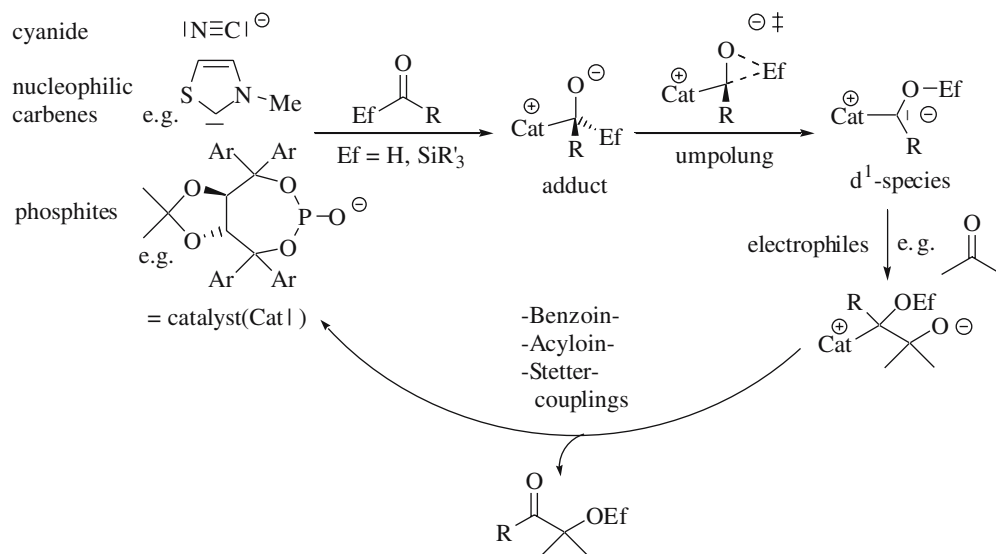
Scheme 2 Relative electronic energies for the cyanide-induced umpolung of formaldehyde (THF solvent, CPCM-B3LYP/6-31G*) referring to isolated reactants (cf. Table 1) and the electronic activation energy E_a
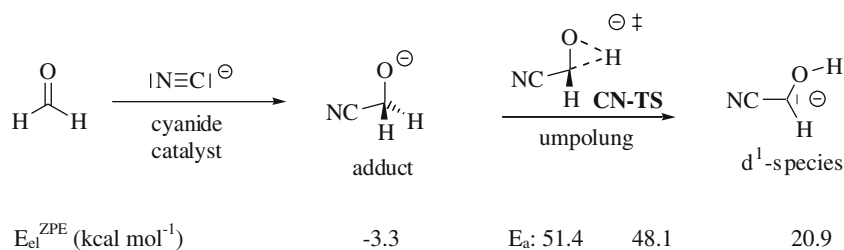
solvent environments (here THF) are more suitable than gas-phase computations. Additional diffuse functions provide only small corrections (Tables 1, 2). Relative to isolated reactants, a stable adduct forms from cyanide with formaldehyde (−3.3 kcal mol⁻¹, Scheme 2), but formation of this adduct is endergonic if entropy is considered (+5.9 kcal mol⁻¹, Table 1). The adduct transforms via 1,2-H-migration in transition structure CN-TS (Scheme 2, Fig. 1) to the unstable (20.9 kcal mol⁻¹) carbanionic d¹-species (Scheme 2, Table 1).

Substituted (R) aldehydes form less stable adducts with cyanide than formaldehyde (Scheme 3, Tables 3, 4). Because of these thermodynamically instable adducts with R ≠ H, even lower activation barriers for the umpolung step relative to formaldehyde (E_a = 51.4 kcal mol⁻¹) are apparent for benzaldehyde

Table 1 Relative energies (kcal mol⁻¹) for the cyanide-induced umpolung of formaldehyde (Scheme 2)

	Adduct formation	TS	d¹-species formation
E_{el}^{ZPE}	−3.3, −4.3,[a] −9.3[b]	48.1, 50.4,[a] 39.3[b]	20.9, 19.5,[a] 11.8[b]
ΔH	−4.6, −5.7,[a] −10.5[b]	46.8, 49.1,[a] 38.0[b]	19.4, 18.5,[a] 10.7[b]
ΔG	5.9, 4.9,[a] −0.2[b]	57.3, 59.6,[a] 48.5[b]	30.2, 28.3,[a] 20.8[b]

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar), relative to isolated adducts (cf. Table 2)
[a]CPCM-THF B3LYP/6-31 + G*
[b]Gas-phase B3LYP/6-31 + G*

and acrolein (E_a = 46.0 and 45.3 kcal mol⁻¹, Scheme 3, Table 3). The carbanionic d¹-species are also less destabilized for phenyl (only 12.1 kcal mol⁻¹) and especially vinyl substituents (only 9.8 kcal mol⁻¹) relative to formaldehyde (20.9 kcal mol⁻¹, Scheme 3) (Glorius et al. recently reported successful umpolung reactions with acrolein derivatives using a nucleophilic carbene catalyst: [42, 43]). The methyl substitution in acetaldehyde increases the kinetic barrier (E_a = 52.3 kcal mol⁻¹) and the thermodynamic destabilization of the d¹-species (25.9 kcal mol⁻¹, Scheme 3, Table 3).

A comparison among the three types of catalysts, i.e., cyanide, N-methylthiazol−2-ylidene, as an exemplary nucleophilic carbene, and a glycol-based phosphite (phosphonate), emphasizes the extraordinary quality of carbenes for the umpolung of aldehydes (Scheme 4, Tables 5, 6) (Glorius et al. recently reported successful umpolung reactions with acrolein derivatives using a nucleophilic carbene catalyst: [42, 43]). The thiazole-2-ylidene catalyst exhibits by far the strongest tendency for adduct formation with formaldehyde (−12.2 kcal mol⁻¹, Scheme 4). Despite the high stability of this carbene adduct, the activation barrier (E_a = 41.4 kcal mol⁻¹) is much lower than for cyanide (51.4 kcal mol⁻¹) or for the phosphite catalyst (52.4 kcal mol⁻¹, Scheme 4). Furthermore, the crucial d¹-species is excellently stabilized by the carbene catalyst forming a neutral, electron-rich alkene (−11.8 kcal mol⁻¹). Cyanide is slightly superior to the phosphite with respect to thermodynamic

Table 2 Total energies (a.u.) for the cyanide-induced umpolung of formaldehyde (Scheme 2)

	$O=CH_2$	CN^-	Adduct	TS	d^1-species
E_{el}^{ZPE}	−114.48361	−92.93493	−207.42374	−207.34183	−207.38523
H	−114.47979	−92.93163	−207.41868	−207.33677	−207.38051
G	−114.50528	−92.95398	−207.44991	−207.36792	−207.41107
E_{el}^{ZPEa}	−114.49402	−92.95992	−207.46082	−207.37360	−207.42293
H^a	−114.49020	−92.95661	−207.45582	−207.36849	−207.41730
G^a	−114.51570	−92.97896	−207.48692	−207.39963	−207.44964
E_{el}^{ZPEb}	−114.48259	−92.86068	−207.35803	−207.28068	−207.32449
H^b	−114.47878	−92.85738	−207.35285	−207.27561	−207.31908
G^b	−114.50426	−92.87974	−207.38429	−207.30677	−207.35078

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar)
[a] CPCM-THF B3LYP/6-31 + G*
[b] Gas-phase B3LYP/6-31 + G*

and kinetic criteria of the umpolung sequence (Scheme 4).

The similarity between cyanide- and phosphite-catalysts is not only apparent from similar activation and reaction energies but also from similar geometries of the transition structures for the 1,2-H-migrations. Regarding the transfer of the proton from carbon to oxygen, the carbene tr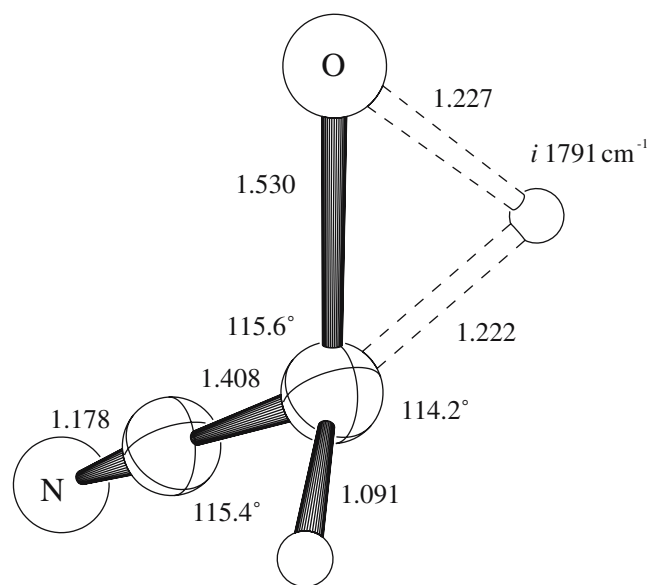ansition structure SN-TS is early on the reaction coordinate with short C–H (1.205 Å) and long O–H distances (1.296 Å, Fig. 2). In contrast, CN-TS (Fig. 1) and PO-TS (Fig. 3) represent late transition structures with longer C–H (1.222, 1.219 Å) and shorter O–H distances (both 1.227 Å). Despite the early nature of SN-TS, its crucial carbon atom is much more planar coordinated by the catalyst, the hydrogen (fixed), and the oxygen atoms (angle sum: 353.8°) than in CN-TS (angle sum: 345.2°) or PO-TS (angle sum: 344.3°). This points to very strong conjugation and double bond formation in SN-TS and explains both the low activation barrier and the high stability of the d^1-species.

Fig. 1 CN-TS, transition structure of cyanide-induced umpolung of formaldehyde (CPCM-THF-B3LYP/6-31G*, bond distances in Angstrom, angles at carbon refer to fixed substituents)

Table 3 Relative energies (kcal mol^{-1}) for the cyanide-induced umpolung of different aldehydes (Scheme 3)

R =	Energy (kcal mol^{-1})	Adduct formation	TS	d^1-species formation
H	E_{el}^{ZPE}	−3.3	48.1	20.9
	ΔH	−4.6	46.8	19.4
	ΔG	5.9	57.3	30.2
Methyl	E_{el}^{ZPE}	3.3	55.6	25.9
	ΔH	2.2	54.6	25.1
	ΔG	13.2	65.4	34.8
Phenyl	E_{el}^{ZPE}	5.2	51.2	12.1
	ΔH	4.4	50.4	11.6
	ΔG	15.0	61.2	21.9
Vinyl	E_{el}^{ZPE}	4.9	50.2	9.8
	ΔH	4.0	49.2	9.2
	ΔG	14.7	60.1	19.3

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar), relative to isolated adducts (cf. Table 4)

Scheme 3 Relative electronic energies (E_{el}^{ZPE}, kcal mol^{-1}) for the cyanide-induced umpolung of different aldehydes (THF solvent, CPCM-B3LYP/6-31G*) referring to isolated reactants (cf. Table 3) and the electronic activation energies E_a
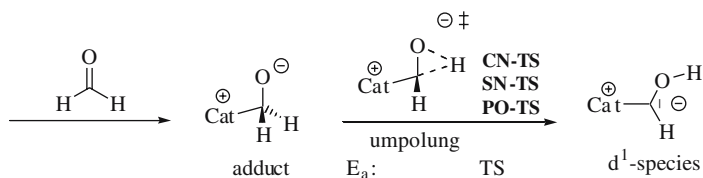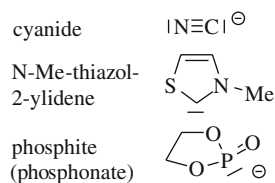
Cat =		adduct	E_a:	TS	d^1-species
	Cyanide	-3.3	51.4	48.1	20.9
	Carbene	-12.2	41.4	29.2	-11.8
	Phosphite	-0.2	52.4	52.2	21.1

Table 4 Total energies (a.u.) for the cyanide-induced umpolung of different aldehydes (Scheme 3)

	Formaldehyde	Adduct	TS	d^1-species
R = H				
E_{el}^{ZPE}	−114.48361	−207.42374	−207.34183	−207.38523
H	−114.47979	−207.41868	−207.33677	−207.38051
G	−114.50528	−207.44991	−207.36792	−207.41107
R = methyl Acetaldehyde				
E_{el}^{ZPE}	−153.78571	−246.71535	−246.63201	−246.67937
H	−153.7809	−246.70902	−246.62557	−246.67258
G	−153.81059	−246.74357	−246.66039	−246.70911
R = phenyl Benzaldehyde				
E_{el}^{ZPE}	−345.47650	−438.40311	−438.32983	−438.39216
H	−345.46918	−438.39372	−438.32053	−438.38239
G	−345.50702	−438.43713	−438.36349	−438.42614
R = vinyl Acrolein				
E_{el}^{ZPE}	−191.86247	−284.78956	−284.71741	−284.78174
H	−191.85714	−284.78243	−284.71036	−284.77406
G	−191.88875	−284.81938	−284.74698	−284.81202

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar). Cyanide E_{el}^{ZPE}: −92.93493 a.u., enthalpy: −92.93163 a.u., free energy: −92.95398 a.u. (cf. Table 1)

Table 5 Relative energies (kcal mol^{-1}) for umpolung transformations of formaldehyde with different catalysts (Scheme 4)

Catalyst =		Adduct formation	TS (activation energy)	d^1-species formation
Cyanide	E_{el}^{ZPE}	−3.3	48.1	20.9
	ΔH	−4.6	46.8	19.4
	ΔG	5.9	57.3	30.2
Carbene	E_{el}^{ZPE}	−12.2	29.2	−11.8
	ΔH	−13.1	28.3	−12.1
	ΔG	−0.8	40.6	−1.2
Phosphite	E_{el}^{ZPE}	−0.2	52.2	21.1
	ΔH	−1.1	51.3	20.4
	ΔG	11.1	63.7	32.5

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar), relative to isolated adducts (cf. Table 6)

**Table 6** Total energies (a.u.) for umpolung transformations of formaldehyde with different catalysts (Scheme 4)

Catalyst =	Cyanide	Adduct	TS	d^1-species
E_{el}^{ZPE}	−92.93493	−207.42374	−207.34183	−207.38523
H	−92.93163	−207.41868	−207.33677	−207.38051
G	−92.95398	−207.44991	−207.36792	−207.41107
Catalyst =	Carbene			
E_{el}^{ZPE}	−608.24051	−722.74359	−722.67765	−722.74285
H	−608.23395	−722.73466	−722.66858	−722.73296
G	−608.26981	−722.77631	−722.71034	−722.77699
Catalyst =	Phosphite			
E_{el}^{ZPE}	−645.74505	−760.22901	−760.1455	−760.19507
H	−645.73836	−760.21986	−760.13644	−760.18565
G	−645.77471	−760.26225	−760.17854	−760.22812

CPCM optimization in THF, B3LYP/6-31G*, and ZPE (scaled by 0.9806) corrected electronic, enthalpic, and free energies (298 K, 1 bar). Formaldehyde E_{el}^{ZPE}: −114.48361 a.u., enthalpy: −114.47979 a.u., free energy: −114.50528 a.u. (cf. Table 1)
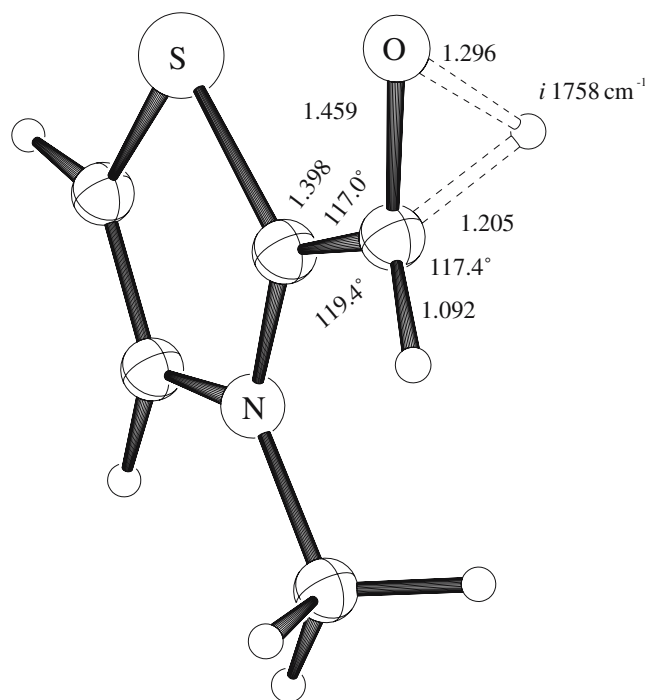
Fig. 2 SN-TS, transition structure of carbene-induced umpolung of formaldehyde (CPCM-THF-B3LYP/6-31G*, bond distances in Angstrom)

Conclusions

Aldehyde substrates with π-conjugation, i.e., phenyl or vinyl substituents, form the crucial carbanionic d^1-intermediate more easily than formaldehyde or aldehydes with alkyl substituents. Phosphites, the new class of umpolung catalysts, resemble more cyanide than nucleophilic carbenes in umpolung reactions due to
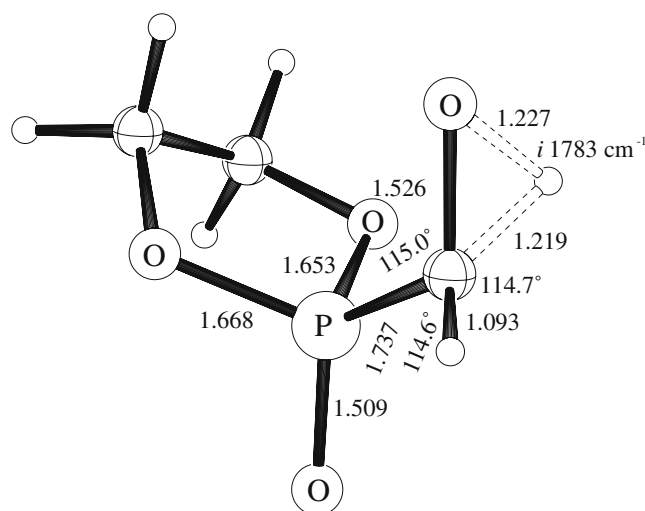
Fig. 3 PO-TS, transition structure of phosphite-induced umpolung of formaldehyde (CPCM-THF-B3LYP/6-31G*, bond distances in Angstrom, angles at carbon refer to fixed substituents). A *syn* OPCO conformer is less stable

kinetic, thermodynamic, and geometric assessments. *N*-methylthiazol-2-ylidene, was found to be by far the strongest umpolung catalyst, both with regard to nucleophilic attack on the aldehyde as well as kinetic and thermodynamic stabilization of 1,2-H-migration and of the d^1-intermediate. Further studies with focus on the role of counterions and other electrofuges (e.g., SiR$_3$ in Brook rearrangements) will provide an even better understanding of umpolung catalysis.

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