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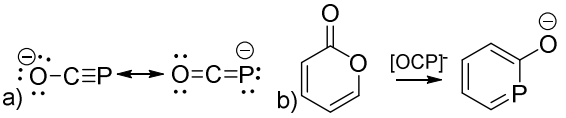
Tetrazines react with OCP^{-1} through reverse electron demand Diels-Alder process to produce 3,6-disubstituted-1,2,4-diazaphosphinin-5-olates. DFT calculations reveal that both Diels-Alder and subsequent aromatization barriers are low for both EWG and ED tetrazine substituents. The structure of the solid sodium salt shows interaction of Na^+ with aryloxide and also both nitrogens of a neighboring anion, leading to coordination polymer character. 1,2,4-Diazaphosphinin-5-olates react as nucleophiles towards MeI and R_3SiCl, respectively, and were installed on the $(Ph_3P)_2Ru(CO)H$ fragment to investigate their properties as ligands.

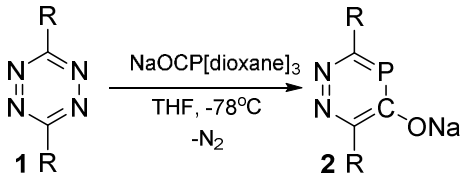
Nitrogen containing cyclic molecules are the most widespread heterocycles: they are part of natural amino acids and DNA, key components in numerous drugs, organic materials and ligands for metal complexes. At the same time their phosphorous analogs are much less explored and remain laboratory curiosities mainly because of the absence of simple, inexpensive and scalable procedures of their synthesis; even phosphorine, the P-analog of pyridine requires a complicated synthesis[1] and is not commercially available. Recently a large scale convenient synthesis of NaOCP was developed,[2] and the utility of this salt for the synthesis of six-membered phosphorous-containing heterocycles was demonstrated[3, 4]. Inverse-electron demand Diels-Alder reactions of *tetrazines* and different dienophiles is a powerful click-chemistry tool for different applications, such as bioconjugation[5, 6] and the synthesis of heterocycles[7]; the reaction can be extremely fast[8, 9] and N_2 is usually the only byproduct. Tetrazines with different substituents in 3,6-positions are easily accessible from inexpensive and simple precursors[10], expanding the availability of tetrazines for click chemistry. A few examples (synthetic[3, 4] and computational[11]) of OCP^{-1} reactivity in cycloaddition reactions were reported but none of them considered tetrazines as important partners. For comparison, the ionization potential of RCP is lower than that of RCN, consistent with heteroatom electronegativity. While the reactivity of OCP^{-1} is varied, it is generally predictable based on phosphorus being nucleophilic, as is true in one Lewis structure (Scheme 1a), or as originating from the resonance structure which has a PC *triple* bond; in neither resonance structure is carbon electrophilic. Consistent with this logic, electron poor dienes react faster with OCP^{-1} than electron rich ones, which makes tetrazines ideal partners for a [4 + 2] reaction, analogous to its established chemistry (Scheme 1b) with α–pyrones, where CO_2 is extruded[3]. This makes tetrazines ideal partners for OCP^{-1} in the synthesis of P-containing heterocycles, a topic which we describe here. The advantage of OCP^{-1} as a dienophile is that it simultaneously installs a



valuable alkoxide ring substituent, and located *ortho* (i.e. conjugated) to the phosphorus.

Scheme 1 OCP^{-1} resonance structures and reaction with pyrones.

Reaction of equimolar pink **1a** with NaOCP in THF, initially at – 78 °C, gives immediate color change to colorless with intensive gas evolution (Scheme 2).



Scheme 2. Reactions of 3,6-disubstituted tetrazines with OCP^-; **1a**, **2a** R = Me, **1b**, **2b** R = Et, **1c**, **2c** R = Ph, **1d**, **2d** R = 2-pyridyl.

Removal of volatiles quantitatively yielded a spectroscopically pure white solid. ^{31}P NMR of the product showed a singlet at 117 ppm shifted more than 500 ppm vs.

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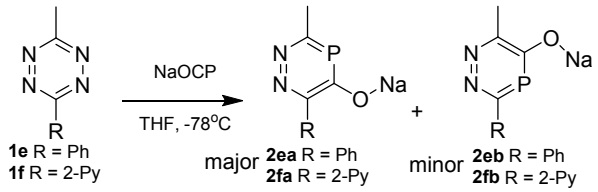
the starting OCP^{-1} salt. ^1H NMR showed signals of two inequivalent methyl groups at 2.18 ppm (singlet) and at 2.43 ppm (doublet) with J_{HP} = 11.9 Hz. The ESI (-) mass spectrum of this compound in THF shows the intact anion, while the APCI(+) shows an ion two mass units higher, consistent with doubly protonated form.

To broaden reaction scope, we tested tetrazines with alkyl (**1a**,**1b**), aryl (**1c**) and heteroaryl (**1d**) substituents (Scheme 2). All of them react completely and cleanly with the OCP^{-1} salt in 5 min at -78°C yielding, after removal of the solvent, colorless solids for alkyl substituents and yellow solids for aryl/heteroaryl. To analyze regioselectivity of OCP^{-1} attack on tetrazine two compounds (**1e, 1f**) bearing electron donating (Me) group at 3-position and EWG (phenyl and 2-pyridyl) substituents at the 6-position of tetrazine ring were used as reaction partners (Scheme 3.). In both cases two isomers were formed based on ^{31}P NMR spectra in a ~1:5 ratio (Scheme 3). Methyl group ^1H NMR signals of the major isomer appear at 2.59 ppm as a doublet with $J_{H,P}$ = 12.3 Hz confirming ortho-location with respect to the P-atom. Methyl group of the minor isomer is a singlet at 2.24 ppm, showing that resonance withdrawing (hetero)aryl effect on the para carbon dominates direct local sigma donating influence of methyl.

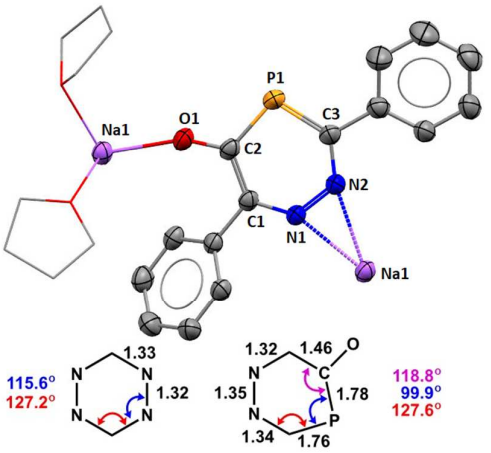


Scheme 3 Reaction of $[OCP]^{-1}$ with unsymmetrical 3,6-disubstituted tetrazines.

Single crystal X-ray diffraction of **2c** (Figure 1) is consistent with spectroscopic data. Na^+ binds to both N of one tetrazine and to the ring O of a second anion, together with two THF; the third THF fills lattice voids. The linking of anions by Na^+ leads to a polymeric chain in the solid state, and thus solution characteristics will depend heavily on the solvent chosen, since it may well break up the polymer. The addition of a larger heteroatom distorts the six-membered ring, exhibiting long C-P bonds and an exceptionally compressed C-P-C bond angle of 99.9° compared to an unaltered tetrazine ring (Figure 1).

The phenyl and the tetrazine rings are twisted by 15 and 43°. The CN and NN distances are short, 1.3 – 1.4 Å, and the one CC distance is longer, at 1.46 Å; the two PC distances are longest, and they thus distort the hexagon, but still leave the PN_2C_3 ring planar to within 0.03 Å. The O atom lies 0.13 Å from that plane and the two Na^+ lie 0.18 and 0.3 Å from that plane. The Na^+ to O(THF) distances are both ~ 2.3 Å, and the Na/O(ring) distance is shorter, at 2.2 Å. There are no short contacts to the P, suggesting that it is not the site of any formal negative charge from the alkoxide oxygen, and instead any such conjugation involves mainly the N para to the OC ring site. Hard/soft acid base concepts also rationalize the lack of any Na/P contacts. Using the NN midpoint, the six angles around four coordinate Na^+ average to 109°, but range from 90° (O-Na-O) to 123° (NN midpoint-Na-O).

An attempt to isolate a neutral form of the reaction product - a 3,6-disubstituted-1,2,4-diazaphosphinin-5-ol by

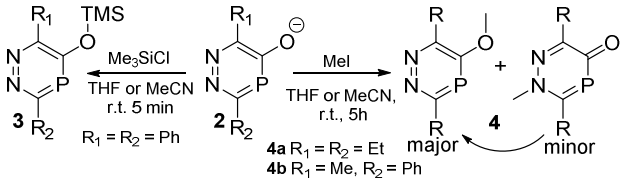


protonation with water or HCl in ether was unsuccessful and multiple products were formed based on NMR.

Fig. 1 ORTEP presentation of molecular structure **2c**, unlabeled atoms are carbons, two coordinated THF molecules presented as wireframe for clarity. Comparison of selected bond lengths and angles for sym-tetrazine; selected bond distances (Å) Na1-O1, 2.198(2); Na1-O3, 2.324(2); Na1-O21, 2.308(9); Na1-N1, 2.380(2); Na1-N2, 2.500(3); Na1-O2, 2.290(6).

It is likely that compounds **2** are only stable in anionic form. Product **2** seems to be a strong nucleophile but four resonance forms could be drawn with negative charge located on various ring atoms. It is known that analogous 1,2,4-triazin-5-ols can be alkylated both on the O atom and on the 2-N position, depending on reaction conditions[12, 13]. We used MeI and Me_3SiCl electrophiles (Scheme 4) to investigate regioselectivity. Reaction with Me_3SiCl yielded corresponding silyl ethers in almost quantitative yields. Those compounds are much more sensitive to water compared to parent salts and must be handled with caution. MeI was added to the solution of **2b** in THF-d_8 and the reaction was monitored with NMR. After 5 minutes, two sets of product signals were detected by both ^{31}P and ^1H NMR in 1:10 ratio. The predominant product is an O-alkylated one based on careful 2D-NMR assignment and the minor one is likely an N-alkylated product; ^{31}P NMR chemical shift and absence of ^1H-^{31}P coupling of Me-group protons rules out P-alkylation and C-alkylation is not consistent with Et group proton chemical shifts. Reaction was complete in 5h, at which time only one set of signals remained, because of isomerization from N-alkylated to O-alkylated product.

Scheme 4. Alkylation of 1,2,4-diazaphosphinin-5-olates.



We carried out DFT calculations of the reaction between OCP^{-1} and tetrazines targeting the following questions: 1) what

is the most favorable reaction pathway: [4+2] or [4+1] cycloaddition, 2) how sensitive are reaction barriers to substituents on 3,5-position of the tetrazine ring, 3) how regioselective is the reaction of unsymmetrical 3,5-disubstituted tetrazines with OCP^{-1}.

In contrast to the [4 + 2] Diels Alder reaction of a butadiene with an olefin, which is synchronous in forming two new CC single bonds, the unsymmetrical character of the PC bond in OCP^{-1} means that this mechanism can be asynchronous[14]. DFT calculations of the potential energy surface (Figure 2) involving dimethyltetrazine and PCO^{-1} at the B3LYP/6-31G(d,p) level of theory reveals a reaction that is highly favored thermodynamically and has only low barriers, hence fast, but does involve one intermediate which lives in a very shallow (~ 5 kcal/mol) energy minimum. This is an energy profile which causes no buildup of intermediate, and also shows that a tetrazine does not form a spectroscopically detectable amount of "adduct" with PCO^{-1}; the barrier to form intermediate **II** is larger than the barrier for **II** to convert to **III** + N_2[15].

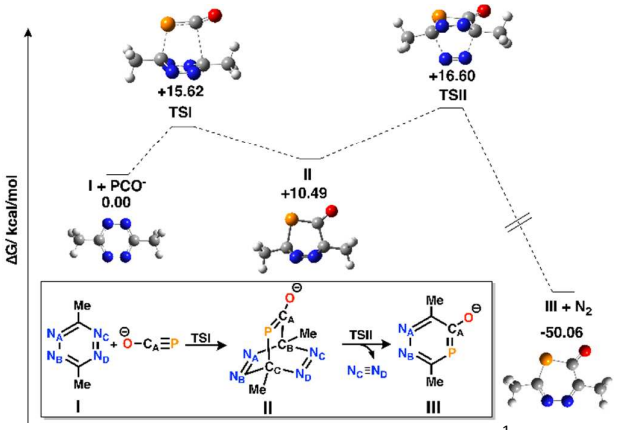


Fig. 2 Calculated PES for the reaction of **I** + OCP^{-1} to **III** + N_2. Free energies are illustrated.

The bicyclic intermediate **II** indeed has (see ESI) single bonds, PC_C and C_AC_B, from tetrazine **I** ring carbons to the newly arrived PCO fragment and thus both NN distances are shorter than in tetrazine and the N_CN_D distances become even shorter going through the subsequent transition state to form the triple bonds of released dinitrogen, while N_AN_B lengthens again as ring delocalization returns. Elimination of N_2 involves a very early transition state, **TSII**, because it is so highly exothermic, in agreement with the Hammond postulate.[16] Animations of both transition states are available in ESI. We were also interested in probing the effect of electron donating or withdrawing tetrazine substituents on overall reaction thermodynamics and regioselectivity of the OCP^{-1} addition to unsymmetrical tetrazine, and therefore calculated a range of tetrazines with methyl group in the 3 position and one varied substituent in 6 position. Energy difference in TS of two possible regioisomers are within 2 kcal/mol (with one exception of C_6F_5 substituent, see S2-S3) therefore we are not expecting high selectivity even at low temperature, which is in agreement with our observations (Scheme 3). We discuss here the data for the more favorable isomer. The data for the less stable isomer is available in the ESI, and does not change any conclusion discussed here. The presence of an electron withdrawing group on the tetrazine renders it more electron deficient, and thus more susceptible to nucleophilic attack by incoming OCP^{-1}, which should make the reaction more thermodynamically favorable. For all substituents, the formation of **III** is exceptionally exergonic (Fig. 3): 48 to 65 kcal/mol; the reaction is broadly applicable, or substituent-tolerant.

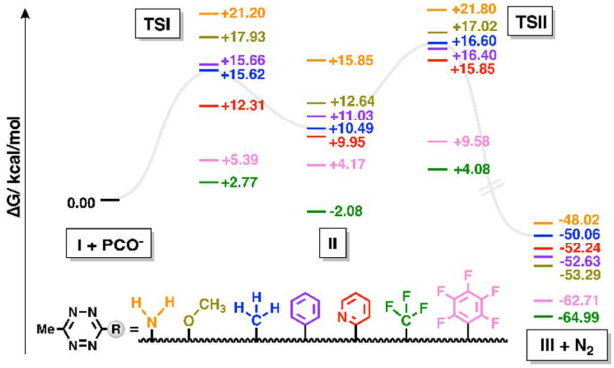


Fig. 3 PES of a variety of disubstituted tetrazines.

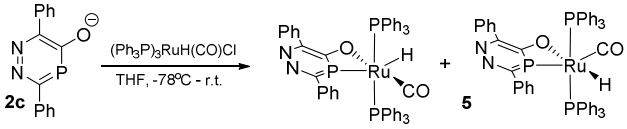
The *range* of substituent effects on ΔG^{o} in species **II**, 17.8 kcal/mol, is very similar to the range for the various species **III**, 17.0 kcal/mol; the substituent effect is comparable in the bicyclic compound and in the aromatic heterocycle, after N_2 has been lost. Overall, Fig. 3 supports the claim that electron withdrawing groups on the tetrazines contribute to overall lower energy intermediates and products, due to their more electrophilic character: predictions based on tetrazine electrophilicity are reliable. Notably, the CF_3 substituent actually makes the intermediate, **II**, lower in energy than the reactants. The CF_3 and C_6F_5 groups also have the lowest energy products, and they are over 15 kcal/mol lower in energy than the products containing electron donating groups. The substituent effect on transition state energies is remarkably simple: it displays the same range, ~18 kcal/mol, from donating to withdrawing substituents, so both ground and transition state effects are essentially linear in energy. In spite of the large variation in energy of various **II**, *all* of these lie only ~5 kcal/mol below *both* **TS1** and **TS2**: **II** sits in a symmetrical energy well.

Biorthogonal chemistry requires reactions that are extremely fast to make the conversion possible on micro or nanomolar levels, which made tetrazine plus *trans*-cyclooctene Diels-Alder reactions so attractive[5, 6, 8]. The fastest *trans*-cyclooctene based partners showed barriers of 14-15 kcal/mol[9, 17] thus *higher* than the tetrazine cases reported here.

The chemistry of phosphinines and OCP^{-1} and their transition metal complexes is limited[18-25]. There are a few examples of 2-oxyphosphinine complexes with $W(CO)_5$ fragment[26-28], with Cr[29], Cu[30, 31] and Au[31]. Our examples, if bound through both P and O, would have the special advantage of being a potentially redox active ligand (lower ring

reduction potential due to three heteroatoms) with compact κ^2 connectivity.

Reaction of equimolar **2c** with $(PPh_3)_3Ru(CO)H(Cl)$ in THF occurs within 4-6 hours (Scheme 5). Assay by ^{31}P NMR shows no remaining $(PPh_3)_3Ru(CO)H(Cl)$, production of free PPh_3, together with two products (ratio of 2:1), *each* of which shows two P environments (relative intensity 1:2): two AX_2 spin systems. The two A signals appear as triplets with $J_{P,P}$ = 6 Hz and chemical shifts at 139.3 and 135.5 ppm, shifted 15 ppm downfield compared to **2c**. The two X signals have chemical shifts of 43.8 and 43.2 (both doublets $J_{P,P}$ = 6 Hz) within the region of coordinated PPh_3. This suggests two isomeric products of formula $(Ph_3P)_2Ru(O\sim P)H(CO)$. Two isomeric structures are also indicated by the hydride region ^1H NMR spectrum, which shows two triplets, again consistent with two isomers, with H/P coupling to the PPh_3 ligands.



Scheme 5 Formation of Ru complex with diazaphosphininolate.

Two isomeric structures arise naturally in a *six* coordinate structure (Scheme 5) and these differ by whether the hydride is cis or trans to ring P. If the OP ligand were monodentate, through only O, that *five* coordinate species has only one isomeric structure; seeing two isomers establishes that the ring P does bond to Ru, and this bond is better than one to the expelled PPh_3. The IR spectrum of a sample rich in one isomer shows a weak absorption at 2227 cm^{-1} (ν_{RuH}) and a strong one at 1924 cm^{-1} (ν_{CO}).

This κ^2 ligand also needs to be viewed in comparison to *ortho*-hydroxy pyridine, as a proton responsive ligand, but P~O offers lower π^* orbital energies, due to the several ring nitrogens. Another variable in the P/N ring comparison is the misalignment of the P/N lone pair, which will probably be worse for P, since its bond distances to ring carbons are longer than for the N analog (compare Fig. 1).

In conclusion, we have shown reactivity of various 3,6-disubstituted tetrazines with $[OCP]^{-1}$ both experimentally and computationally. The products 3,6-disubstituted-1,2,4-diazaphosphinin-5-olates were characterized by spectroscopy, and by reactivity toward electrophiles and coordinating potential on Ru(II). Reaction barriers are shown to be very low, making this reaction relevant for bioorthogonal chemistry.

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Conflicts of interest

There are no conflicts to declare.

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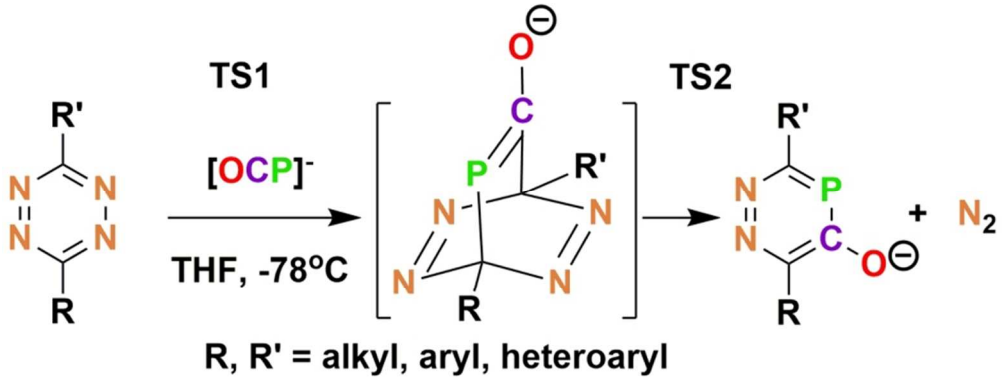

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