1 Diiminium Nucleophile Adducts are Stable and Convenient Lewis Superacids

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- 7 Dedicated to the memory of Gerhard Maas.

8 Abstract:

9 Strong Lewis acids are essential tools for a manifold of chemical procedures that aim to react weakly basic 10 centres but their scalable deployment is severely limited by their costs and safety concerns. We report that dicationic relatives of guanidinium can be conveniently synthesised in a two-step one-pot procedure from 11 12 tetramethylurea. Triflic anhydride is used to generate an isouronium intermediate. Substitution of the 13 bound triflate with pyridines yield the dicationic tetramethyldiiminium ditriflate nucleophile adducts 14 (TMDINu). Their proposed diiminium character is demonstrated by substituting pyridine from the 15 corresponding adduct with other nucleophiles. The observation of a chelation effect in the 2,2'-bipyridine 16 adducts supports Lewis acidic character of the diiminium π -system and flexibility towards accepting 17 another bond. High fluoride, hydride, and oxide affinities are demonstrated, leading to their classification 18 as soft and hard Lewis superacids. An example reaction is reported which shows that the 19 tetramethyldiiminium ditriflate pyridine complex (TMDIPy) is more effective than conventional reagents 20 in the activation of electron-poor amines for amide couplings.

1 Main Text:

2 Lewis acidic reagents and catalysts are essential tools for the activation of basic functional groups, e.g., in

esterification and amidation reactions, in the hydrogenation of carbonyls, and in the depolymerisation of
 polyesters (1-4). Trivalent boron and aluminium compounds are affordable and have a broad utility in

5 this context (5-8). Divalent cationic nitrenium and tetravalent cationic phosphonium reagents are

6 promising competitors (9, 10). Stronger reagents were generated based on structures isoelectronic to

7 neutral trivalent boron centres such as silicon cations (*11-13*) and even phosphorous dications (*14, 15*).

8 Efforts regarding carbon-based Lewis acids mostly focussed on trityl cations, wherein particularly the

9 more acidic fluorinated examples are rarely isolable (16-19). The more reactive Lewis acids typically

10 require inconvenient and costly procedures during their preparation and application. We envisioned

11 generating Lewis superacids by utilising neutral leaving groups for interim stabilisation of one of the

12 charges of carbodications. This enabled the synthesis of diiminium dications under mild conditions.

13 Even urea halides with their mediocre leaving groups can be used as synthetic equivalents for carbodications (20, 21). The π -stabilisation from the two nitrogen substituents leads to dissociation of one 14 15 of the halides, even in the case of chlorides. This is also the case with isouronium salts such as 1, which 16 contain the same reactive formamidinium unit as their halide parents but bear better leaving groups. They 17 can be generated with triflic anhydride directly from urea derivatives (Tf₂O, Figure 1A) (22-24). Seminal 18 studies by Maas showed that isouronium anhydride 3 as access point to diiminium chemistry but they 19 were not utilized as Lewis acidic reagents, which was discussed in more detail within this work (25-27). 20 We report herein our findings on dicationic salts that can be regarded as tetramethyldiiminium (TMDI, 21 further abbreviated as DI) nucleophile adducts (DINu). A convenient, inexpensive, and scalable one-pot 22 synthesis was designed, and their Lewis acidic properties were investigated computationally and in 23 fluoride, hydride, and oxide abstraction reactions, the latter was applied in an amide coupling.

24 O-triflyl tetramethylisouronium triflate 1 was generated in a single step from commercially available 25 tetramethylurea (TMU) with triflic anhydride in 98% yield (Figure 1A) (22). The salt 1 is a moisture-26 sensitive, viscous ionic liquid with a melting point of 19 °C. This salt appears to be mildly temperature-27 sensitive, showing "charring" at room temperature (r.t.) after a few days. Substitution of the bound triflate with pyridine (Py), which succeeds in a one-pot procedure directly from TMU, leads in an exergonic 28 reaction to the precipitation of the salt DIPy. The suspension is filtered and washed with dichloromethane 29 30 (DCM) to give the pure adduct DIPy in 98% yield which was upscaled to a 100 mmol scale (47 g). Maas 31 synthesised **DIPy** by adding Py to Stang's anhydride **3** (22, 25, 26). We were able to isolate **3** in an improved 32 69% yield with an increased reaction time (Stang reported 19%). The route to DIPy via 3 remains 33 uncompetitive as it involves a sacrificial equivalent (eq.) of TMU, 2 eq. of Py, and the use of 3 enforced a 34 more polar solvent choice (MeCN) which does not lead to the convenient precipitation of DIPy and a slightly lower yield (94%) (25-27). While mild hygroscopic behaviour was observed, DIPy did not show 35 36 decomposition during benchtop storage and frequent use over one month. Hydrolysis restoring the TMU 37 was observed in wet CD₃CN above 80 °C. Our computational model supported a simple addition-38 elimination mechanism (SN2t) with a rate-determining initial association of Py with a free energy barrier 39 of 54 kJ mol⁻¹ (level of theory: DLPNO-CCSD(T)/aug-cc-pVTZ//PBEh-3c/def2-mSVP, solvation model: 40 CPCM(DCM); a detailed description and references can be found in the supporting material). A barrierless dissociation of the triflate ion follows to give DIPy (overall -25 kJ mol⁻¹). Addition of a second Py molecule 41

1 was strongly disfavoured (50 kJ mol⁻¹). Single crystal X-ray diffraction (SCXRD) shows C–NMe₂ bond
2 lengths of 1.31 Å (1.307(2) Å and 1.312(3) Å) and a C–pyridinium-N bond length of 1.448(2) Å, which is

3 shorter than average bond lengths in amines (1.47 Å) (28). Our model agreed within < 0.01 Å or 1° with all

4 bond lengths and angles within the CN₃ unit and predicted no distortions > 0.01 Å or 1° when comparing

5 the gas phase with solution models in DCM and MeCN.

6 It required 44 h and an excess of the donor 2,2'-bipyridine (Bipy) to form the adduct DIBipy in a poor yield (33%, Figure 1A). This can be expedited to only 1 h in a microwave (MW) at 100 °C (yield ~ 70%) but 7 these more drastic conditions lead to the formation of minor impurities which we were not able to remove. 8 9 The added driving force through precipitation of the product appears to be crucial, as this compound was 10 inaccessible through the route via 3 in MeCN (26). A computed barrier of 40 kJ mol⁻¹ separates the singly 11 coordinated **DIBipy** from the doubly coordinated structure **B3**, which is just 10 kJ mol⁻¹ less stable (Figure 12 1C). A few related carbodicationic Bipy adducts $[R_2C(Bipy)]^{2+}$ (R = H, Ph) are known (29, 30). No chelation 13 effect was observed in these cases, which was supported by our model determining the chelated form of 14 [Ph₂C(Bipy)]²⁺ to be 147 kJ mol⁻¹ more stable than the open form. The diiminium carbon atom in **DIBipy** 15 assumes a trigonal pyramidal structure in the solid state with the lone pair of the non-covalently bound pyridyl nitrogen atom donating to the empty π -orbital at the diiminium carbon atom (Figure 1B). The 16 17 structure of **DIBipy** was surprisingly rigid in the crystalline form with a distance from the diiminium C to the dangling pyridyl nitrogen atom of 261 pm being determined both at -153 °C (2.609(1) Å) and at 18 107 °C (2.612(3) Å). The orientation of the pendant pyridyl indicates the strong electrophilicity of the 19 diiminium carbon atom, as steric considerations would suggest the opposite orientation. Only four 20 21 resonances were observed in the ¹H nuclear magnetic resonance (NMR) spectrum (CD₃CN, 600 MHz, 22 26 °C) of DIBipy. Combined with the computational data, this supports fast exchange of the coordination 23 sites via the doubly coordinated B3. The rotation barriers of the C-NMe₂ bonds were determined by 24 variable temperature NMR in CD₃CN to be 54 kJ mol⁻¹ which is significantly lower than in **DIPy** with 25 69 kJ mol⁻¹ (modelled: 64 kJ mol⁻¹). Attempts to model the corresponding rotational transition state of 26 DIBipy failed. But the determined barrier that is traversed during C-NMe₂ rotation from the chelate B3 (55 kJ mol⁻¹ from **DIBipy**) is in excellent agreement with the experiment which supports chelation as the 27 main cause for the lowered rotational barrier. Aligning with the increasing weight of evidence that the 28 29 concepts of coordination chemistry apply well to carbon better than previously assumed (31-34), we found here a classic chelation effect with one dangling pyridyl in fast exchange with the coordinated pyridyl. 30

Pyridine appeared to strike the ideal balance between a quick reaction with 1 and selectivity for the 31 32 formation of the desired complex. This reaction appeared previously impossible as Maas described that 1 33 and similar compounds tend to triflylate nucleophiles rather than participating in substitution reactions 34 (23, 24). Even 4-(dimethylamino)pyridine (DMAP), which is closely related to Py, attacked at the triflyl sulphur atom to give the N-triflyl DMAP triflate 2 (Figure 1D). A detour via 3 was also reported to enable 35 36 the synthesis of **DIDMAP** but involves again a sacrificial eq. of the urea (26). Substitution of pyridine with DMAP succeeded smoothly in DIPy without triflylation and demonstrated enhanced diiminium 37 38 reactivity over 1. A soluble intermediate was formed almost instantaneously on addition of DMAP to a 39 suspension of **DIPy** in DCM. The dicationic product **DIDMAP** precipitated and was isolated by filtration 40 in good yield (78%).

1 **Figure 1.** Synthesis and structure of diiminium complexes **DINu**.



2

A, The synthesis of diiminium adducts DIPy and DIBipy succeeds from the isouronium salt 1. DIPy can be used for coupling stronger nucleophiles than pyridine. Reactant additions were partially performed at decreased temperatures, see supporting information for details. B, Solid state structures of DIPy (and LUMO) and DIBipy (and HOMO) at 50% probability level.
Hydrogen atoms are omitted in the SCXRD structures. C, Computed free energy profile of the reaction of 1 with Py (structures A) and Bipy (structures B). The inlay shows the aromatic region of the ¹H NMR spectrum (CD₃CN, 600 MHz) of DIBipy. D, As opposed to DIPy, 1 acts as triflylating agent when reacting with DMAP. E, Isouronium anhydrides 3 can be formed from 1 with remaining TMU.

Monitoring the reaction of DIPy with DMAP in CD₃CN by ¹H NMR showed the rapid formation of 10 11 intermediate D1 with broken pyridine-aromaticity (Figure 2A), an often favourable reaction in pyridinium 12 salts (35). Minor amounts of the substitution product **DIDMAP** were already detected after 5 min; full conversion was seen after 18 h. Our computational model predicted very low barriers for both ortho- and 13 14 para-addition (39 and 46 kJ mol⁻¹) which suggests rapid equilibration between these species to give the 15 more stable para-adduct D1 (Figure 2B). Equilibration by re-aromatisation under elimination of DMAP 16 allows traversing of the rate-determining barrier of 71 kJ mol⁻¹ (95 kJ mol⁻¹ from D1) associated with the addition of DMAP to the diiminium carbon atom of DIPy. Elimination of pyridine gives the 17 thermodynamic product **DIDMAP** (-60 kJ mol⁻¹). Maas reacted **DIPy** with the monoanions of several 18 19 geminal CH-diacids which led to ring-opening of the pyridinium moiety under the formation of a double 20 bond with the former Py-C2 (26, 36, 37). Only select methylene-active nucleophiles (e.g. the malonitrile 21 anion [HC(CN)₂]-) in combination with specific **DINus** lead to substitution at the diiminium carbon atom

1 (26). We could not detect any ring-opening reactivity with nucleophiles that do not allow the formation of

2 a double bond. **DIPy** acted isoelectronic to trivalent boron compounds with their electron-deficient π -

3 system but, after Lewis pair formation, was able to restore this isoelectronic relationship and a Lewis acidic

4 character by elimination of the previously assumed base.

5 **Figure 2.** Mechanistic insights into substitution of pyridine with DMAP in **DIPy**.



6

A, Monitoring the reaction of DIPy with DMAP by ¹H NMR monitoring allowed the observation of the *para*-addition intermediate
 D1, whereas the substitution product was found after 18 h. B, Computational reaction free energy profile of the three potential
 addition/ substitution reactions between DMAP and DIPy modelled in MeCN.

10 The ³¹P NMR shift of Et₃PO shifts strongly upon coordination of the oxygen atom to Lewis acids which is 11 commonly used to gauge their strength. When we attempted to employ this Gutmann-Beckett method 12 (38, 39), we observed the formation of TMU from our reagents. 1 and DIPy both abstracted oxygen from 13 Et₃PO leading to the formation of [Et₃POPEt₃](OTf)₂ (POP, Figure 3A). Some related reagents [R₃POPR₃](OTf)₂ were published in a work titled "Seeking the ideal dehydrating reagent" (known as 14 15 Hendrickson reagents) (40, 41). Their dehydrating capability can be reasoned with the thermodynamically 16 favourable formation of a P=O bond when they capture oxygen from a substrate. Triflic anhydride 17 (experiments are described in the supporting material) or thionylium dications can promote the same 18 transformation (42). DIPy reacted slower than 1 and needed a temperature of 60 °C rather than already 19 reacting at -30 °C but **DIPy** led to a much more controllable process. **1** acted as triflylating agent and 20 breaks down POP to form [Et₃POTf]OTf when 1 eq. or more were present. Similar off-track reactivity was 21 not observed with DIPy. Excess 1 also decomposed to a mixture of compounds when heated or reacted 22 for prolonged periods, whereas no signs of decomposition of DIPy were visible after 18 h at 60 °C.

Lewis acids that can abstract fluoride ions from SbF₅ are considered Lewis superacids (LSA) (5). We were not able to observe fluoride abstraction from 1.5 eq. AgSbF₆ with **1** or **DIPy** at r.t. in CD₃CN. Heating the mixtures in CD₃CN in a microwave (180 °C, 1 h) showed that the pyridinium complex **DIPy** was a competent LSA. A yield of 55% of the tetramethylfluoroformamidinium triflate **4** (Figure 3B) was

determined by quantitative NMR (qNMR). The thermal instability of 1 led to its decomposition without 1 2 the production of significant amounts of the fluoroformamidinium 4. Soft Lewis superacidity (sLSA) was 3 probed by a competition experiment in which a minor excess of **DIPy** and B(C₆F₅)₃ (1.1 eq. each) were 4 reacted with Et₃SiH at r.t. for 90 min in CD₃CN. 44% of the *para*-addition product 8 (determined by qNMR) 5 were found with DIPy (Figure 3C). Increased reaction times or temperatures lead to a loss in yield. Substitution of Py with hydride at the diiminium unit to give the formamidinium 5 was computed to be 6 7 exergonic but was not observed. This may be due a lack of a hydride shuttle mechanism after 8 decomposition of the silvl cation. No formamidinium 5 was detected when using the isouronium salt 1; it was outcompeted by the borane. The diiminium adduct DIPy was determined to be a competent soft and 9 hard Lewis superacid whereas the isouronium salt 1 was ineffective in this regard. 10

11 To quantitatively determine the hard and soft Lewis acidities of the **DINu** salts, we computed gas phase 12 fluoride and hydride ion affinities (FIA, HIA) according to Greb's and Krossing's scheme (43-46). The 13 nucleophile-stabilised **DINu** were computed to show exceptionally high *FIAs* (907–982 kJ mol⁻¹) and *HIAs* 14 (1079–1243 kJ mol⁻¹). All of them surpass the HIA of the trimethylsilyl cation, and DIPy surpassed even 15 its FIA (Figure 3D) (5, 45). The isolable meta-hexafluoromethylated trityl cation as one of the strongest trityl-based Lewis acids, in comparison, has an HIA of 960 kJ mol⁻¹ (16). DIDMAP and DIBipy have a 16 17 slightly reduced *FIA* but **DIDMAP** has an even higher *HIA* than **DIPy**. The anhydride **3** was found to be 18 very competitive with a placement on both scales between **DIPy** and **DIBipy**. An associative mechanism 19 (giving 6 and 7) was favoured in gas phase enthalpies in almost all cases whereas free energies in solution 20 dissociation of the donor to give tetramethylfluoroformamidinium predict 4 or the

21 tetramethylformamidinium 5, respectively.



22 Figure 3. Gauges of the Lewis (super-)acidity of 1 and diiminium adducts DINu.

23 24

A, The attempted Gutmann-Beckett analysis showed that 1 and DIPy abstract oxygen from EtaPO under formation of TMU. 1 acts 25 again as triflylating reagent when used in stochiometric amounts or in excess. B, DIPy can abstract fluoride from AgSbF6 while 26 decomposition was observed with 1. C, DIPy outcompetes B(C₆F₅)₃ in the hydride abstraction from Et₃SiH while no conversion 27 of 1 was observed. D, Computational gas phase hydride and fluoride ion affinities (HIA/XIA) of the DINus DINu and the

isouronium 1. XIA [kJ mol⁻¹]: DIPy: 982, DIBipy: 883, DIDMAP: 907, 1: 652, 3: 919. HIA [kJ mol⁻¹]: DIPy: 1153, DIBipy: 1079,
 DIDMAP: 1243, 1: 820, 3: 1130 (dissociative to give 5).

3 The DINus **DINu** are closely related to the successful guanidinium/isouronium-based peptide coupling

- 4 reagents (including, e.g., the compounds dubbed as O-HATU, HAPyU, and COMU) (47). They typically
- 5 feature anionic leaving groups. We expected the dicationic salts **DINu** with their neutral leaving groups
- 6 to be more active reagents than these relatives for the activation of electron-deficient amines. The reaction
- 7 of the bulky diphenylacetic acid with 4,6-dimethylpyrimidine in the presence of 1.5 eq. of coupling reagent
- 8 and 2.25 eq. of diisopropylethylamine (DIPEA) after 18 h at 80 °C, indeed, gave isolated yields of the
- 9 amide 9 of 87% with **DIPy** and 88% with **DIDMAP**. Only 68% were received with the commonly used *O*-
- 10 (7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-hexafluorophosphate (*O*-HATU, Figure 4A). The
- 11 use of O-HATU was also discouraged for its explosive properties (48). Bis(tetramethylene)fluoro-
- 12 formamidinium hexafluorophosphate (BTFFH) was previously introduced for tackling such problematic
- amide formations (49-51) We obtained 90% of the amide **9** with BTFFH under our modified conditions
- 14 (88% were reported) (49). Both O-HATU and BTFFH, however, are relatively expensive. Both **DINu**
- 15 performed comparably to BTFFH giving 87% (**DIPy**) and 88% (**DIDMAP**) of **9**.

Figure 4. Performance of DIPy, DIDMAP, O-HATU, and BTFFH in an amide formation with a bulky carboxylic acid and an
 electron-deficient amine. The amines were added, and heating was commenced, after stirring at r.t. for 30 min.



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The presented diiminium nucleophile adducts are a group of conveniently available and handleable Lewis superacids with strong fluoride, hydride, and oxide abstraction properties. Our preliminary results combined with price and safety considerations suggest that they are competitive amide coupling reagents. We anticipate these reagents to find broad application through the development of derivatives and the investigation of their performance in the activation of further pucleophiles.

23 investigation of their performance in the activation of further nucleophiles.

Data availability: The data that support the findings in this work are available within the paper and
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Author contributions: F.F.M. conceived the work and designed the study. J. W. and K.R. designed and conducted crystallographic experiments and analysed structural features. F. F. M., W.-B. H., and P.W. performed the pyridine substitution reactions. A.K.B. computed the substitution reaction free energy profile. A.B. explored potential applications. N.B., F.F.M., A.K.B., and P.W. performed the amide couplings. F.F.M. conducted all remaining parts. F.F.M. directed the research and wrote the draft. All authors contributed and agreed to the manuscript.

7 **Competing interests:** The authors declare no competing interests.

8 Additional information

9 **Supplementary information:** The online version contains supplementary material available at XXXXXXXXX.

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12 Figure Legends

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12