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Acidity of Di- and Triprotected Hydrazine Derivatives in Dimethyl Sulfoxide and Aspects of Their Alkylation

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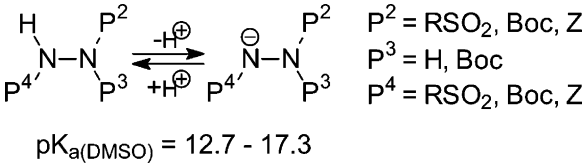

The pK_a values in DMSO for 22 di- and triprotected hydrazine NH acids and two monosubstituted hydrazines have been determined using potentiometric titration. The results of density functional theory calculations at the B3LYP/6-311+G** level of gas-phase acidities of a representative selection of mono-, di-, and trisubstituted hydrazines are compared with both the relevant published and novel experimental titration data. In the course of this work, a rough estimation of the pK_a value of hydrazine in DMSO (ca. 38.0) has been deduced. For typical triprotected compounds of this kind containing moderately electron-withdrawing carbamate and imidodicarbonate or arenesulfonylcarbamate functions the pK_a values fall in the range 15.1−17.3, whereas for *N*,*N*′-diprotected hydrazines with a carbamate and an aromatic sulfonyl group the corresponding values are 12.7−14.5. Several of these triprotected derivatives have recently been applied preparatively in stepwise synthesis of substituted hydrazines using alkyl halides as electrophiles in the presence of a phase transfer catalyst, and a few of them, with varying success, have been examined in model experiments with benzyl alcohol, triphenylphosphine, and diethyl azodicarboxylate in the Mitsunobu reaction. The dependence of the reactivity on the intrinsic acidity of the hydrazines in this reaction is highlighted. Furthermore, the regioselective alkylation of an *N*,*N*′-diprotected hydrazine can be rationalized on the basis of the presented data.

Introduction

Substituted hydrazines are nowadays of great technical and commercial importance,[1] and a large number of methods for their synthesis have been developed.[2] Direct substitution of one or more hydrazine hydrogens often presents considerable experimental difficulties, which are particularly pronounced in the preparation of alkylated derivatives on a laboratory scale, where, as a rule, mixtures of starting material, the desired product, and overalkylated hydrazines are obtained. These difficulties could, in principle, be reduced by application of suitable amino-protecting groups.[3] Some time ago it occurred to us that *triprotected* hydrazine derivatives[4] would allow substitutions to be driven to completion without formation of multisubstituted products, and a prototypic re-

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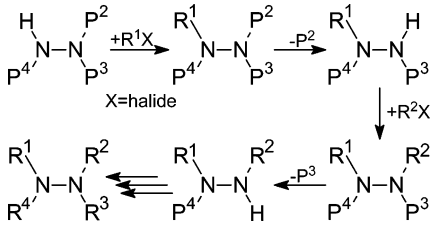
TABLE 1. Acidity of Hydrazine Derivatives[a] in DMSO (pK_a) and in the Gas Phase (GA)

Part A. Based on Published p$K_{a(DMSO)}$ Data							Part B. Di- and Triprotected Derivatives						
entry	P^2	P^3	P^4	ref	pK_a	GA[b] this work	entry	P^2	P^3	P^4	source	pK_a[g]	GA[b]/ category[h]
	H	H	H	–	–	391.7	1	Ts	Boc	Z	9a	15.5	A
1	H	H	Ph	8c	28.8[c]	354.9[d]/370.2[e]	2	Ts	Boc	Boc	4c	16.0	A
2	H	H	CH_3CO	8b	21.8[c]	350.7	3	1-Ns	Boc	Z	4c	15.1	A
3	H	H	PhCO	8b	18.9[c]	341.0	4	2-Ns	Boc	Z	4c	15.4	A
4	H	H	CO_2Et	8c	22.2[c]	354.4	5	Cbs	Boc	Z	4b,c	12.6	A
5	H	H	$PhSO_2$	8b	17.1[c]	339.1	6	Z	H	Ts	9a	14.0	B
6	Ph	H	Ph	8b	26.2[c]	343.4	7	Boc	H	Ts	4c	14.5	B
7	Ph	H	CH_3CO	8c	18.4	344.6	8	Z	H	1-Ns	9b	13.4	B
8	CH_3CO	H	CH_3CO	8c	16.7[c]	332.5	9	Z	H	2-Ns	9b	13.6	B
9	PhCO	H	PhCO	8c	13.7	326.3	10	Z	H	Cbs	4b,c	12.7	B
10	Ph	Ph	Ph	8c	24.5	–	11	Boc	H	TFA	this work	10.0	318.2/B
11	Ph	Ph	DNP	8c	12.1	–	12	TFA	H	TFA	21	7.4	304.8/B
12	Ph	Ph	PhCO	8c	17.9	–	13	Boc	H	Tf	12	8.2	315.3/B
13	Me	Me	PhCO	8d	19.7	340.0	14	CH_3CO	H	PPh_3^+	this work	11.4	B
14	Me	Me	$PhSO_2$	8b	15.8	337.7	15	Boc	H	PPh_3^+	9c	9.9	B
15	maleic hydrazide		H	8c	13.2	322.5	16	Ts	Boc	H	9d	15.9	B
16	phthalic hydrazide		H	8c	12.7[c]	323.9	17	Boc	Boc	Boc	4a,9e	17.3	C
17	H	H	Tf	–	12.0[f]	321.8	18	Z	Boc	Boc	9e,f	17.1	C
18	Tf	H	Tf	–	4.6[f]	300.4	19	$(CH_2)_2CN$	Boc	Boc	9e	17.1	C
19	Tf	Tf	Tf	–	0.4[f]	288.2	20	Ph	Boc	Boc	9g	17.8	C
20	TFA	TFA	TFA	–	4.3[f]	299.5	21	Ph	Boc	Z	9g	16.9	C
21	TFA	H	TFA	–	17.0[f]	336.5	22	Ph	H	Z	13	17.1	C
							23	H	H	TFA	this work	16.6[c,i]	330.7
							24	H	H	PPh_3^+	14	14.3	–

[a] For labeling of substituents, see Scheme 1. Abbreviations: DNP, 2,4-dinitrophenyl, Boc, *tert*-butoxycarbonyl; Cbs, 4-cyanobenzenesulfonyl; 1- and 2-Ns, 1- and 2-naphthalenesulfonyl; PPh_3^+, triphenylphosphonium; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetyl; Ts, tosyl; Z, benzyloxycarbonyl. [b] Calculated in this work at the DFT/B3LYP 6-311+G** level, in kcal/mol units. [c] Hydrazine used to derive eq 3. [d] Deprotonation in the α-position to the phenyl ring. [e] Deprotonation in the β-position to the phenyl ring. [f] pK_a values calculated from eq 2. [g] Measured in this work. [h] Based on their pK_a values the di- and triprotected derivatives were assigned to category A, B, or C as discussed below. [i] The pK_a of CF_3CONH_2 (17.2) is given in ref 8b.

SCHEME 1. Stepwise Synthesis of Tetrasubstituted Hydrazines from a Triprotected Reagent



agent (entry 17 in Table 1, Part B) of this kind was prepared and investigated.[4a] Subsequently, another reagent (entry 5) with three orthogonal protecting groups was developed and used for the first synthesis of tetrasubstituted derivatives in which all substituents were different.[4b] These syntheses were accomplished in a stepwise fashion, each substitution (with RX) being followed by a selective removal of a protecting group (P) as shown in Scheme 1.

Initially, these N-alkylations were carried out with halides under phase transfer catalysis (PTC) conditions.[4a] Subsequently, alcohols[4b,c,5] have also been applied in the first alkylation step under Mitsunobu conditions, that is, in the presence of triphenylphosphine and an azodicarboxylate, which requires an acidic nitrogen component.[6]

In a previous article, it was demonstrated that for imidodicarbonates and tosylcarbamates there is a clear connection between their pK_a in DMSO solution and the yield of product with a selected alcohol in the Mitsunobu reaction.[7] Therefore, to understand and rationalize the behavior of these protected hydrazines upon alkylation with alcohols in this way, it would obviously be helpful to know their pK_a values in this solvent, in particular since such values for only simple and distantly related derivatives and not for hydrazine itself have been determined previously.[8] Altogether the literature contains more than 30 pK_a values related to DMSO of aryl, acyl, benzenesulfonyl, ethoxycarbonyl, and similar, mostly mono- and disubstituted, predominantly acyclic hydrazines, hydrazides, and hydrazones in the range from 28.8 ($PhNHNH_2$) to 12.1 ($2,4\text{-}(NO_2)_2C_6H_3NHNPh_2$). A few p$K_a$'s of acylated hydrazines, including $BocHNNBoc_2$, were also measured in aqueous solution.[5a]

In this article, a number of di- and triprotected hydrazine reagents[4,9] with arenesulfonyl and alkyloxycarbonyl and, in three cases, triphenylphosphonium

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protecting groups have been studied, and their pK_a values in DMSO (p$K_{a(DMSO)}$) determined by analogy with imidodicarbonates and tosylcarbamates previously.[7] Also, for the sake of comparison with these experimental values, the gas-phase acidities (GA) of a representative selection of 22 hydrazines with widely different structures and p$K_{a(DMSO)}$ were calculated using a density functional theory (DFT) approach at the B3LYP/6-311+G** level.[10] The computations were carried out using the Gaussian 2003 series of programs. DFT calculations were performed using the B3LYP hybrid functional. Full geometry optimizations and vibrational analyses were performed using the 6-311+G** basis set except for hydrazine, for which also the 6-311++G** basis set with diffusion functions on hydrogen atoms was used. This approach has been demonstrated by some of us to describe with reasonable accuracy both the gas-phase basicities and acidities of a wide variety of relatively simple molecules.[10] All stationary points were found to be true minima ($N_{imag} = 0$). Unscaled B3LYP 6-311+G** frequencies were used to calculate the GA of neutral acids AH and proton affinities (PA(A^-)) of the conjugated anionic bases (A^-) to take into account the zero-point frequencies, finite temperature 0−298 K correction, the pressure−volume work term, and the entropy terms as appropriate. The terms GA and PA refer to the following equilibrium (eq 1) and are defined as follows:

$$\mathrm{AH} \underset{\mathrm{GA} = \Delta G_{acid}\quad \mathrm{PA(A^-)} = \Delta H_{acid}}{\overset{\Delta G_{acid},\ \Delta H_{acid}}{\rightleftharpoons}} \mathrm{A^-} + \mathrm{H^+} \qquad (1)$$

Most of the calculated GA values (in kcal/mol units) alongside some representative literature p$K_{a(DMSO)}$ data are given in Table 1A, whereas some directly related to our present experimental study are found in Table 1B. The calculated energies, enthalpies, and free energies of the substituted hydrazines and corresponding deprotonated species as well as proton affinities PA(A^-) are presented in the Supporting Information.

The new solution and GA data are interpreted on a structural basis and used to rationalize previously reported work dealing with the application of such compounds in the synthesis of multisubstituted hydrazines. Alkylhydrazines and hydrazine itself are too weak NH acids for measurement of their p$K_{a(DMSO)}$ due to autoprotolysis (pK_{auto} = 35 for DMSO)[8b] like alkylamines and ammonia (an indirect estimate by Bordwell and Algrim[8a] places the p$K_{a(DMSO)}$ of ammonia at 41 ± 1). Therefore, in this article we also make an attempt to estimate the p$K_{a(DMSO)}$ of hydrazine by using (1) a correlation between the calculated gas-phase and solution (DMSO) acidities for substituted hydrazines (eq 2 below), (2) another correlation of p$K_{a(DMSO)}$ data for ammonia and hydrazine derivatives (eq 3 below), and (3) a linear relation between experimental gas-phase acidities and p$K_{a(DMSO)}$ as described in ref 11.

Results and Discussion

In Table 1, Part A, we have collected p$K_{a(DMSO)}$ values from the literature for a selection of relevant hydrazines and supplemented them with calculated GA data. In Part B, the results of our pK_a determinations dealing with a number of recently prepared di- and triprotected hydrazine reagents (entries 1−19) and a few simple derivatives are presented, together with some additional GA data. It also contains such information for two monoprotected hydrazines prepared for comparison purposes.

Inspection of Table 1 shows that, for the set of hydrazines studied, both the calculated GA and the experimental p$K_{a(DMSO)}$ vary widely, the former by ca. 104 kcal/mol corresponding to a difference in equilibrium constants of 76 powers of ten, and the latter by more than 21 units. The data fit the linear relation (2):

$$\mathrm{GA} = a + b \cdot \mathrm{p}K_{a(DMSO)} \qquad (2)$$

where $a = 287.0 \pm 3.2$ and $b = 2.91 \pm 0.20$, $n = 15$, $r = 0.971$, and $s = 3.4$

Equation 2 holds for most mono-, di-, and trisubstituted hydrazines, including compounds with electron-acceptor substituents, starting with 1,2-bistrifluoroacetyl hydrazine (pK_a = 7.4) and ending with $H_3CCONHNH_2$ and EtO(O)CNHNH$_2$ (pK_a = 22.2). Surprisingly, the pK_a of phenylhydrazine fits the same straight line only on condition that the calculated GA value refers to deprotonation from the NH_2 group (β-position to the phenyl group) (eq 2). Relationships similar to eq 2 between the experimental GA and pK_a values in DMSO or aqueous solution were earlier observed to hold for other classes of NH acids (anilines, imides, amides, heterocycles, etc.).[11] Equation 2 shows that upon going from the gas phase into DMSO solution the effects of substituents on the GA of hydrazines are rather significantly attenuated (compare with ref 11). Equation 2 allows one to make rough estimates of solution-phase acidities of some hydrazines that are either hard to prepare (e.g., TfNHNH$_2$) or are predicted to be too acidic (e.g., TfNHNHTf, Tf$_2$NNHTf, etc.) or too weak (e.g., methylhydrazines) to be measured directly in DMSO solution. A few such p$K_{a(DMSO)}$ values are given at the end of Part A and will be discussed later in the article.

The first five compounds in Part A illustrate the acidifying effect of a single phenyl or acyl substituent in hydrazine. $PhSO_2NHNH_2$ is by ca. 5 powers of 10 a stronger acid than EtOCONHNH$_2$, used here to estimate the influence of a single carbamate protecting group such as Z or Boc, for which literature data is missing. As follows from eq 2, even much higher acidity (ca. 12) could be expected for trifyl hydrazine. Unfortunately, all of our attempts to synthesize that compound (compare also ref 15) have thus far been inconclusive. Upon going from mono- to diacylated hydrazines (entries 8 and 9 in Part A), a significant trend toward higher acidity is noticeable. TfNHNHBoc, TFANHNHTFA, and TFANHNHBoc are of the same type and, as can be seen, the acidifying effect of the Tf and TFA groups is much stronger than that of others studied. This is evident also for 1,2-bistrifyl hydrazine, for which the calculated GA reaches that of sulfuric acid.[10b]

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The trisubstituted derivatives (entries 10−14 in Part A) are all too different in structure from those in Part B to provide a meaningful comparison. Among the latter are first some triprotected hydrazines, whose aromatic sulfonyl residues P^2 (Ts, 1-Ns, 2-Ns, Cbs; entries 1−5) together with P^3 form sulfonylcarbamates, whereas P^4 are carbamate functions. These substances have p$K_{a(DMSO)}$ values in the range 15.1−16.0, with the exception of the last one. For the corresponding 1,2-diprotected substances (entries 6−10) with a hydrogen at the sulfonamide nitrogen, these values are 12.7−14.0, thus giving rise to two fairly well-defined sets of hydrazine derivatives, called A and B below. Although acidity in general should be determined primarily by the substituent directly attached to the deprotonation site, the significant difference in this respect between $EtOCONHNH_2$ and category A compounds demonstrates an additional considerable contribution from the electron-withdrawing sulfonylcarbamate NP^2P^3 moiety. This seems to partly offset the effect of the sulfonyl groups in type B compounds, and as a result, the gap in p$K_{a(DMSO)}$ between these two categories is reduced to 2−3 units. Among the 1,2-disubstituted compounds experimentally studied, two contain the positively charged PPh_3^+ group (entries 14 and 15), which makes them more acidic than those with an aromatic sulfonyl group. This indicates not only that the PPh_3^+ group has stronger electron-withdrawing properties, but also that it can presumably better stabilize the zwitterionic species formed on protolysis by electrostatic ion−ion interaction. For the compound in entry 15, the increase in acidity approaches five and three pK_a units as compared to those in entries 7 and 10, respectively.[16]

The next compound, $H_2NNTsBoc$ (entry 16), is a rare example of a diprotected hydrazine that has both substituents (P^2 and P^3) on the same nitrogen atom. Structurally, it is related to the triprotected derivatives in entries 1 and 2 with about the same acidity, which again demonstrates the strongly acidifying effect of its sulfonylcarbamate moiety. Roughly similar acidity (17.1) is predicted via eq 2 also for $(TFA)_2NNH_2$ and Ac_2NNH_2 on the basis of their calculated GA. The rather moderate acidity of this class of compounds results from the lack of a resonance-stabilizing electron acceptor group at the deprotonation site.

The three following triprotected derivatives without both sulfonyl and phenyl moieties (entries 17−19) exhibit p$K_{a(DMSO)}$ values in the very narrow range 17.1−17.3 (category C). Comparing data for the two C compounds containing only Z- and Boc-groups with those of category A, it appears that the acidifying effect of a sulfonylcarbamate in relation to an imidodicarbonate moiety is less than two pK_a units. Similar low values, 16.9−17.8, are exhibited by the three phenylhydrazines studied (entries 20−22; therefore referred to category C) with BocNHNPhBoc of lowest acidity among all the compounds in this study, spanning 8 orders of magnitude (cf. also Part A entries 1, 7, and 12).

The only previous pK_a determinations on trisubstituted hydrazines that we know of have been performed in DMSO by Bordwell et al.[8b−d] and in aqueous solution by Jamart-Grégoire et al.[5a] In DMSO, literature values range from 24.5 to 12.1 (entries10−14 in Part A), the last value referring to a compound with the strongly electron-withdrawing 2,4-dinitrophenyl substituent at the NH site.

On the basis of DFT calculations and eq 2, the p$K_{a(DMSO)}$ for Tf_2NNHTf and $(TFA)_2NNHTFA$ can be estimated to be around 0.4 and 4.3, respectively. The calculated GA values of those compounds equal or exceed that of triflic acid[10] and are determined by a combination of the field inductive effects of the substituents (Tf and NTf_2 or TFA and $N(TFA)_2$) at the N-atoms and most strongly by resonance stabilization of the anionic species by the electron-accepting substituents (Tf or TFA groups) at the ionization center. Therefore, due to the lack of such stabilization, the acidifying effect of the NTf_2 or $N(TFA)_2$ moieties should be weaker.

The data for two of our tosyl derivatives (entries 6 and 7, Part B) should also be compared with the p$K_{a(DMSO)}$ for tosyl amide, for which values of 15.74 and 16.3 have been reported,[7,17] indicating a moderately acidifying effect of the additional substituted nitrogen. In aqueous solution,[5a] the pK_a values of the only three compounds studied, two *N*-alkoxycarbonylaminophthalimides and $BocNHNBoc_2$ identical with that in entry 17, are around 11 or, more exactly, 11.3 for the last compound, that is, ca. 6 pK_a units lower than in DMSO, which is in reasonable agreement with earlier findings for neutral NH acids of similar structure and acid strength.[7,17]

Although this triprotected hydrazine reagent (entry 17) is among the least acidic substances in our set of compounds, it could be alkylated readily by halides under various PTC conditions.[4a,9e] A related reagent (entry 18) exhibits a similar p$K_{a(DMSO)}$ and could also be efficiently alkylated in this way,[9d,e] although extended reaction times should be avoided due to the increased sensitivity to bases of its imidodicarbonate function. Since, in our experience, sulfonylcarbamates are completely stable toward many strong bases, procedures based on PTC techniques were reliable for alkylation of triprotected hydrazine reagents containing such functions. Detailed experimental conditions have been given elsewhere.[4c,9a]

On the other hand, Jamart-Grégoire et al. reported that all attempts to alkylate $BocNHNBoc_2$ using the Mitsunobu protocol failed.[5a] Using benzyl alcohol, triphenylphosphine (TPP), and diethyl azodicarboxylate (DEAD), we obtained a maximum of 7% of benzylated product with this reagent as estimated by ^1H NMR. Similarly with the Boc_2Z-reagent (entry 18), even with considerable excess of TPP and DEAD, the yield of 1-benzyl-1,2-Boc_2-2-Z-hydrazine was low (37%; not included in the Experimental Section). These results differ from those first obtained with a more acidic reagent[4b] (entry 5) and from other ones belonging to Category A, as shown in the Experimental Section and Supporting Information. Simple benzyl alcohols[4b,c] and also 2-propanol[18] have been shown to react essentially quantitatively. We conclude that reagents of Category C, contrary

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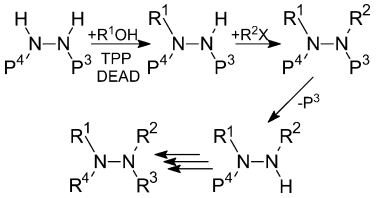
SCHEME 2. Simplified Stepwise Synthesis of Tetrasubstituted Hydrazines from a Diprotected Reagent[a]



[a] P^3 = Z or Boc; P^4 = $ArSO_2$; TPP = triphenylphosphine; DEAD = diethyl azodicarboxylate; X = halide.

to A reagents, are too weakly acidic to undergo smooth Mitsunobu reaction under these conditions.

Interestingly, the presented pK_a data also rationalizes the behavior of a *diprotected* derivative (entry 7) which undergoes perfectly regioselective benzylation on its most acidic nitrogen under Mitsunobu conditions (see Experimental Section[4c]). Similar 1,2-diprotected compounds (e.g., entries 6 and 8−10) of similar acidity might also be attractive synthetically (Scheme 2), because, in addition to being simple to prepare, they provide a shortcut to tri- and tetrasubstituted hydrazines by elimination of one step, as shown in Scheme 2.

On several occasions, a third method to alkylate protected hydrazines in addition to halides under PTC and alcohols under Mitsunobu conditions has been attempted; namely, with triflates made from alcohols. One successful example based on $BocNHNBoc_2$ can be found in the Experimental Section, in which deprotonation is accomplished by BuLi. Another simple example is given in the Supporting Information, demonstrating use of a triflate in the second alkylation step. Other attempts at alkylation of hydrazines with triflates have thus far given less satisfactory results.

Comparison of the intrinsic, gas-phase acidities of ammonia (ΔG_{acid} = 396.1 kcal/mol)[11] and hydrazine (GA = 392.0 kcal/mol, value calculated at the DFT/6-311++G** level)[19] shows that the latter molecule is, in terms of absolute acidity, 4.9 kcal/mol (or 3.6 pK_a units) more acidic than ammonia. This may be due to dominance of the acidifying effect of the modestly electronegative N-amino substituent over the increased lone-pair−lone-pair repulsion acting in the opposite direction in the anionic form of hydrazine (see also ref 20).

As mentioned in the Introduction, the p$K_{a(DMSO)}$ of the extremely weak NH acids, ammonia and hydrazine, cannot be determined experimentally due to autoprotolysis of the solvent but the former has been estimated to be 41 ± 1. The simplest possibility to estimate an approximate p$K_{a(DMSO)}$ for hydrazine is now at hand in eq 2, which leads to a value of 36.0 ± 1, indicating that, like in the gas phase, hydrazine is by ca. 5 pK_a units a stronger acid than ammonia.

Another possibility to gain an approximate hypothetic p$K_{a(DMSO)}$ for H_2NNH_2 is based on the observation that in both the ammonia[8a,b] (XNH_2) and hydrazine[8b,c] ($XNHNH_2$) series the introduction of a single, polarizable, electron-accepting nonalkyl substituent X (e.g., Ar, CH_3-CO, PhCO, COOEt, TFA, and $PhSO_2$) has a drastic influence on the acidity. A similar effect can be noticed also for cyclic substituents (e.g., in phthalimide and the respective phthalic hydrazide or symmetrically disubstituted derivatives Ph_2NH and Ac_2NH). The relevant experimental data related to these two reaction series for the six above-mentioned monosubstituted derivatives, for disubstituted Ph- and Ac-derivatives and for phthalic hydrazide and phthalic imide can be expressed as follows (eq 3):

$$pK_a(XNHNH_2) = (1.6 \pm 2.6) + (0.86 \pm 0.12)pK_a(XNH_2) \quad (3)$$

with parameters n = 9, r = 0.940, s = 1.9

The roughly linear relationship (3) holds over a pK_a(X-NH_2) interval of ca. 17 powers of 10 and shows that the sensitivity toward substituent effects is slightly lower for the hydrazines than that for the amines. On the basis of eq 3, extrapolation to Bordwell's value for ammonia (pK_a = 41) produces a very rough estimate (ca. 36.9) for the p$K_{a(DMSO)}$ of hydrazine, again indicating that it is expected to be somewhat more acidic than ammonia.

A third possibility to estimate a rough value of the pK_a of hydrazine in DMSO solution stems from earlier findings by some of us[11] that the experimental gas-phase acidities in two reaction series (meta-substituted anilines on one hand, and meta-substituted anilines and ammonia on the other hand) depend linearly on their respective pK_a values in DMSO. The insertion of ΔG_{acid} = 392.0 kcal/mol[19] for hydrazine into the corresponding equation[11] leads to a third estimate (ca. 40 ± 1) for the pK_a of hydrazine in DMSO. The average of this value and that obtained by extrapolation via eq 2 leads to the estimate 38.0 ± 1 for the pK_a of hydrazine in DMSO, which would make it roughly three pK units stronger acid than NH_3.

In conclusion, it can be stated that for the protected hydrazine compounds under study, the p$K_{a(DMSO)}$ values distinctly reflect structural features and exhibit a total span of about 21 units. Hydrazine derivatives with typically three alkoxycarbonyl groups are weakest (Category C), whereas such derivatives with one arenesulfonyl instead of an alkoxycarbonyl group on the double-protected nitrogen are of medium acidity (Category A). *N*,*N*′-Diprotected hydrazines with trifyl, TFA, or arenesulfonyl-N*H* function are of highest acidity (Category B). The novel pK_a data rationalize previously reported work with selected Category A and B reagents under Mitsunobu conditions as well as an unsuccessful experiment with one such belonging to Category C.

Experimental Section

Determination of pK_a for Protected Hydrazines in DMSO. The pK_a determinations in DMSO were performed by potentiometric titration in parallel with a solution of Bu_4NOH in a mixture of benzene and *i*-PrOH (4:1, v/v)[7] and with a solution of *t*-BuP_4 superbase (Fluka) in a mixture of benzene and DMSO (from 1:1 to 1:3 v/v, the concentration of titrant was ca. 10^{-2} M and that of hydrazine ca. 10^{-3} M).[7,11] In the pK_a range from ca. 9 to 18, the results in both titration series were the same within the limits of 0.2−0.3 pK_a units. It shows

(19) This work. No experimental value for the gas-phase acidity of hydrazine is available. The ΔG_{acid} value given here (392.0 kcal/mol) is the result of high-level quantum chemical calculations (DFT B3LYP approach at the 6-311++G** level). At the more moderate 6-311+G** level, this value becomes 391.7 kcal/mol (see Table 1A).

(20) Burk, P.; Koppel, I. A.; Rummel, A.; Trummal, A. *J. Phys. Chem.* **1995**, *99*, 1432.

that the leveling effect of the water formed from the first titrant is not significant, at least for pK_a values up to 18. All manipulations with the superbasic titrants were performed in the Mbraun professional drybox. TFANHNHTFA (entry 12, Part B) was synthesized according to a published procedure and had the same data of analyses.[21]

1-Benzyl-1-benzyloxycarbonyl-2-*tert*-butyloxycarbonyl-2-(4-toluenesulfonyl)-hydrazine (1-Bn-2-Boc-2-Ts-1-Z-Hydrazine). (Typical alkylation procedure using an alcohol under Mitsunobu conditions.) A solution of ZNHNTsBoc[9a] (1.26 g, 3.00 mmol) and benzyl alcohol (357 mg, 3.30 mmol) in dry THF (10 mL) was chilled to −10 °C under argon, and recrystallized triphenylphosphine (946 mg, 3.60 mmol) was introduced slowly with rapid stirring. The resulting clear solution was then treated dropwise, under thorough mixing, with diethyl azodicarboxylate (678 mg, 3.90 mmol) in THF (3 mL) over a period of 30 min and then allowed to react for 1 h, whereafter the cooling bath was removed. After 16 h, TLC (CH_2Cl_2/Et_2O 9:1) indicated complete reaction, and most of the solvent was stripped off at reduced pressure. The yellowish oily residue was dissolved in CH_2Cl_2 and chromatographed on silica (chromatographic system as above), providing 1.52 g (99%) of the pure title compound, a white, microcrystalline solid, mp 89.5−90 °C (from Et_2O; ∼5 mL/g; −20 °C), in all respect identical with an authentic sample.[9a]

1-Benzyl-2-*tert*-butyloxycarbonyl-1-(4-toluenesulfonyl)-hydrazine (1-Bn-2-Boc-1-Ts-Hydrazine). (Example illustrating benzylation on sulfonyl nitrogen of a diprotected reagent under Mitsunobu conditions.) This synthesis was described elsewhere.[4c]

(21) Groth, R. H. *J. Org. Chem.* **1960**, *25*, 102.

1,1,2-Tri-*tert*-butyloxycarbonyl-2-methyl-hydrazine (1,1,2-Boc$_3$-2-Me-Hydrazine). (Use of a triflate.) BocNHNBoc$_2$[4a,9e] (665 mg, 2.00 mmol) was dissolved in dry THF (4 mL) and cooled to −78 °C under argon. A solution of BuLi (1.62 M in hexane, 1.24 mL, 2.01 mmol) was then added dropwise with rapid stirring over a period of 15 min and after a further 15 min cautiously treated dropwise with methyl triflate (394 mg, 2.40 mmol). After 1 h of being stirred at −78 °C and 2 h at −30 ± 2 °C, the reaction mixture was diluted with Et_2O (80 mL), washed in turn with 0.2 M citric acid, 1 M $NaHCO_3$, and brine (3 × each), and dried ($MgSO_4$). The yield of pale yellow oil was 695 mg (100%), essentially pure by ^{1}H NMR and TLC (Et_2O/light petroleum 1:2). The analytical specimen was obtained after chromatography on silica in the above solvent mixture. ^{1}H NMR: δ (major/minor conformer): 1.44/1.49 (2s, 9H), 1.513/1.505 (2s, 18H), 3.06/3.08 (2s, 3H). ^{13}C NMR: δ (major/minor conformer): 27.9, 28.13/28.17, 35.6/37.0, 81.0/81.2, 83.2, 150.0/150.3, 153.86/153.81.

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Supporting Information Available: Synthetic procedures for novel substances including spectral data and results of DFT calculations of acidities of hydrazines. This material is available free of charge via the Internet at http://pubs.acs.org.

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