Proton-Transfer Chemistry of Urazoles and Related Imides, Amides, and Diacyl Hydrazides

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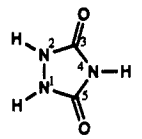
Equilibrium acidity constants have been determined for 1,2,4-triazolidine-3,5-dione (urazole), several substituted urazoles, and other related acids, in both dimethyl sulfoxide (DMSO) and aqueous solution. In DMSO, urazole has a pK_a of 13.1. In water, urazole has a pK_a of 5.8. In general, *N*-methyl and *N*-phenyl substituents are found to acidify the urazole moiety, in both DMSO and water. The acidifying effects of these substituents are attenuated by a factor of 3.3 in water. The solvent effects are ascribed to the aqueous stabilization of urazole anions via hydrogen-bonding interactions and the aqueous-promoted relief of lone pair–lone pair electronic interactions that manifest themselves upon deprotonation of a hydrazyl proton in 1 and related species. That a hydrazyl proton in 1 is at least as acidic as the imide proton in 1 is confirmed by comparison of ^{13}C NMR spectra for the urazoles and related nitrogen acids with ^{13}C spectra for the conjugate bases derived from these species. Upon loss of an imide proton, in both DMSO-d_6 and D_2O solutions, carbonyl carbon atoms present in succinimide as well as appropriately substituted urazoles and hydantoins experience substantial (13–17 ppm) downfield shifts. In contrast, deprotonation of 4-substituted and 1,4-substituted urazoles, 4,4-dimethylpyrazolidine-3,5-dione, and diacetylhydrazine (species that contain hydrazyl acidic protons) results in shifts in the positions of the carbonyl resonances that range from 5 ppm upfield to 3 ppm downfield. Deprotonation of species containing both imide and hydrazyl protons (i.e., urazole and 1-substituted urazoles) results in shifts in the carbonyl carbon resonances consistent with hydrazyl proton removal. Comparison of DMSO-phase pK_a's for acetamide (25.5), diacetylhydrazine (16.7), 4,4-dimethylpyrazolidine-3,5-dione (13.5), and urazole (13.1) suggest that the remarkable acidity of the hydrazyl proton in urazole and substituted urazoles is due mainly to its cyclic diacyl hydrazide structure.

The acidity constants of urazole (IUPAC name: 1,2,4-triazolidine-3,5-dione) and substituted urazoles are of some interest because of the varied uses of these species and their respective conjugate bases. For example, the sodium salt of 1,2-diisopropylurazole possesses antidepressant activity,[1a] while potassium salts of various urazoles have been incorporated into polycarbonates because the addition of the urazolides has been shown to increase the fire resistance of the polymer.[1b] In addition, selected urazoles have also been shown to possess fungicidal properties.[1c]

Recent articles have described investigations of the acidic properties of urazole[1] (1) and 1-substituted urazoles, in both aqueous[2] and dimethyl sulfoxide[3] (DMSO) solution. In water, it was estimated that a hydrazyl proton



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(i.e., a proton bonded to 1N or 2N) in 1 is about 1.5 pK_a units more acidic than the imide proton present in the same species,[2] while in DMSO, the two varieties of protons in 1 are of comparable acidity.[3] Examinations of the DMSO and aqueous-phase acid–base chemistry of 1 and its *N*-methyl and *N*-phenyl derivatives have now been completed. In this paper, explanations are provided for the magnitudes of the Brønsted acidities of the protons present in 1 and related species, in both DMSO and aqueous solution.

The acidities of substituted urazoles and related species have been examined by several investigators. Without reference to which proton was removed, urazole (1; in aqueous solution) was determined to have a pK_a of 5.8.[4] Other published aqueous-phase pK_a's for substituted urazoles and related species include data for 4-phenylurazole (5.29),[5] 1-phenylurazole (4.85 and 4.96),[6] 1-methyl-2-phenylurazole (6.97),[6] 1-(2-propenyl)-4-phenylurazole (4.71),[5] diacetylhydrazine (10.8),[7a] and 1-phenyl-4,4-dimethylpyrazolidine-3,5-dione (4.7).[7b] It was concluded from the 1-phenylurazole/1-methyl-2-phenylurazole results that the anion that results when the imide proton is removed from 1-phenylurazole is about 100 times less stable than the anion that results when the hydrazyl proton is removed from the same species.[6] These and related observations prompted our initial investigations of urazole acidities.[2,3]

In this article, we pose and attempt to answer the following questions: (a) What are the reasons for the enhanced acidity of the hydrazyl proton in urazole and urazole-related species? (b) What are the effects of DMSO and water solvent molecules on urazole and urazole-treated acidities?

Results and Discussion

Listed in Table I are equilibrium acidity constants (expressed as pK_a's) for 24 variously substituted urazoles, hydantoins, and related amides, imides, and diacyl hydrazides, in DMSO solution. Aqueous-phase pK_a's for 20 of these acids are also listed in Table I. While caution must be exercised in comparing absolute acidity constants for

(1) (a) Burke, T. F.; Templar, D. I. *Curr. Ther. Res., Clin. Exp.* **1968**, *10*, 335–341. (b) Perthuis, J.; Poisson, P. Fr. Demande FR 2,569,172; *Chem. Abstr.* **1986**, *105*, P154151y). (c) Shigematsu, T.; Tomita, M.; Shibahara, T.; Nakazawa, M.; Munakata, S. Japan Kokai 77 83,562; *Chem. Abstr.* **1976**, *85*, P117969u).

(2) Bausch, M. J.; Selmarten, D.; Gostowski, R.; Dobrowolski, P. *J. Phys. Org. Chem.* **1991**, *4*, 67–69.

(3) Bausch, M. J.; David, B.; Dobrowolski, P.; Prasad, V. *J. Org. Chem.* **1990**, *55*, 5806–5808.

(4) Gordon, P. G.; Audrieth, L. F. *J. Org. Chem.* **1955**, *20*, 603–605.

(5) Ohashi, S.; Leong, K.; Matyjaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467–3471.

(6) Gordon, A. A.; Katritzky, A. R.; Popp, F. D. *Tetrahedron Suppl. No. 7*, 213–217.

(7) (a) Weber, R.; Hofer, W.; Heer, W.; Brenner, M. *Helv. Chim. Acta.* **1961**, *44*, 2154–2159. (b) Woodruff, M.; Polya, J. B. *Aust. J. Chem.* **1975**, *28*, 1583–1587.

(8) Branch, G. E. K.; Clayton, J. O. *J. Am. Chem. Soc.* **1928**, *50*, 1680–1686.

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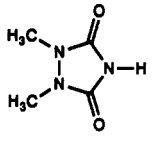
Table I. Equilibrium Acidity Constants (pK_a's, in Dimethyl Sulfoxide and Aqueous Solution for Urazole, Substituted Urazoles, and Related Acids)

acid	pK_a (DMSO)	pK_a (water)
urazole (1)	13.1[a]	5.8[b]
1-methylurazole (2)	12.2[a]	5.3[b]
4-methylurazole (3)	12.3[a]	5.8[b]
1,2-dimethylurazole (4)	12.3_5[a]	7.5[b]
hydantoin (5)	15.0[a]	9.0[b]
1-methylhydantoin (6)	14.7[a]	9.1[b]
1,4-dimethylurazole (7)	11.4[a]	5.3[b]
1-phenylurazole (8)	9.9[a]	4.8[c]
4-phenylurazole (9)	11.0[a]	5.2[d]
1,4-diphenylurazole (10)	7.9[a]	4.3[e]
4-(4-methoxyphenyl)urazole	11.4	
4-(4-methylphenyl)urazole	11.3	
4-(4-chlorophenyl)urazole	10.6	
4-(3-chlorophenyl)urazole	10.4	
1-phenyl-4-methylurazole (11)	9.0[a]	4.7
1-methyl-4-phenylurazole (12)	10.1_5[a]	4.7[c]
acetamide (13)	25.5[f]	15.1[g]
succinimide (14)	14.7[f]	9.5[b]
diacetylhydrazine (15)	16.7	10.6[h]
4,4-dimethylpyrazolidine-3,5-dione (16)	13.5	6.0
diacetamide (17)	17.9[i]	11.2[e]
acetanilide (18)	21.4[f]	13.8[j]
barbituric acid (19)	8.4[f]	4.0[k]
uracil (20)	14.1[f]	9.4[k]

[a] Reference 2. [b] Reference 3. [c] Literature values: 4.85 and 4.96. [d] Literature value: 5.3.[5] [e] Estimate. See text. [f] Reference 9. [g] Reference 8. [h] Reference 7a. [i] Reference 21. [j] Reference 33. [k] Reference 32.

species dissolved in DMSO and water (since the pK_a scales in these two solvents are based on different standard states), the DMSO pK_a for urazole (13.1) suggests substantial differential stabilization of the urazole anion in water (compared to DMSO), since the published aqueous pK_a for urazole is 5.8.[4]

DMSO Acidities: Methyl Effects. Inspection of the DMSO-phase data in Table I (and Scheme I) reveals that 1-methyl (2), 4-methyl (3), and 1,2-dimethyl (4) substituents acidify the urazole moiety to approximately the same extent (0.8–0.9 pK_a units). If one assumes that the imide proton in urazole (1, pK_a = 13.1) is most acidic, then each methyl group in 1,2-dimethylurazole (4, pK_a = 12.3_5) acidifies the imide proton in 1 by 0.3–0.4 pK_a units. The



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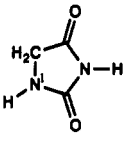

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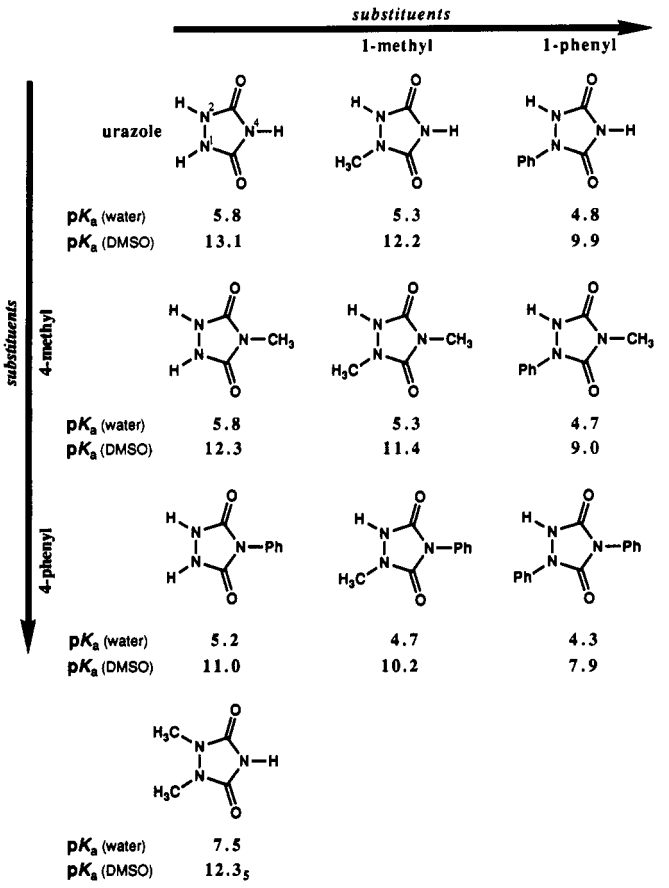
pK_a data for hydantoin (5, pK_a = 15.0) and 1-methylhydantoin (6, pK_a = 14.7) are analogous to the urazole/1,2-dimethylurazole comparison in suggesting that substitution of an *N*-methyl for hydrogen on a nitrogen atom separated from an imide N–H bond by a carbonyl group acidifies the imide proton in question by about 0.3 pK_a units. It follows from these data that the acidifying effect of the 1-methyl substituent in 1-methylurazole (2) should be 0.3–0.4 pK_a units, if the imide N–H bond is most sensitive to base. As described earlier, the difference in acidities between 1 and 2 is 0.9 pK_a units. An identical 0.9 pK_a unit difference is observed when evaluating the effects of a 1-methyl substituent on the acidity of 4-methylurazole (3), since the pK_a's for 4-methylurazole (3) and 1,4-dimethylurazole (7) are 12.3 and 11.4, respectively. Neither 3 nor 7 contains imide protons. Furthermore, it is interesting to note the additive nature of the 1-methyl and 4-methyl acidifying effects. These data provide circumstantial evidence that the hydrazyl proton in 1 and 2 is at least as acidic as the imide proton in each of these species.

Scheme I



That 1,2-dimethylurazole (4, pK_a = 12.3_5) is more acidic than urazole (1, pK_a = 13.1) is not surprising, in light of the 0.5 pK_a unit difference in the acidities of urea (pK_a = 27.0)[9] and 1,1-dimethylurea (pK_a = 26.8).[10] That 1,4-dimethylurazole (7, pK_a = 11.4) is more acidic than 4-methylurazole (3, pK_a = 12.3) is somewhat surprising, since replacement of the (emboldened) hydrazyl hydrogens in $C_6H_5C(O)NHN\mathbf{H}_2$ (pK_a = 18.9) with methyls, as in $C_6H_5C(O)NHN(\mathbf{CH}_3)_2$ (pK_a = 19.7), results in a net deacidifying effect.[11] In the 1-methylated urazoles, the methyl substituent is bonded to a hydrazyl nitrogen, rather than to an imide nitrogen, and may be constrained to be relatively coplanar with the imide urazolyl moiety. It is thus likely that an *N*-methyl substituent in urazole destablizes the nearby carbonyl moiety in the neutral urazole. It is this ground-state destabilization that is at least in part responsible for the 0.9 pK_a unit acidifying effects of *N*-methyl substituents on urazoles that contain hydrazyl protons.[12]

DMSO Acidities: Phenyl Effects. Both 1-phenylurazole (8, pK_a = 9.9) and 4-phenylurazole (9, pK_a = 11.0)

(9) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
(10) The relative acidities for urea (four acidic protons) and 1,1-dimethylurea (two acidic protons) have been corrected for differing number of acidic protons in these two species.
(11) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330–3336.
(12) (a) Alkyl effects on CH acidities in DMSO solution are usually small and often complicated.[12b,c] (b) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095–3101. (c) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1982**, *47*, 2504–2510.

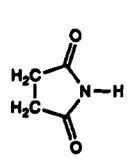
are more acidic than urazole (pK_a = 13.1). These data, combined with acidity data for 1,4-diphenylurazole (**10**, pK_a = 7.9), suggest that the acidifying effects of 1-phenyl and 4-phenyl substituents are additive. The phenyl effects data are therefore also consistent with the hypothesis that the hydrazyl protons in urazole and 1-substituted urazoles are at least as acidic as the imide protons found in these species. The large 1-phenyl acidifying effect is at least partially a result of the proximity of the 1-phenyl (compared to 4-phenyl) substituent to the incipient acyl hydrazide anion.

Also listed in Table I are DMSO-phase pK_a values for 4-(4-methoxyphenyl)urazole (11.4), 4-(4-methylphenyl)-urazole (11.3), 4-(3-chlorophenyl)urazole (10.6), and 4-(4-chlorophenyl)urazole (10.4). The imide nitrogen atom in the monoanion derived from 4-phenylurazole (**9**, pK_a = 11.0) therefore has modest interactions with the charge density in **9**, since a plot of the pK_a's for **9** and its aryl-substituted derivatives vs Hammett σ is linear (r = 0.99) with slope 1.6.[13]

Also from Table I, it is relevant to note that the acidity data for 1-phenyl-4-methylurazole (**11**, pK_a = 9.0) and 1-methyl-4-phenylurazole (**12**, $pK_a = 10.1_5$) are consistent with the notion that 1N and 4N substituent effects on urazole acidities are additive. For example, while the 1-phenyl substituent in 1-phenylurazole (**8**, pK_a = 9.9) acidifies urazole (**1**, pK_a = 13.1) by 3.2 pK_a units and the 4-methyl substituent in 4-methylurazole (**3**, pK_a = 12.3) acidifies urazole (**1**) by 0.9 pK_a units, the simultaneous presence of 1-phenyl and 4-methyl substituents (as in **11**) acidifies **1** by 4.1 pK_a units.

Relative Acidities of the Urazole Hydrazyl and Imide Protons in DMSO. The observed additivities in the urazole pK_a values in Table I suggest that the hydrazyl proton(s) present in urazole (**1**), 1-methylurazole (**2**), and 1-phenylurazole (**8**) are at least as acidic as the imide protons present in these species. It is therefore appropriate to ascribe to the hydrazyl protons in **1**, **2**, and **8** pK_a values of 13.1, 12.2, and 9.9, respectively. The additivities in the data also allow predictions of the pK_a values for the imide protons in **1**, **2**, and **8**. Since (a) 1,2-dimethylurazole (**4**, $pK_a = 12.3_5$) possesses only imide protons and (b) the effect of replacing the 1N-H in hydantoin (**5**, pK_a = 15.0) with methyl (as in 1-methylhydantoin (**6**), pK_a = 14.7) acidifies **5** by 0.3 pK_a units, it is likely that the pK_a of the imide proton in urazole (**1**) is also about 13. Utilizing this estimate for the imide acidity of urazole (**1** enables assessment of the acidity of the imide proton in 1-methylurazole ($pK_a \approx 12.7$).

The imide N–H bond in urazole is therefore quite amenable to base-induced heterolytic cleavage in DMSO solution. Acidity data for related species (formamide, acetamide, and urea: pK_a's = 23.4, 25.5, and 27.0, respectively[9]) indicate that increasing electron donation (i.e., H < H_3C– < H_2N–) to the carbonyl carbon atoms deacidifies the amide proton in these species. Succinimide (**14**)



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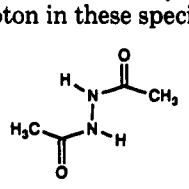

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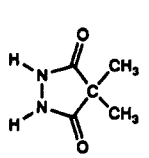

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and hydantoin (**5**) (pK_a's = 14.7[9] and 15.0, respectively) follow this trend. On the other hand, urazole (imide $pK_a \approx 13.0$) is more acidic than either **5** or **14**. Among the possible reasons for the enhanced acidity of urazole (relative to **5** and **14**) include the stabilization of the urazole (imide) monoanion that results from the presence of the adjacent heteroatomic nitrogen.

Insight into the reasons for the acidities of the hydrazyl protons in urazole and 1-substituted urazoles can be gained by noting that the pK_a's for acetamide (**13**) and diacetylhydrazine (**15**) are 25.5_9 and 16.7 (Table I). These data indicate that the presence of an adjacent amide moiety (bonded via nitrogen) acidifies an amide proton by about 8.8 pK_a units. This remarkably large acidifying effect is probably due to a combination of (a) a destabilization of the neutral **15**, relative to the stabilization that each amide moiety would feel if the two nitrogens present in **15** were not linked in the hydrazyl linkage, and (b) a stabilization of the anion derived from diacetylhydrazine (**15** – H^+) that results from field effects analogous to those responsible for the large α-NH_2 acidifying effects in carbohydrazides.[11]

Further insight into urazole acidities is gained from a comparison of the acidities for diacetylhydrazine (**15**, pK_a = 16.7) and 4,4-dimethylpyrazolidine-3,5-dione (**16**, pK_a = 13.5). A comparison of this sort is reminiscent of the Meldrum's Acid/dimethyl malonate acidity issue.[14] The 3.1 pK_a unit greater acidity of the cyclic analogue 4,4-dimethylpyrazolidine-3,5-dione (**16**) (compared to the acyclic diacetylhydrazine (**15**)) is probably due in some measure to unfavorable lone pair–lone pair interactions in the cyclic **16** that result from the incorporation of the adjacent nitrogen atoms into a five-membered ring. As in the Meldrum's Acid comparison, it is also likely that the cyclic nature of the anion derived from 4,4-dimethylpyrazolidine-3,5-dione (**16** – H^+) enforces some coplanarity that enables maximum stabilization in **16** – H^+.[14]

It is also relevant to compare the acidities of urazole (pK_a = 13.1) and 4,4-dimethylpyrazolidine-3,5-dione (**16**, pK_a = 13.5), both of which are heterocyclic. While **1** is 0.4 pK_a units more acidic than **16**, urea (pK_a = 27.0) is 1.5 pK_a units less acidic than acetamide (**13**, pK_a = 25.5).[9] These data suggest an anion stabilizing effect that results from replacement of the isopropylidene linkage in 4,4-dimethylpyrazolidine-3,5-dione with the N–H moiety in urazole. The data are therefore further evidence for the importance of the cyclic structure of urazole in its relative acidity, since the heterocyclic nature of urazole must play a role in this stabilization, in light of the aforementioned urea/acetamide comparison.

Aqueous Urazole Acidities: Methyl and Phenyl Effects. Also listed in Table I are equilibrium acidity constants (expressed as pK_a's) for 20 variously substituted urazoles, hydantoins, and related amides, imides, and diacetylhydrazine, in aqueous solution. Aqueous-phase pK_a's obtained in this study for urazole (5.8),[4] 4-phenylurazole (5.2),[5] hydantoin (9.0), succinimide (9.5),[15] and diacetylhydrazine (10.6)[7] agree nicely with published aqueous-phase pK_a's for these species. Further inspection of the data in Table I reveals that, in water, the acidifying effect of a 1-methyl substituent (1-methylurazole (**2**); pK_a = 5.3) is much greater than that of a 4-methyl substituent, which appears to have a negligible effect on the acidity of **1** (4-methylurazole (**3**); pK_a = 5.8). Aqeuous-phase pK_a's of hydantoin (**5**) and 1-methylhydantoin (**6**) are approxi-

(13) David, B. M.S. Thesis, Southern Illinois University at Carbondale, 1989.

(14) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.

(15) Literature aqueous-phase pK_a's for succinimide (9.7) and hydantoin (9.5): Albert, A. *Heterocyclic Chemistry, 2nd ed.*; Oxford University Press: New York, 1968; pp 30, 246.

mately equal (9.0 and 9.1, respectively). These data, combined with the pK_a for 1,2-dimethylurazole (7.5), suggest that the "imide pK_a" for urazole itself (in water) is also about 7.5.

A comparison of the published aqueous-phase acidity data for 1-phenylurazole (8, pK_a = 4.8)[6] with the data obtained in this study for 4-phenylurazole (9, pK_a = 5.2) reveals that the aqueous and DMSO results both suggest that 1-phenyl acidifies to a greater extent than 4-phenyl. As in DMSO solution, methyl as well as phenyl substituents at 1N and 4N have additive effects on the aqueous phase acidities of urazoles. For example, the acidifying effects of 1-methyl and 4-phenyl substituents (when present in 2 and 9) are cumulatively observed when both of these substituents are present in the same species (1-methyl-4-phenylurazole (12, pK_a = 4.7)). The additivities in the acidity data enable estimate of the aqueous-phase pK_a value for the water-insoluble 1,4-diphenylurazole (10, $pK_a \approx 4.3$). The additivities in the aqueous-phase acidity data also suggest that the hydrazyl protons in urazole, 1-methylurazole, and 1-phenylurazole are at least as acidic as the imide protons in these species. As described previously, the aqueous phase "imide pK_a" for urazole (1) itself is about 7.5, a value nearly 2 pK units higher than the measured value of 5.8 for 1. Utilizing this estimate for the aqueous-phase imide acidity of urazole (1) allows an estimate of the acidity of the "imide pK_a" for 1-methylurazole (2, $pK_a \approx 7.5$). Recall that the aqueous-phase pK_a's for hydantoin and 1-methylhydantoin are 9.0 and 9.1, respectively.

Pyrazolidinedione and Diacetylhydrazine Aqueous-Phase Acidity Data. As in DMSO, the highly acidic nature of the hydrazyl proton(s) in urazole and 1-substituted urazoles (when dissolved in water) is best rationalized by comparing the aqueous-phase acidities of the urazoles with similar data obtained for diacetylhydrazine ((15), pK_a = 10.6)[7] and 4,4-dimethylpyrazolidine-3,5-dione ((16), pK_a = 6.0). The diacyl hydrazide nature of 15 results in a nearly 5 pK_a unit enhancement in the acidity of the NH proton, relative to the aqueous-phase acidity of acetamide ((13), pK_a = 15.1).[8] Indicative of further similarities between the aqueous and DMSO phase data, cyclization of 15 (resulting in 4,4-dimethylpyrazolidine-3,5-dione (16)) results in a further 4.6 pK_a unit increase in acidity. The aqueous phase results for urazole (1) and 4,4-dimethylpyrazolidine-3,5-dione (16) (pK_a's = 5.8 and 6.0, respectively) provide additional evidence for the acidifying effect of the imide nitrogen atom present in 1.

^{13}C NMR Investigations of Urazole Acid–Base Chemistry. Facts from Table I regarding the acid–base chemistry of substituted urazoles and related species therefore indicate that the hydrazyl proton bonded to 1N in urazole is surprisingly acidic. In an effort to further evaluate the structure and reactivities of urazoles and their conjugate bases, ^{13}C NMR investigations of substituted urazoles and their conjugate bases have been undertaken. Listed in Table II are the DMSO-d_6-phase chemical shifts of the carbonyl carbon atoms for 21 various urazoles and related species, as well as similar spectra for the conjugate bases derived from these species. The analogous D_2O-phase data for most of these species are listed in Table III.

It is convenient to discuss the DMSO-d_6 data first. All spectra in DMSO-d_6 were collected at substrate concentrations of 0.1 M. It is thus likely that ion pairing, hydrogen bonding, and other concentration-dependent phenomena are of some significance.[16] Nevertheless, the data in Table II are useful for the following comparisons.

^{13}C absorptions for the carbonyl carbons present in acetamide (13) and urea indicate that replacement of the $-CH_3$ group in acetamide with $-NH_2$ results in an upfield shift of about 12 ppm. These data are reasonable in light of the 24 ppm difference in the positions of the carbonyl resonances for succinimide and urazole (179.2[17] and 155.9 ppm, respectively). Assignment of the carbonyl resonances

(16) (a) Porter, D. M.; Brey, W. S. *J. Phys. Chem.* **1967**, *71*, 3779–3783. (b) ul Hasan, M. *Org. Mag. Res.* **1980**, *14*, 447–450.

Table II. ^{13}C Chemical Shifts for the Carbonyl Carbon Atoms Present in Urazoles, Substituted Urazoles, and Other Imides and the Conjugate Bases Derived from These Species, in DMSO-d_6 Solution (0.1 M)

	DMSO-phase carbonyl ^{13}C chemical shifts[a] (ppm)					
	C(O) in HA		C(O) in A^-		Δ[HA − A^-]	
acid (HA)	A	B	A	B	A	B
urazole (1)	155.9	155.9	158.6	158.6	−2.7	−2.7
1-methylurazole (2)	154.9	154.2	156.2	154.9	−1.3	−0.7
4-methylurazole (3)	155.1	155.1	156.1	156.1	−1.0	−1.0
1,2-dimethylurazole (4)	154.9	154.9	171.8	171.8	−16.9	−16.9
hydantoin (5)	173.7	158.2	188.1	176.3	−14.4	−18.1
1-methylhydantoin (6)	171.7	156.9	185.3	174.1	−13.6	−17.2
1,4-dimethylurazole (7)	154.5	153.7	156.1	153.2	−1.6	+0.5
1-phenylurazole (8)	153.9	151.2	156.3	152.8	−2.4	−1.6
4-phenylurazole (9)	153.3	153.3	154.7	154.7	−1.4	−1.4
1,4-diphenylurazole (10)	152.0	149.3	154.5	150.8	−2.5	−1.5
1-phenyl-4-methylurazole (11)	152.5	152.0	153.9	151.6	−1.4	+0.4
1-methyl-4-phenylurazole (12)	153.5	151.2	156.3	152.8	−2.2	−1.0
acetamide (13)	171.3	171.3	175.2	175.2	−4.9	−4.9
succinimide (14)	179.2	179.2	194.9	194.9	−15.7	−15.7
diacetylhydrazine (15)	167.8	167.8	162.9	162.9	+4.9	+4.9
4,4-dimethylpyrazolidine-3,5-dione (16)	174.7	174.7	177.2	177.2	−2.5	−2.5
diacetamide (17)	171.0	171.0	178.6	178.6	−7.6	−7.6
acetanilide (18)	168.1		170.1		−2.0	
benzamide	167.8		170.7		−2.9	
1,2-dimethyl-4-phenylurazole	152.8	152.8				
1,2,4-trimethylurazole	154.6	154.6				

[a] The A and B designations for each carbonyl carbon atom refer to atoms 3 and 5 for the urazole, 4 and 2 for the hydantoin, and 2 and 5 for the succinimide heterocycles.

Table III. ^{13}C Chemical Shifts for the Carbonyl Carbon Atoms Present in Urazoles, Substituted Urazoles, and Other Imides and the Conjugate Bases Derived from These Species in D_2O Solution

	D_2O-phase carbonyl ^{13}C chemical shifts[a,b] (ppm)					
	C(O) in HA		C(O) in A^-		Δ[HA − A^-]	
acid (HA)	A	B	A	B	A	B
urazole (1)	158.9	158.9	161.2	161.2	−2.3	−2.3
1-methylurazole (2)	157.2	156.7	159.9	156.3	−2.7	+0.4
4-methylurazole (3)	158.8	158.8	159.5	159.5	−0.7	−0.7
1,2-dimethylurazole (4)	156.6	156.6	169.9	169.9	−13.3	−13.3
hydantoin (5)	179.5	162.9	192.8	176.6	−13.3	−13.7
1-methylhydantoin (6)	177.7	161.3	191.6	175.2	−13.9	−13.9
1,4-dimethylurazole (7)	157.4	156.9	159.8	155.9	−2.4	+1.0
4-phenylurazole (9)	157.4	157.4	158.8	158.8	−1.4	−1.4
acetamide (13)	180.1	180.1				
succinimide (14)	185.9	185.9	202.3	202.3	−16.4	−16.4
diacetylhydrazine (15)	176.0	176.0	171.9	171.9	+4.1	+4.1
4,4-dimethylpyrazolidine-3,5-dione (16)	179.3	179.3	183.1	183.1	−3.8	−3.8
diacetamide (17)	176.9	176.9				
1,2-dimethyl-4-phenylurazole	155.8	155.8				
1,2,4-trimethylurazole	157.2	157.2				

[a] The A and B designations for each carbonyl carbon atom refer to atoms 3 and 5 for the urazole, 4 and 2 for the hydantoin, and 2 and 5 for the succinimide heterocycles. [b] The data for 1–9 and 14 (as well as the conjugate bases derived from these species) have been published previously[2] and were collected at substrate concentrations of 0.3 M. The balance of the data were collected at substrate concentrations of 0.1 M.

in hydantoin (173.7 and 158.2 ppm) are thus straightforward and agree with previous assignments.[17] Further inspection of the data in Table III indicate that *N*-methyl and *N*-phenyl substituents shield the carbonyl carbon atoms present in urazole by a few (1–3) ppm. These results are consistent with published ^{13}C spectra for urea and its methyl and phenyl derivatives.[17]

It is also important to recognize the regularity in the effects of substituents on urazole ^{13}C carbonyl absorptions. The carbonyl carbon atoms present in urazoles 1–4 and 7–12 (all of which possess at least one acidic NH proton), as well as the tri-N-substituted species 1,2,4-trimethylurazole and 1,2-dimethyl-4-phenylurazole, have ^{13}C absorptions within 6.5 ppm of each other. These data, combined with examinations of DMSO-phase IR spectra collected for all of the urazoles listed in Table II,[18] provide further confirmation for the importance of the dioxo forms for the DMSO-phase urazoles in this study.

Acidity data in Table I suggest that cyclization acidifies imide and hydrazyl protons. NMR data in Table II indicate that cyclization results in the expected deshielding of the carbonyl resonances in diacetylhydrazine and 4,4-dimethylpyrazolidine-3,5-dione (167.8 and 174.7 ppm, respectively) as well as diacetamide and succinimide (171.0 and 179.2 ppm, respectively).[17] Interestingly, the deshielding effects of cyclization on ^{13}C carbonyl resonances in the monoanions derived from diacetylhydrazine and 4,4-dimethylpyrazolidine-3,5-dione (162.9 and 177.2 ppm, respectively) as well as diacetamide and succinimide (178.6 and 194.9 ppm, respectively) are about twice as large as those observed in the neutral acids.

Effects of Deprotonation on ^{13}C Spectra of Imides, Amides, and Diacyl Hydrazides. The main focus of the NMR data presented in Table II is the examination of the relative positions of the ^{13}C carbonyl resonances for various amides, imides, and diacyl hydrazides both before and after deprotonation, in DMSO-d_6 solution. Upon *imide* NH deprotonation, the Δ[HA – A$^-$] data indicate that the carbonyl carbon atoms present in the cyclic imides 1,2-dimethylurazole (4), hydantoin (5), 1-methylhydantoin (6), and succinimide (14) are deshielded by 13–17 ppm. Deprotonation of the acyclic imide diacetamide (17) results in an 8 ppm deshielding of the carbonyl carbons. Upon *amide* deprotonation, Δ[HA – A$^-$] data indicate that the carbonyl carbon atoms present in acetamide (13), acetanilide (18), and benzamide are deshielded by 5, 2, and 3 ppm, respectively.

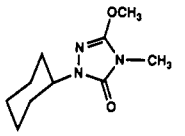
Upon deprotonation, the Δ[HA – A$^-$] data in Table II indicate that the carbonyl carbon atoms present in 4-methylurazole (3), 1,4-dimethylurazole (7), 4-phenylurazole (9), 1,4-diphenylurazole (10), 1-phenyl-4-methylurazole (11), 4-phenyl-1-methylurazole (12), and 4,4-dimethylpyrazolidine-3,5-dione (16), species that possess only *hydrazyl* NH protons, experience shifts ranging from 0.4 ppm upfield to 2.5 ppm downfield. There is a substantial difference in the ^{13}C response of carbonyl carbons to NH deprotonation, depending on the nature of the N–H bond. The carbonyl carbons in diacetylhydrazine, upon deprotonation, experience an upfield shift of about 5 ppm. The fact that deprotonation of amide, imide, and hydrazyl NH protons yields distinctive Δ[HA – A$^-$] values enables critical evaluation of the structures of the anions that result when species that possess both imide and hydrazyl protons are subjected to treatment with an appropriate Brønsted base.

Upon deprotonation, the carbonyl carbons present in urazole (1), 1-methylurazole (2), and 1-phenylurazole (8) (all three possessing both imide and hydrazyl protons) experience downfield shifts of 1–3 ppm. Thus, it is likely that the hydrazyl proton is removed when potassium dimsylate is allowed to react with these species, in DMSO-d_6, at concentrations of 0.1 M, since imide proton removal would likely result in much larger downfield shifts for the carbonyl carbons present in these species. These results confirm our suspicions concerning the relative protonic acidities of the hydrazyl and imide protons in urazole (1), 1-methylurazole (2), and 1-phenylurazole (8), in DMSO solution. Specifically, while the ^{13}C absorptions for the carbonyl carbons present in urazole (1), 1-methylurazole (2), 4-methylurazole (3), 1,4-dimethylurazole (7), and 1,2-dimethylurazole (4) are all within 2.5 ppm of one another, the ^{13}C absorptions for the carbonyls in the anion derived from 1,2-dimethylurazole (4) differ by the anions derived from **1**, **2**, **3**, and **7** by 12.6–14.7 ppm. The data emphasize differences between an imidide anion (such as the 1,2-dimethylurazole anion) and a diacyl hydrazide anion (such as the 1,4-dimethylurazole anion).

D_2O-Phase ^{13}C Spectra of Imides, Amides, and Diacyl Hydrazides. Listed in Table III are the ^{13}C chemical shifts for the carbonyl carbon atoms present in several urazoles, hydantoins, and other imides and diacyl hydrazides, and the conjugate bases of these species as well, in D_2O solution. Inspection of the data in Table III reveals that the ^{13}C D_2O-phase data are remarkably similar to the ^{13}C DMSO-d_6 data presented in Table II. For example: (a) carbonyl absorptions in succinimide are 17 ppm downfield of those in urazole; (b) carbonyl absorptions in urazole are shifted upfield by 1–3 ppm when 1-methyl and 4-phenyl substituents are present; (c) carbonyl absorptions for all of the urazoles are with 3.1 ppm of each other, including the tri-N-substituted species 1,2,4-trimethylurazole and 1,2-dimethyl-4-phenylurazole; (d) cyclization of diacetamide into succinimide results in a 9 ppm deshielding of the carbonyl carbons; (e) upon *imide* NH deprotonation, the D_2O-phase Δ[HA – A$^-$] data indicate that the carbonyl carbon atoms present in the cyclic imides 1,2-dimethylurazole (4), hydantoin (5), 1-methylhydantoin (6), and succinimide (14) are deshielded by 13–16 ppm; (f) upon *hydrazyl* deprotonation, the D_2O-phase Δ[HA – A$^-$] data indicate that the carbonyl carbon atoms present in the cyclic species 4-methylurazole (3), 1,4-dimethylurazole (7), 4-phenylurazole (9), 4-methyl-1-phenylurazole (11), 1-methyl-4-phenylurazole (12), and 4,4-dimethyl-

(17) Values for the ^{13}C chemical shifts for the carbonyl carbons in succinimide, hydantoin, as well as urea and its *N*-methyl and *N*-phenyl derivatives are found in Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley-Interscience: New York, 1980, pp 136–164.

(18) (a) The imidate-like functionality in 1-cyclohexyl-3-methoxy-4-methyl-Δ^2-1,2,4-triazolin-5-one (**22**) has been shown to be responsible for absorption peaks at 1513 and 1605 cm^{-1}.[18b]



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Inspection of the DMSO-phase IR spectra of urazoles 1–4 and 7 indicates no absorptions near 1500 and 1600 cm^{-1}. Inspection of DMSO-phase IR spectra for phenyl-substituted urazoles 8–12 indicates the presence of two peaks in the 1500–1600 cm^{-1} region; these absorptions are assigned to the aromatic C–C stretches of the phenyl moieties, rather than to structural similarities to **22**. Examination of the DMSO-phase IR spectra of urazoles 1–4, 7–12, and 1,2,4-trimethylurazole and 1,2-dimethyl-4-phenylurazole reveals that all possess two C=O stretches at ca. 1710–1730 and 1770–1780 cm^{-1}, in accord with published data (Nujol and CCl_4) for similar species.[6,18b] (b) Pirkle, W. H.; Gravel, P. L. *J. Org. Chem.* **1978**, *43*, 808–814.

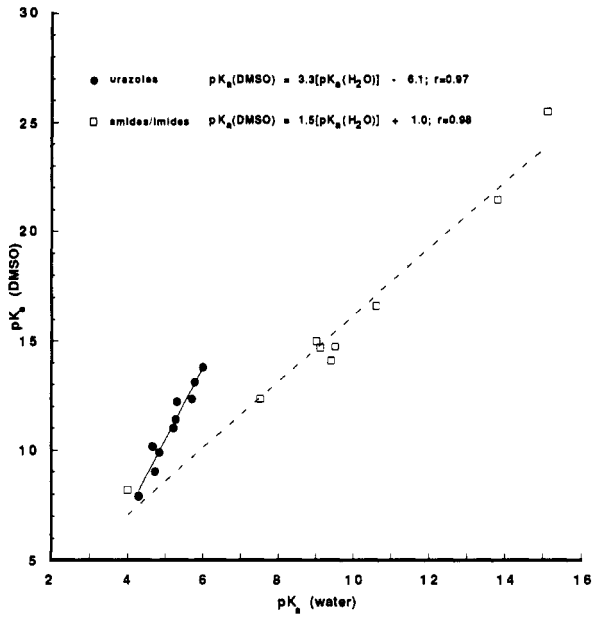


Figure 1. DMSO-phase acidities for urazoles, amides, imides, and related nitrogen acids plotted as a function of aqueous-phase acidities for the same species.

pyrazolidine-3,5-dione (**16**) experience shifts ranging from 1.0 ppm upfield to 3.8 ppm downfield, while the carbonyl carbon atoms present in the acyclic diacetylhydrazine (**15**) are shielded by 4 ppm; and (g) upon deprotonation, the carbonyl carbons present in urazole (**1**) and 1-methylurazole (**2**) (both possessing both imide and hydrazyl protons) experience shifts ranging from 0.4 ppm upfield to 2.7 ppm downfield. Taken as a whole, these data provide support for our observations of the greater aqueous-phase acidities of the hydrazyl proton(s) present in urazole (**1**) and 1-methylurazole (**2**) compared to the imide proton present in these species.

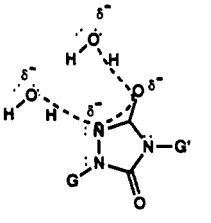
Comparisons of DMSO-d_6 and D_2O ^{13}C NMR Spectra. Comparison of the data in Tables II and III reveals that the carbonyl carbons in **1–20** and their anions are deshielded when dissolved in D_2O, compared to DMSO-d_6. The hydrogen bond donating ability of water is the likely source of these shifts.[19] Further inspection of the data in Tables II and III reveals that (in DMSO-d_6) replacement of the imide proton in urazole (**1**) and 1-methylurazole (**2**) with a methyl group (forming 4-methylurazole (**3**) and 1,4-dimethylurazole (**7**)) results in the shielding of the carbonyl carbons in these species by 0.4–0.8 ppm. In D_2O, 4-methylation of **1** and **2** has little or no effect (0.1 ppm shielding to 0.2 ppm deshielding). While wary of overanalyzing effects of this magnitude, the NMR comparisons are of interest in light of their similarities with the acidity data in DMSO and water. While DMSO data for urazole (**1**, pK_a = 13.1) and 4-methylurazole (**3**, pK_a = 12.3) and 1-methylurazole (**2**, pK_a = 12.2) and 1,4-dimethylurazole (**7**, pK_a = 11.4) suggest that a 4-methyl substituent acidifies the urazole moiety by 0.7–0.8 pK_a units, comparisons of aqueous-phase acidities for the same species (**1** vs **3** and **2** vs **7**) indicate a negligible 4-methyl acidifying effect. The data are similar in that 4-methyl substituents appear to have rather minor effects on the acidity and ^{13}C data in water, compared to DMSO.

Comparisons of DMSO and Aqueous Acidity Data. Shown in Figure 1 are DMSO-phase pK_a's for **1–16** and **17–20** plotted as a function of aqueous-phase pK_a's for the same species. Inspection of the data displayed in Figure 1 reveals that (a) DMSO- and aqueous-phase pK_a's for urazoles **1–3**, **7–12**, and 4,4-dimethylpyrazolidine-3,5-dione (**16**) are linearly related (slope = 3.3, r = 0.97) and (b) 1,2-dimethylurazole (**4**), hydantoin (**5**), 1-methylhydantoin (**6**), succinimide (**14**), and diacetylhydrazine (**15**) data points deviate from the aforementioned urazole line.

Acidity data for acetamide (**13**), acetanilide (**18**), barbituric acid (**19**), and uracil (**20**) are also included in Figure 1. The second line in Figure 1 (slope = 1.5, r = 0.98) represents the linear regression analysis for **4–6**, **13–15**, and **18–20**. The linearity of the data allow an accurate estimate of the aqueous-phase acidity of diacetamide (**17**). **17**, when subjected to aqueous hydroxide, undergoes base-catalyzed hydrolysis,[20] precluding potentiometric determination of its aqueous-phase pK_a. An aqueous-phase pK_a of 11.2 for diacetamide can be estimated from the least-squares line of slope 1.5 in Figure 1, combined with the DMSO pK_a of 18.0 for **17**.[21] The fact that two distinct lines correlate the acidity data in DMSO and aqueous solution for the species listed in Table I is somewhat surprising.

The structural feature common to the species that comprise the line of slope 3.3 is the presence of a base-sensitive proton that is bonded to a cyclic diacylhydrazyl nitrogen atom. Both 1,2-dimethylurazole (**4**) and diacetylhydrazine (**15**) deviate from the solid line in Figure 1: the acidic proton of **4** is of the imide variety, while the hydrazyl proton in **15** is bonded to a nitrogen atom that is not part of a heterocyclic structure. The data therefore strongly suggest that it is the heterocyclic nature of the hydrazyl linkage in the urazoles and 4,4-dimethylpyrazolidine-3,5-dione that is responsible for the unique slope of the solid line in Figure 1.

Published research suggests that differences in hydrogen bonding are among the primary considerations when comparing the effects of DMSO and water on equilibrium acidities.[9,22] The "protic" (i.e., possesses protons bonded to oxygen) nature of water renders it a much better hydrogen bond donating solvent than DMSO, and "aprotic" (or nonhydroxylic) solvent. Acidity data listed in Table I and depicted in Figure 1 indicate that the acidity constants for cyclic diacyl hydrazides possessing acidic diacylhydrazyl protons are 3.3 times as sensitive to substituent effects when dissolved in DMSO, compared to the effects of the identical substituents in water. One explanation for the lack of sensitivity to substituent changes in aqueous solution is that water (via hydrogen bonding) plays a substantial role in stabilizing the conjugate bases derived from **1–3**, **7–12**, and **16** (as depicted in **21** where G and G′ represent H, H_3C–, and/or C_6H_5–). Water-



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solvent molecules may provide an exceptionally large stabilization for the anions derived from **1–3**, **7–12**, and **16** since the magnitude of the destabilizing lone pair–lone

(19) Maciel, G. E.; Ruben, G. C. *J. Am. Chem. Soc.* **1963**, *85*, 3903–3904.

(20) Edward, J. T.; Terry, K. A. *J. Chem. Soc.* **1957**, 3527–3530.
(21) Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809–812.
(22) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

pair electronic interactions present in **21** is potentially much greater in the cyclic diacyl hydrazides, compared to an acyclic diacyl hydrazide such as diacetylhydrazine (**15**). Published research has shown that, while both DMSO and water reduce (via solvation) the destabilizing effects of such lone pair–lone pair interactions, water has a greater ability to "solvate" the neighboring electrons and thus has a greater stabilizing effect, compared to DMSO.[23] The assumption that the difference in the aqueous (pK_a = 5.8) and DMSO (pK_a = 13.1) acidities for urazole (**1**) is primarily a result of the ability of water to better stabilize the urazole monoanion further suggests that substituents will have a *smaller* effect on aqueous-phase urazole monoanion stabilities, since the aqueous solvent molecules are themselves effective contributors to the stabilization of the urazole monoanions. In other words, an aqueous-induced saturation effect of some sort is operational in the urazole anions.

The fact that the DMSO and aqueous-phase acidities for the amides, imides, and (acyclic diacyl hydrazide) diacetylhydrazine (**4–6**, **13–15**, and **18–20**) correlate to the extent that they do (with slope 1.5) in Figure 1 is somewhat surprising. The aforementioned estimates of the aqueous ($pK_a \approx 7.5$) and DMSO ($pK_a \approx 13$) acidities of the imide proton in urazole are substantiated since a data point with these coordinates falls nearly on the amide/imide line of slope 1.5. The observed linearities in the acidity data are indicative of similarities in the differential (DMSO vs H_2O) solvation of the anions derived from these species, relative to the differential solvation of **4–6**, **13–15**, and **18–20**. That such a relationship exists for such disparate species as 1,2-dimethylurazole, acetamide, succinimide, diacetylhydrazine, and barbituric acid is probably fortuitous. Nevertheless, the linearity in Figure 1 indicates similarities in the differential solvent effects for proton transfer reactions in water and DMSO solutions for the species listed in Table I.

Summary

The remarkable acidity of the hydrazyl proton in urazole (**1**) is due to a combination of three factors: (a) the diacylhydrazyl nature of **1**; (b) the heterocyclic nature of **1**; and (c) the fact that the heterocyclic nature of **1** includes an imide nitrogen atom. The effects of substituents on the aqueous-phase acidities of urazole, 1- and 1,4-substituted urazoles, and 4,4-dimethylpyrazolidine-3,5-dione (cyclic species that possess a hydrazyl proton) are attenuated by a factor of 3.3, compared to DMSO solution. The magnitude of the slope of the urazole DMSO/H_2O line is best rationalized by invoking the participation of aqueous solvent molecules in stabilization of the cyclic diacyl hydrazide anion via (a) traditional hydrogen bonding at the electron-rich carbonyl oxygen atoms and (b) interactions with the hydrazyl nitrogen atoms that relieve destabilizing lone pair–lone pair electronic interactions. A linear relationship also exists between DMSO and aqueous-phase acidity constants for 1,2-dimethylurazole, diacetylhydrazine, succinimide, acetamide, and various other imides and amides. The data for these species suggest that changes in acidities for these species are attenuated by a factor of 1.5 in aqueous solution, relative to DMSO solution.

Work is ongoing in our laboratories that has as its goal the attainment of a more complete understanding of the effects of water, DMSO, and other solvent molecules on proton-transfer equilibria that involve neutral organic acids and their respective anionic conjugate bases.

Experimental Section

Materials. Urazole, hydantoin, 1-methylhydantoin, acetamide, succinimide, diacetylhydrazine, diacetamide, and benzamide were obtained from Aldrich Chemical Co. and purified by crystallization. 1-Phenyl-, 4-methyl-, and 1,4-diphenylurazole were gifts from Prof. J. H. Hall.

1-Methylurazole was prepared via modification of a published synthesis of 1-phenylurazole.[24] A mixture of 1-methylhydrazine (2 mL, 40 mmol), biuret (4.12 g, 40 mmol), and amyl alcohol (25 mL) was refluxed for 9 h. The resulting mixture was filtered. The residue was recrystallized from ethanol yielding a white solid: mp 245–246 °C (lit.[25] mp 245–246 °C); ^1H NMR (DMSO-d_6) δ 2.91 (s, 3 H, CH_3), 10.11 (s, 1 H, 2-NH), 10.90 (s, 1 H, 4-NH).

1,2-Dimethylurazole was prepared in a fashion similar to that described for 1-methylurazole except that 1,2-dimethylhydrazine was substituted for 1-methylhydrazine. Recrystallization from ethyl acetate gave a white solid: mp 171–172 °C (lit.[26] mp 169–171 °C); ^1H NMR ($CDCl_3$) δ 3.15 (s, 3 H, CH_3), 8.38 (s, 1 H, NH).

1,4-Dimethylurazole was synthesized as described by Zinner and Gebhard.[25] Methylhydrazine (7.85 mL, 0.15 mol) and diethyl carbonate (18.15 mL, 0.15 mol) were mixed, and the solution was refluxed for 24 h. The mixture was distilled in vacuo, and the fraction boiling at 50–53 °C (at 200 mTorr) was collected (lit.[25] bp 84–86 °C at 12 mTorr) and identified as 1-methyl-1-carbethoxyhydrazine (2.8 g, semisolid): ^1H NMR ($CDCl_3$) δ 6.3 (s, 1 H, NH), 3.9 (s, 1 H, NH), 4.15 (q, 2 H, CH_2), 2.6 (d, 3 H, CH_3NH), 1.35 (t, 3 H, CH_3).

To a solution of 1-methyl-1-carbethoxyhydrazine (2 g, 18 mmol) in dry benzene (20 mL) was added methyl isocyanate (1.4 mL, 33 mmol) dropwise with stirring. After being refluxed for 30 min, the mixture was cooled to room temperature and filtered. The white residue, 1-carbethoxy-2,4-dimethylsemicarbazide, was recrystallized from benzene: mp 156–157 °C (lit.[25] mp 156–157 °C); ^1H NMR ($CDCl_3$) δ 6.35 (s, 1 H, H-1), 5.26 (s, 1 H, H-4), 4.2 (q, 2 H, CH_2), 3.5 (s, 3 H, CH_3N), 2.8 (d, 3 H, CH_3NH), 1.28 (t, 3 H, CH_3).

1-Carbethoxy-2,4-dimethylsemicarbazide (1.5 g, 10 mmol) in KOH_{aq} (10 mL, 4 N) was then heated on a steam bath for 20 min. The resulting solution was cooled to room temperature and acidified with concentrated HCl. The solution was concentrated to dryness and extracted with absolute ethanol. Evaporation of ethanol yielded an off-white solid. Recrystallization from ethyl acetate gave the fine white solid 1,4-dimethylurazole: mp 122.5–123.5 °C (lit.[25] mp 124–125 °C); ^1H NMR ($CDCl_3$) δ 3.10 (s, 3 H, 1-CH_3), 3.20 (s, 3 H, 4-CH_3), 8.25 (s, 1 H, NH).

4-Phenylurazole was prepared exactly as described in ref 27a. The 4-arylurazoles (i.e., **4-(4-methoxyphenyl)urazole**; **4-(4-methylphenyl)urazole**; **4-(3-chlorophenyl)urazole**; **and 4-(4-chlorophenyl)urazole**) were synthesized as follows. In general, the 4-aryl-1-carbomethoxysemicarbazides were prepared by first dissolving methyl hydrazinocarboxylate (50–100 mmol) in anhydrous benzene (200mL). A solution of substituted phenyl isocyanate was then added over a period of 10 min. After stirring for ca. 20 min, a precipitate formed and was filtered. In all cases, the semicarbazides were pure as indicated by their melting points and no further crystallization was necessary for the next step. The substituents, yield, melting point, ^1H NMR and IR are as follows: (a) ***p*-methoxy**, white solid, (83%) mp 179–181 °C; ^1H NMR (DMSO-d_6) δ 3.60 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, OCH_3), 6.83–7.35 (m, 4 H, aryl protons); IR (KBr) 1635 (C=O), 1720 (C=O), 3280 (NH), 830 cm^{-1} (Bz); (b) ***p*-chloro**, white solid, (90%); mp 209–211 °C; ^1H NMR (DMSO-d_6) δ 3.60 (s, 3 H, CH_3), 7.3–7.5 (m, 4 H, aryl protons), 8.1 (s, 1 H, NH), 8.9 (s, 1 H, NH), 9.0 (s, 1 H, NH); IR(KBr) 3314 (NH), 1712, 1702 cm^{-1} (C=O); (c) ***m*-chloro**, white

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solid, (83%); mp 154–155 °C; ^{1}H NMR (DMSO-d_6) δ 3.6 (sl, 3 H, CH_3), 8.20 (s, 1 H, NH), 8.95 (s, 1 H, NH), 9.0 (s, 1 H, NH), 6.98–7.45 (m, 4 H, aryl protons); (d) ***p*-methyl**, white solid, (98%), ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3 H, CH_3), 3.6 (s, 3 H, OCH_3), 7.03 (d, 2 H, ortho-H), 7.32 (d, 2 H, m-H).

The 4-arylurazoles were then synthesized by heating (on a steam bath with occasional shaking) a suspension of the appropriate semicarbazide (50 mmol) in ca. 25 mL of 4 M KOH (100 mmol) for 45 min. The hot solution was filtered, cooled to room temperature, and acidified with concentrated HCl. The precipitated solid was filtered and washed thoroughly with water. Recrystallization from water gave the urazoles. The yield, melting point, and ^{1}H NMR data are as follows: (a) ***p*-methoxy**, white solid mp 219–220 °C (lit.[27b] mp 219.5–220.5 °C); ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3 H, OCH_3), 7.00–7.35 (m, 4 H, aryl protons), 10.32 (s, 2 H, NH); (b) ***p*-chloro**, white solid, (72%); mp 233.5–234 °C (lit.[27c] mp 246 °C); ^{1}H NMR (DMSO-d_6) δ 7.20 (m, 4 H, aryl protons), 10.52 (s, 2 H, NH); (c) ***m*-chloro**, white solid, (71%); mp 185–186.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.4–7.6 (m, 4 H, aryl protons), 10.6 (s, 2 H, NH); (d) ***p*-methyl**, off white, (60%); mp 249–251 °C (lit.[27c] mp 243–244 °C); ^{1}H NMR (DMSO-d_6) δ 4.0, (s, 3 H, CH_3), 7.3 (m, 4 H, aryl protons).

1-Phenyl-4-methylurazole was prepared via an adaptation of the published preparation of 4-phenylurazole.[27a] To a cold solution of phenylhydrazine (4.9 mL, 50 mmol) and pyridine (4.0 mL, 50 mmol) in CH_2Cl_2 (30 mL) was added ethyl chloroformate over a period of 15 min. The initial addition of the ethyl chloroformate resulted in the formation of precipitate; the mixture thickened when half of the ethyl chloroformate was added. Upon completion of the addition of ethyl chloroformate, the mixture was stirred for an additional 30 min at 0–5 °C. About 100 mL of distilled water was added to dissolve the pyridine hydrochloride. The two layers were separated. The CH_2Cl_2 layer was washed with 100 mL water, followed by dilute H_2SO_4 and then water. The solution was dried over $MgSO_4$, and the solvent was evaporated. Recrystallization of the solid formed from hexane afforded 5.44 g (60%) of the white solid 2-phenylhydrazinecarboxylic acid ethyl ester, mp 79.5–81 °C (lit.[28] mp 71–75 °C): ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3 H, CH_3), 4.05 (q, 2 H, CH_2), 6.65–7.15 (m, 5 H, C_6H_5), 7.60 (s, 1 H, 1-NH), 9.0 (s, 1 H, 2-NH).

Methyl isocyanate (0.78 mL, 12 mmol) was then added dropwise to a solution of 2-phenylhydrazinecarboxylic acid ethyl ester (2 g, 12 mmol) in dry benzene. The resulting solution was refluxed for 4 h. The solvent was evaporated and gave 2.5 g of the white solid 1-carbethoxy-2-phenyl-4-methylsemicarbazide, mp 128–130 °C (93%).

A solution of 1-carbethoxy 2-phenyl-4-methylsemicarbazide (1.5 g, 7 mmol) in KOH (5.25 mL, 4 N) was heated on a steam bath for 30 min. The yellow solution was diluted with 20 mL of water, cooled to room temperature, and acidified with concd HCl. A white solid was formed. It was filtered and washed well with water. Recrystallization from ethanol gave white crystals of 1-phenyl-4-methylurazole: mp 223–225 °C (lit.[28] mp 223 °C); ^{1}H NMR ($CDCl_3$) δ 3.20 (s, 3 H, CH_3), 7.30–7.60 (m, 5 H, C_6H_5).

1-Methyl-4-phenylurazole was prepared in a fashion similar to that described for 1-phenyl-4-methylurazole, except that methylhydrazine was substituted for phenylhydrazine, and phenyl isocyanate was substituted for methyl isocyanate. The 1-methyl-4-phenylurazole obtained via this route was recrystallized from water, mp 188–189 °C (lit.[25] mp 188–189 °C).

4,4-Dimethylpyrazolidine-3,5-dione was prepared by allowing a sodium ethoxide/ethanol solution to react with a mixture of diethyl dimethylmalonate (1.88 g, 0.01 mol) and anhydrous hydrazine (0.32 g, 0.01 mol) under an argon atmosphere. The resulting mixture was heated on a oil bath at 140–160 °C to distill off the alcohol. The remaining solution was refluxed for 0.5 h and then evaporated via rotary evaporation, yielding a white residue. The residue was dissolved in ca. 10 mL of water, extracted with ether, separated with the aid of a separatory funnel, and acidified with 20% hydrochloric acid. Concentration of the acidic solution produced the white solid product 4,4-dimethylpyrazolidine-3,5-dione. The dione was recrystallized from absolute alcohol, mp 257 °C (lit.[29] mp 256–260 °C): ^{1}H NMR (DMSO-d_6) δ 1.4 (s, 6 H, CH_3), 10.5 (s, 2 H, NH).

1,2-Dimethyl-4-phenylurazole was prepared by allowing potassium dimsylate (2.2 equiv) to react with a DMSO solution of methyl iodide (1 equiv). White crystals were obtained in 75% yield, mp 243–245 °C (authentic sample from Prof. J. H. Hall melted at 242 °C).

1,2,4-Trimethylurazole was prepared by allowing 1,4-dimethylurazole (1 g, 8 mmol) to react with 1 equiv of aqueous solution of KOH. Water was evaporated, and the product (the potassium salt of 1,4-dimethylurazole) was dried in a vacuum dessicator.

The potassium salt of 1,4-dimethylurazole (0.66 g, 4 mmol) was dissolved in 50 mL of absolute ethanol. Methyl iodide (1.13 g, 8 mmol) was added in portions with stirring. After 48 h of stirring the solvent was evaporated and white residue was extracted with boiling petroleum ether. Yellow crystals (ca. 50 mg) were obtained after evaporation of petroleum ether. This product was recrystallized from petroleum ether to give 30 mg of white crystals; mp 59–61 °C (lit.[30] 64–66 °C).

Dimethyl sulfoxide was purified, and potassium dimsylate was synthesized, exactly as described by Matthews and Bordwell.[31]

DMSO-Phase Equilibrium Acidity Determinations. Acquisition of the DMSO-phase acidity data listed in Table I was facilitated by the use of an overlapping indicator method identical with that described previously.[31] DMSO acidity data obtained in this way are typically accurate to ≤0.1 pK_a unit.[31] Facts regarding indicators, number of "runs" (each run consists of several titration points), and the pK_a's obtained for each indicator for all of the acids in Table I have been published previously, except for **4-(4-methoxyphenyl)urazole** (indicator 1, 9-(phenylsulfonyl)fluorene (pK_{HIn} = 11.5$_5$), 3 runs, pK_a = 11.4; indicator 2, 9-(methoxycarbonyl)fluorene (pK_{HIn} = 10.3$_5$), 5 runs, pK_a = 11.4), **4-(4-methylphenyl)urazole** (indicator 1, 9-(phenylsulfonyl)fluorene, 3 runs, pK_a = 11.3; indicator 2, 9-(methoxycarbonyl)fluorene, 2 runs, pK_a = 11.3); **4-(3-chlorophenyl)-urazole** (indicator 1, 9-(phenylsulfonyl)fluorene, 2 runs, pK_a = 10.4; indicator 2, 9-(methoxycarbonyl)fluorene, 3 runs, pK_a = 10.4), **4-(4-chlorophenyl)urazole** (indicator 1, 9-(phenylsulfonyl)-fluorene, 3 runs, pK_a = 10.6; indicator 2, 9-(methoxycarbonyl)-fluorene, 2 runs, pK_a = 10.5); **diacetylhydrazine** (indicator 1, 9-(phenylthio)fluorene (pK_{HIn} = 15.4), 3 runs, pK_a = 16.6; indicator 2, 9-phenylfluorene (pK_{HIn} = 17.9), 3 runs, pK_a = 16.7), and **4,4-dimethylpyrazolidine-3,5-dione** (indicator 1, 9-fluorenone, (4-chlorophenyl)hydrazone (pK_{HIn} = 14.1$_5$), 1 run, pK_a = 13.50; indicator 2, 9-fluorenone, (2,4-dichlorophenyl)hydrazone (pK_{HIn} = 11.98), 2 runs, pK_a = 13.4). All of the urazoles were well-behaved in that the internal agreements within a run (σ) were typically less than 0.05 pK_a units; the σ values for diacetylhydrazine and 4,4-dimethylpyrazolidine-3,5-dione were about 0.1 pK_a unit.

Aqueous-Phase Equilibrium Acidity Determinations. A Fisher Model 930 pH meter was standardized using a two-point (pH 7 and pH 10) buffer system. The acids were titrated against aqueous KOH (0.1 N). The pK_a data were obtained via the method described in ref 32. At least two trials were performed for each acid, and the initial nitrogen acid concentrations were 0.1 M. The standard deviations for the collected pK_a's within a given run were generally ≤0.06. We estimate that the pK_a's listed in Table II are accurate to ±0.1 pK_a unit. The Debye–Hückel correction to zero ionic strength was not applied to these data.

NMR Data. A Varian VXR-300 MHz spectrometer was used to collect the NMR data listed in Tables II and III. The DMSO-phase neutral acids were present in concentrations of 0.1 M; TMS was used as an internal standard. The DMSO-phase conjugate bases of the various nitrogen acids were generated by allowing, in the NMR tube, the respective acids to react with

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$K^+H_2CS(O)CH_3$ (1 equiv, 0.1–0.2 M in DMSO). The D_2O-phase neutral species were present in concentrations of 0.3 M (or 0.1 M as indicated); DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt), an NMR reference, was present in concentrations of 0.05 M. Total NMR tube solution volumes were about 0.7 mL. The conjugate bases of the various nitrogen acids were generated by allowing, in the NMR tube, the respective acids to react with aqueous KOH (1 equiv, 2.5 M). All spectra were collected at 25 ± 1 °C.

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Registry No. 1, 3232-84-6; 1 anion, 133476-04-7; 2, 34771-28-3; 2 anion, 133476-05-8; 3, 16312-79-1; 3 anion, 133476-06-9; 4, 5302-26-1; 4 anion, 133476-08-1; 5, 461-72-3; 5 anion, 133476-09-2; 6, 616-04-6; 6 anion, 133476-10-5; 7, 34771-26-1; 7 anion, 133476-07-0; 8, 6942-46-7; 8 anion, 135257-88-4; 9, 15988-11-1; 9 anion, 135257-89-5; 10, 34874-03-8; 10 anion, 135257-90-8; 11, 14500-23-3; 11 anion, 135283-77-1; 12, 28538-67-2; 12 anion, 135283-78-2; 13, 60-35-5; 13 anion, 31108-39-1; 14, 123-56-8; 14 anion, 28627-67-0; 15, 3148-73-0; 15 anion, 135257-91-9; 16, 29005-43-4; 16 anion, 135257-92-0; 17, 625-77-4; 17 anion, 93588-74-0; 18, 103-84-4; 1-methylhydrazine, 60-34-4; biuret, 108-19-0; 1,2-dimethylhydrazine, 540-73-8; diethyl carbonate, 105-58-8; 1-methyl-1-carbethoxyhydrazine, 760-81-6; methyl isocyanate, 624-83-9; 1-carbethoxy-2,4-dimethylsemicarbazine, 34771-20-5; 4-(4-methoxyphenyl)urazole, 13274-46-9; 4-(4-methylphenyl)urazole, 79491-05-7; 4-(3-chlorophenyl)urazole, 52039-91-5; methyl hydrazinecarboxylate, 6294-89-9; *p*-methoxyphenyl isocyanate, 5416-93-3; *p*-chlorophenyl isocyanate, 104-12-1; *m*-chlorophenyl isocyanate, 2909-38-8; *p*-methylphenyl isocyanate, 622-58-2; 4-(4-methoxyphenyl)semicarbazide, 62774-59-8; 4-(4-chlorophenyl)semicarbazide, 69194-89-4; 4-(3-chlorophenyl)semicarbazide, 51707-42-7; 4-(4-methylphenyl)semicarbazode, 62774-57-6; phenylhydrazine, 100-63-0; ethyl chloroformate, 541-41-3; 1-carbethoxy-2-phenylhydrazine, 6233-02-9; 1-carbethoxy-4-methyl-2-phenylsemicarbazide, 64739-43-1; diethyl dimethylmalonate, 1619-62-1; hydrazine, 302-01-2; barbituric acid, 67-52-7; uracil, 66-22-8; 4-(4-chlorophenyl)urazole, 52039-87-9.

Stability and Chemical Properties of Thiiranimine

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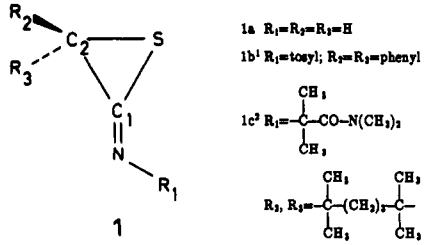
The stabilty and the molecular properties of thiiranimine are studied by using ab initio MO methods. Geometries are optimized at the HF/6-31G* and MP2/6-31G** levels while relative energies are estimated at the MP4/6-31G** level together with the zero-point energies. Our analysis points out that the interaction between the C=N moiety and the three-membered ring is responsible for several unusual properties of thiiranimine such as the high C=N stretching frequency, the relatively small ring strain (as compared with thiirane), and the large proton affinity at nitrogen. Our calculations also suggest that the first photoelectron band is due to an S ionization and that the first UV band arises essentially from an intraatomic sulfur transition. The fragmentation reaction is endothermic, but consideration of entropy terms modifies the picture significantly. The resulting free energies show that thiiranimine is quite stable towards fragmentation into hydrogen isocyanide plus thioformaldehyde in agreement with experiments on substituted thiiranimines. Finally, the regiochemistry of thiiranimine in cycloadditions is also discussed on the basis of the frontier orbitals.

Introduction

For 12 years now, thiiranimines (1), featuring three-membered rings with an exocyclic imine function, have been known as stable compounds.[1] The experimental geometry of some substituted forms (1b,[1] 1c[2]) has been determined. In all cases the substituent R_1 on the nitrogen



1

1a $R_1=R_2=R_3=H$

1b[1] R_1=tosyl; $R_2=R_3$=phenyl

1c[2] R_1=$-\overset{CH_3}{\underset{CH_3}{C}}-CO-N(CH_3)_2$

R_2, R_3=$-\overset{CH_3}{\underset{CH_3}{C}}-(CH_2)_2-\overset{CH_3}{\underset{CH_3}{C}}-$

atom is in a cis position with respect to the sulfur atom. As shown in a previous paper,[3] also the unsubstituted thiiranimine 1a has been calculated with a small but definite cis preference. Other remarkable features of the geometry, such as the long C_2S bond and small bond angle at the sulfur atom, are well reproduced by ab initio Hartree–Fock calculations.[3] On the whole, the theoretical structure of 1a more closely resembles 1c than 1b. This was attributed to the more perturbing nature of the tosyl group on the imine function in 1b in comparison with the alkyl substitutent in 1c.

In the previous paper the emphasis was mainly on the electronic structure and charge distribution in the prototype thiiranimine 1a. In the present paper certain spectroscopic properties relevant to the vibrational and electronic spectra and several aspects of the thermochemical stability will be discussed in more detail. Finally, we will also consider the protonation as a model for electrophilic attack as well as the fragmentation of 1a to isocyanide and thioformaldehyde. This latter reaction has been experi-

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