Strain Effects in Protonated Carbonyl Compounds. An Experimental and ab Initio Treatment of Acyclic Carboxamides and Ketones

H. Homan,[†] M. Herreros,[†] R. Notario,[†] J.-L. M. Abboud,[†,*] M. Esseffar,[‡] O. Mó,[‡] M. Yáñez,[‡,*] C. Foces-Foces,[†] A. Ramos-Gallardo,[†] M. Martínez-Ripoll,[†] A. Vegas,[†] M. T. Molina,[§] J. Casanovas,[∥] P. Jiménez,[†] M. V. Roux,[†] and C. Turrión[†]

Instituto de Química Física " Rocasolano", C. S. I. C. c/ Serrano, 119, E-28006 Madrid, Spain, Departamento de Química, C-9, Universidad Autónoma de Madrid. Cantoblanco, E-28049 Madrid, Spain, Instituto de Química Médica, C. S. I. C. c/ Juan de la Cierva, 3, E-28006, Madrid, Spain, Departament de Química Física, Universitat de Barcelona, Martí i Franquès, 1. E-08028 Barcelona, Catalonia, Spain

Received July 21, 1997[⊗]

Strain effects have been quantitatively evaluated for a set of 22 compounds including ketones (R_2-CO), carboxamides ($RCONH_2$), and *N*,*N*-dimethylcarboxamides ($RCONMe_2$), where R = Me, Et, *i*-Pr, *t*-Bu, 1-adamantyl (1-Ad), in their neutral and protonated forms. To this end, use was made of the gas-phase proton affinities and standard enthalpies of formation of these compounds in the gas phase, as determined by Fourier transform ion cyclotron resonance mass spectrometry (FT ICR) and thermochemical techniques, respectively. The structures of 1-AdCOMe and $(1\text{-Ad})_2CO$ were determined by X-ray crystallography. Quantum-mechanical calculations, at levels ranging from AM1 to MP2/6-311+G(d,p)//6-31G(d), were performed on the various neutral and protonated species. Constrained space orbital variation (CSOV) calculations were carried out on selected protonated species to further assess the contributions of the various stabilizing factors. Taking neutral and protonated methyl ketones as references, we constructed isodesmic reactions that provided, seemingly for the first time, quantitative measures of strain in the protonated species. A combination of these data with the results of theoretical calculations (which also included several "computational experiments") lead to a unified, conceptually satisfactory, quantitative description of these effects and their physical link to structural properties of the neutral and protonated species.

Introduction

The chemistry of the carbonyl group plays an essential role in organic synthesis, as a pivotal functional group useful in a number of transformations.[1] Furthermore, the amide group[2] is the essential structural unit of peptides and proteins,[3] and the knowledge of its structural and thermodynamic properties[4] is necessary, not only in order to reach a better knowledge of these biological materials but, also, for the purpose of designing peptidomimetics[5] (structural features of peptides are determinant as regards their functional role[6] and enzyme catalysis[7]).

Very recently, two studies have appeared on the strain and structures of the β-lactam ring[8] and of small- and medium-sized bridgehead bicyclic lactams,[9] both neutral and protonated**.** However, to our knowledge, *the systematic, quantitative determination of strain effects in protonated acyclic ketones and carboxamides has never been carried out*. This has been done in this work, and, as we shall discuss below, this study also sheds light on important features of the neutral species.

Let us consider, for example, reactions 1 and 2:

$$2\ CH_3COR\ (g) \rightarrow CH_3COCH_3\ (g) + RCOR\ (g) \quad (1)$$

$$2\ (CH_3C(OH)R)^+\ (g) \rightarrow (CH_3C(OH)CH_3)^+\ (g) + (RC(OH)R)^+\ (g) \quad (2)$$

Their corresponding standard enthalpy changes, namely $\Delta H°_1$ and $\Delta H°_2$ can be taken as quantitative measures of differential strain[10] in neutral and protonated ketones, respectively. They are linked through eq 3:

[†] Instituto de Química Física "Rocasolano".
[‡] Universidad Autónoma de Madrid.
[§] Instituto de Química Médica.
[∥] Universitat de Barcelona.
[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) For standard reference texts, see, e.g., (a) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986. (b) House, H. O. *Modern Synthetic Methods*, 2nd ed.; Benjamin Cummins: Menlo Park, 1972. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley: New York, 1992.

(2) Comprehensive reviews on the structure and reactivity of ketones and carboxamides are given in the series *The Chemistry of Functional Groups*. For full details, see, e.g.: Patai, S., *Patai's 1992 Guide to the Chemistry of Functional Groups*. John Wiley: Chichester, 1992.

(3) See, e.g., Perutz, M. F. In *The Chemical Bond, Structure and Dynamics*; Zewail, A. H., Ed., Academic Press: New York, 1992.

(4) See, e. g., Greenberg, A. In *Structure and Reactivity*; Liebman, J. F., Greenberg, A., Eds.; Vol. 7, Molecular Structure and Energetics; VCH Publishers: New York, 1988; pp 139−178.

(5) For recent references: (a) Goodman, M.; Ro, S. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th Ed.; Wolff, M. E., Ed., John Wiley: New York, 1995; Vol.1, p 803. (b) Kahn, M., Ed. *Tetrahedron Symposia-in-Print* no. 30: Peptide Secodary Structure Mimetics. *Tetrahedron* **1993**, *49*, 3433−3681.

(6) (a) The analysis of the conformational parameters enables the design of peptide mimics and new scaffolds (nonpeptide mimics). Marshall, G. R.; *Tetrahedron* **1993**, *49*, 3547−3558. (b) For a classical study, see, e.g., Ramachandran, N.; Sasisekaran, V. *Adv. Protein Chem.* **1968**, *23*, 283−437).

(7) Page, M. I. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Eds.; Pergamon Press: Oxford, 1990, vol. 2, p 45.

(8) Roux, M. V.; Jiménez, P.; Dávalos, J. Z.; Castaño, O.; Molina, M. T.; Notario, R.; Herreros, M.; Abboud, J.-L. M. *J. Am. Chem. Soc.*,**1996**, *118*, 12735−12738.

(9) Greenberg, A.; Moore, D. T.; DuBois, T. D., *J. Am. Chem. Soc.* **1996**, *118*, 8658−8668.

(10) This definition of strain is related but not identical with that of Brown's I-strain: Brown, H. C.; Gerstein, M., *J. Am. Chem. Soc.* **1950,** *72*, 2926−2933.

S0022-3263(97)01330-3 CCC: $14.00

$$\Delta H°_2 = \Delta H°_1 + [\,2\ \mathrm{PA\ (RCOMe)} - \mathrm{PA\ (R_2CO)} - \mathrm{PA\ (Me_2CO)}] \quad (3)$$

wherein the PAs are the experimental proton affinities (equal to $-\Delta H°_{H^+}$ (g), reaction 4) for each of the various neutral species involved:[11]

$$B(g) + H^+(g) \rightarrow BH^+\ (g) \quad (4)$$

In turn, $\Delta H°_1$ can be expressed in terms of their standard enthalpies of formation in the gas phase, $\Delta_f H°_m$ (g), eq 5:

$$\Delta H°_1 = \Delta_f H°_m\ (R_2CO, g) + \Delta_f H°_m\ (Me_2CO, g) - 2\ \Delta_f H°_m\ (RCOMe, g) \quad (5)$$

These equations lead to differential strain effects referred to neutral and protonated methyl ketones. Obviously, this thermodynamic information can be dissected within the framework of various important models currently available.[12] In this work, the term *strain* is taken in the broad, generic sense of Sandström and Wiberg.[12g]

Here, we have examined the cases R = Me, Et, *i*-Pr, *t*-Bu and 1-Ad (1-adamantyl, 1-$C_{10}H_{15}$). This series spans a wide range of sizes[13] and polarizabilities,[14] while field and resonance contributions[14] remain nearly constant. At variance with this, resonance in both the neutral and the protonated forms of carboxamides can be affected by strain.[15]

In what follows, we first present our experimental results, including structural, thermodynamic, and gas-phase reactivity data for the three series of carbonyl compounds. The structures of 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl ethanone (methyl adamantyl ketone, 1-AdCOMe) and bis(tricyclo[3.3.1.1^{3,7}]dec-1-yl) methanone or bis(1-adamantyl) ketone, ((1-Ad)$_2$CO) were determined by X-ray diffraction methods. Standard enthalpies of formation for these and other relevant compounds also originate in part in these laboratories.[16] A number of gas-phase basicities, GB (for a base B, GB(B) = $-\Delta G_{H^+}$(g), reaction 4) for selected ketones, unsubstituted and *N*,*N*-dimethyl carboxamides were determined for the first time by means of Fourier transform ion cyclotron resonance mass spectrometry (FT ICR).[17] A substantial part of the discussion rests on the analysis of the experimental results by means of quantum mechanical techniques, particularly ab initio calculations. The experimental thermodynamic data for neutral and protonated species are used later on to compute strain energies through appropriate isodesmic reactions. The results of the quantum mechanical calculations at different levels of accuracy are presented next. A unified discussion of the results ends the study.

Experimental Section

All compounds used in this work are known. Samples are from the same batches as those used in previous calorimetric[16a−c] and intrinsic reactivity studies.[18a]

Crystal Data for 1-AdCOMe. A colorless prism (0.10 × 0.23 × 0.67 mm), sealed into a Lindeman capillary to prevent the sublimation of the sample, was used for X-ray analysis. The crystal was cooled to 220 K by means of an Oxford Cryostream Cooler apparatus, and data were collected on a Philips PW1100 diffractometer. Data: a = 9.0708(7), b = 6.6897(4), c = 8.2363(5) Å ; β = 98.990(5)°, $P2_1/m$, Z = 2. Cell constants are from a least-squares fit using 69 reflections up to θ = 45° and Cu Kα radiation. The structure was solved by direct methods (SIR92)[19] and refined by least-squares procedures on F_{obs}, $R(R_w)$ = 0.049 (0.062) for 798 observed reflections (917 independent reflections up to θ = 65°). The scattering factors were taken from the International Tables of X-ray Crystallography.[20]

Crystal data for (1-Ad)$_2$CO are as follows: a = 20.819(2), b = 6.749(1), c = 11.694(1) Å, D_c = 1.20 g·cm^{-3}, $Pnma$, Z = 4. 1764 reflections were measured at room temperature on a Seifert XRD-3000S four-circle diffractometer with graphite-monochromated Cu Kα (1.5418 Å) radiation in the $\omega/2\theta$ scan mode (2° < θ < 50°), scan width: 1.50, leading to 923 unique reflections. 568 of them, with $I > 2\sigma(I)$ were considered as observed and used for structure solution and refinement. An empirical absorption correction was applied (maximum and minimum absorption corrections were 1.352 and 0.849, respectively). Structure was solved by direct methods (MULTAN 80)[21] allowing the location of all atoms other than hydrogen. The latter were fixed at the calculated positions. A total of 115 variables were refined by least-squares procedures, leading to $R(R_w)$ = 0.057. In all cases, calculations were carried out

(11) (a) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695−808. (b) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. No. 1.

(12) See, e.g., (a) Ibrahim, M. R. *J. Phys. Org. Chem.* **1990**, *3*, 443−448. (b) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377−2386. (c) Engler, E. M.Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005−8025. (d) DeTar, Del F. *J. Org. Chem.* **1992**, *57*, 902−910 and references therein. (e) Dubois, J.-E.; Herzog, H. *J. Chem. Soc.* **1972**, 932−933. (f) Sellers, P. *J. Chem. Thermodyn.* **1970**, *2*, 211−219. (g) "The concept of strain in organic chemistry is based on the experimentally and theoretically well-founded structure theory, according to which bond lengths, bond angles, dihedral angles involving four atoms joined by three bonds in sequence, and distances between nonbonded atoms, have optimal values, which are determined by the atoms involved and their connectivity. A molecule in which these parameters can attain their optimal values is free from strain. In many molecules, restrictions due to space requiring substituents or cyclic structures prevent one or more of the ideal parameter values being attained. The molecule is subject to strain, *and its energy is increased accordingly*". Sandström, J. In *The Chemistry of Functional Groups, Supplement A3, Part 2*; Patai, S., Ed., John Wiley: Chichester, 1997, Ch. 21 and references therein.

(13) Gallo, R. *Prog. Phys. Org. Chem.* **1983**, *14*, 75−163.

(14) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1−80.

(15) (a) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644−8654. (b) Wiberg, K. B.; Rablen, P. R.; Marquez, M. *J. Am. Chem. Soc.* **1992**, *114*, 8654−8668.

(16) (a) Abboud, J.-L. M.; Jiménez, P.; Liebman, J. F.; López-Mardomingo, C.; Podosenin, A.; Rogers, D. W.; Roux, M. V.; Turrión, C. *J. Phys. Org. Chem.* **1995**, *8*, 15−25. (b) Abboud, J.-L. M.; Jiménez, P.; Roux, M. V.; Turrión, C. *J. Chem. Thermodyn.* **1989,** *21*, 859−864. (c) Abboud, J.-L. M.; Jiménez, P.; Roux, M. V.; Turrión, C., Sanz, G. *J. Chem. Thermodyn.* **1992**, *24*, 217−223. (d) *Ibid.* pp 1299−1304. (e) Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd ed.; Chapman and Hall: London and New York, 1986.

(17) (a) *Gas-Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vols. 1 and 2, 1984; Vol. 3. (b) Lehman, A. T.; Bursey, M. M. *Ion Cyclotron Resonance Spectrometry*; John Wiley: New York, 1976. (c) *Fourier Transform Mass Spectrometry, Evolution, Innovation and Application*; Buchanan, M. V., Ed.; ACS Symposium Series 359; American Chemical Society: Washington, DC, 1987; (d) *FT ICR/MS: Analytical Applications of Fourier Transform Ion Cyclotron Resonance Mass Spectrometry*; Asamoto, B., Ed.; VCH: Weinheim, 1991. (e) *Fourier Transforms in NMR, Optical and Mass Spectrometry*; Marshall, A. G., Verdun, F. R., Eds.; Elsevier: Amsterdam, 1990.

(18) (a) Abboud, J.-L. M.; Mó, O.; de Paz, J. L. G.; Yáñez, M.; Essefar, M.; Bouab, W., El-Mouhtadi, M.; Mokhlisse, R.; Ballesteros, E.; Herreros, M.; Homan, H.; López-Mardomingo, C.; Notario, R. *J. Am. Chem. Soc.* **1993**, *115*, 12468−12476. (b) Abboud, J.-L. M.; Herreros, M.; Notario, R.; Esseffar, M.; Mó, O.; Yáñez, M. *J. Am. Chem. Soc.*, **1996**, *118*, 1126−1130.

(19) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Polidori, G., SIR92. *J. Appl. Crystallogr.* **1994**, *27*, 435.

(20) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, UK, 1974

(21) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN 80. Physics Department, Universities of York, England and Louvain, Belgium, 1980.

with the XRAY,[22] PESOS,[23] and PARST[24] sets of programs running on a VAX 6410 computer.

The final atomic coordinates and equivalent thermal factors for non-hydrogen atoms for 1-AdCOMe and $(1\text{-Ad})_2CO$ are available from the authors upon request.

Gas-phase basicities (GB) were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 FTICR mass spectrometer[25] used in previous studies.[18] The average cell temperature is ca. 333 K. Working pressures were generally in the range 3×10^{-7} to 3×10^{-6} mbar. Pressure readings provided by a Bayard−Alpert gauge were calibrated against an MKS capacitance manometer. These FTICR experiments provide the standard Gibbs energy change, $\delta\Delta G_{H^+}$ (g) for the proton-transfer reaction 6:

$$BH^+(g) + B_{ref}(g) \rightleftarrows B(g) + B_{ref}H^+(g) \qquad K_p, \delta\Delta G_{H^+}(g) \quad (6)$$

The reversibility of reaction 6 was systematically confirmed by means of double resonance experiments.

GB values are obtained by combining $\delta\Delta G_{H^+}$(g) data with the GB of reference bases. The GBs relative to ammonia of the reference bases are mostly published values from Taft's laboratory.[11] These values were anchored to those given in the most recent HPMS determination of GBs and PAs carried out under extremely careful conditions of temperature monitoring.[26] This procedure has already been applied in previous studies[18] and accounts for minor temperature effects.

Computational Techniques. Ab initio molecular orbital calculations were performed using the Gaussian-90 and Gaussian-92 series of programs.[27] The geometries of the different carbonyl compounds under consideration and their protonated species were fully optimized at the Hartree−Fock level of theory using a 6-31G(d) basis set.[28]

The harmonic vibrational frequencies of all neutral and cationic species were calculated using analytical second derivatives techniques in order to ensure that the optimized structures are minima on the potential energy surface and to evaluate the corresponding entropies and zero point energies. The latter were scaled by the empirical factor 0.893 to account for the fact that HF calculations overestimate harmonic frequencies. Only the largest compounds: 1-AdCOMe, $(1\text{-Ad})_2CO$, 1-AdCONH_2, and 1-AdCONMe_2 were excluded from our theoretical treatment at this level. It seemed of interest to apply the AM1 semiempirical method[29] to estimate relative proton affinities and reaction entropies as well as to reproduce possible strain effects. Thus, all systems under investigation were also fully optimized at the AM1 level, using the Spartan 3.1[30] package.

A proper description of gas-phase ion−molecule interactions requires the use of flexible enough basis sets and the inclusion of the electron correlation effects. Thus, final energies for both neutral and protonated species were obtained at the MP2(FC)/6-311+G(d,p)//6-31G(d) level. Proton affinities were obtained as the energy difference between the corresponding protonated and neutral species, after including the ZPE and thermal (298 K) corrections. The latter include $^1/_2RT$ for each translation and rotational degree of freedom plus changes in the vibrational energy due to thermal population of the excited vibrational modes.

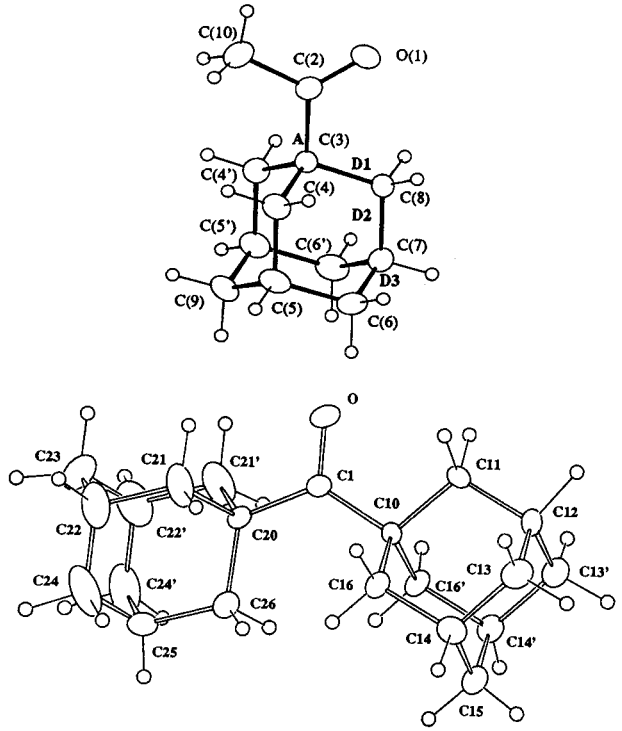


Figure 1. Molecular structures of 1-AdCOMe and $(1\text{-Ad})_2CO$. Ellipsoids are drawn at 30%. Dash stands for atoms related by a crystallographic mirror plane.

The relative importance of electrostatic, covalent, and polarization contributions to the protonation energy were estimated by means of the constrained space orbital variation (CSOV) method.[31a−c] This technique breaks down the SCF energy following some well-defined steps to determine the wavefunction, each one associated with a physical effect.

We have started our calculations by computing the SCF wavefunctions for two interacting units (neutral molecule and H^+ cation) separately. Once these wavefunctions had been computed, the starting point for the total system was obtained by superimposing the two electronic densities. At this first step of the CSOV procedure, the frozen orbital step (FO), no electronic relaxation is allowed, and the total energy accounts for the electrostatic interaction between the two units. In the second step we have taken into account the polarization of the neutral in response to the presence of the H^+ cation by allowing the occupied orbitals of the neutral to vary in its own orbital space. Finally, the charge donation to the H^+ orbitals is obtained in the third CSOV step. At the end of this step, the sum of all the contributions must be close to the total SCF interaction energy, indicating that our decomposition is correct.

In the CSOV analysis, polarization and donation may not be independent processes due to the electronic relaxation accompanying each one of these physical effects. To understand to what an extent polarization and donation are coupled, we have reversed the order of the corresponding steps. Then, a comparison of both sets of results led to upper and lower limits associated with polarization and donation phenomena. In this way we attempted to avoid the problem associated with Morokuma's method,[31d] which computes each contribution separately from the FO step without taking into account the

(22) Stewart, J. M.; Machin, P. A.; Dickinson, C. W.; Ammon, H. L.; Heck, H.; Flack, H. *The X-ray System*. Technical Report TR-446. Computer Science Center. University of Maryland, 1976.

(23) Martínez-Ripoll, M.; Cano, F. H. "PESOS", unpublished program.

(24) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95−98.

(25) For a detailed description of the most salient features of this instrument see, e.g.: Laukien, F. H.; Allemann, M.; Bischofberger, P.; Grossmann, P.; Kellerhals, Hp.; Kofel, P. In ref 17 c, Chapter 5, pp 81−99.

(26) Szulejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 7839−7845.

(27) *Gaussian 92*, Revision D.2, Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Repogle, E. S.; Gompers, R.; Andrés, J. L.; Raghavachari, K.; Binkley, J. S.; González, C.; Martin, R. L; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P., and Pople, J. A. Gaussian Inc.: Pittsburgh, PA, 1992. See also: Curtiss, L. A.; Carpenter, J. E.; Raghavachari, K.; Pople, J. A., *J. Chem. Phys.* **1992**, *96*, 9030−9034.

(28) B. Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.

(29) Dewar, M. J. S. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(30) *Spartan 3.1*, Version A. Wavefunction Inc.: Irvine, California, 1994.

(31) (a) Bagus, P. S.; Herman, K.; Bauschlicher, L. W. *J. Chem. Phys.* **1984**, *80*, 4378−4386. (b) *Ibid.* **1984**, *81*, 1966−1974. (c) Bagus, P. S.; Illas, F. *J. Chem. Phys.* **1992**, *96*, 8962−8970. (d) Umeyama, D.; Morokuma, K. *J. Am. Chem. Soc.* **1976**, *98*, 7208−7220.

Table 1. Experimental Determination of the Gas Phase Basicities of Selected Ketones, Carboxamides, and *N,N*-Dimethyl Carboxamides

compound	standard	$\Delta\Delta G_{H^+}$(std)[a]	$\delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g)(av)
		Ketones			
n-$C_3H_7COCH_3$	$C_2H_5COCH_3$	5.1	−1.14	3.96	4.2 ± 0.2
	$(C_2H_5)_2O$	4.6	−0.68	3.92	
	i-$C_3H_7CO_2CH_3$	3.0	1.47	4.47	
	t-$C_4H_9COCH_3$	2.1	2.20	4.30	
1-$C_{10}H_{15}COCH_3$	$C_6H_5COCH_3$	−1.8	−1.28	−3.08	−3.2 ± 0.1
	$(i\text{-}C_3H_7)_2O$	−2.1	−1.13	−3.23	
	$(n\text{-}C_3H_7)_2S$	−3.7	0.47	−3.23	
	$(CH_3CO)_2CH_2$	−4.0	0.87	−3.13	
		Carboxamides			
$C_2H_5CONH_2$	$(n\text{-}C_3H_7)_2S$	−3.7	−1.59	−5.29	−5.8 ± 0.5
	$(c\text{-}C_3H_5)_2CO$	−6.1	−0.22	−6.32	
	pyrazine	−6.1	0.88	−5.22	
	$(i\text{-}C_3H_7)_2S$	−6.6	0.23	−6.37	
	2-fluoropyridine	−7.9	2.14	−5.76	
i-$C_3H_7CONH_2$	4-cyanopyridine	−6.9	−0.35	−7.25	−7.5 ± 0.2
	2-fluoropyridine	−7.9	0.27	−7.63	
	$C_2H_5OCON(CH_3)_2$	−8.3	0.81	−7.49	
	$HC{\equiv}CCH_2NH_2$	−8.4	0.76	−7.64	
t-$C_4H_9CONH_2$	$C_2H_5OCON(CH_3)_2$	−8.3	−0.73	−9.03	−9.1 ± 0.1
	$HC{\equiv}CCH_2NH_2$	−8.4	−0.79	−9.19	
	$(t\text{-}C_4H_9)_2S$	−10.7	1.55	−9.15	
1-$C_{10}H_{15}CONH_2$	pyridazine	−13.6	−0.92	−14.52	−14.5 ± 0.1
	n-$C_3H_7NH_2$	−15.1	0.69	−14.41	
		N,N-Dimethyl Carboxamides			
i-$C_3H_7CON(CH_3)_2$	*n*-$C_3H_7NH_2$	−15.1	−1.86	−16.96	−17.0 ± 0.1
	neo-$C_5H_{11}NH_2$	−17.4	0.36	−17.04	
t-$C_4H_9CON(CH_3)_2$	neo-$C_5H_{11}NH_2$	−17.4	−0.59	−17.99	−18.1 ± 0.1
	pyridine	−18.8	0.57	−18.23	
1-$C_{10}H_{15}CON(CH_3)_2$	*t*-$C_5H_{11}NH_2$	−20.5	−2.34	−22.84	−23.0 ± 0.1
	3-methylpyridine	−21.7	−1.40	−23.10	
	4-methylpyridine	−22.5	−0.56	−23.06	

[a] Values from Prof. Taft's laboratory[11] and corrected as indicated in the text.

coupling between both phenomena. As a consequence, summation of energy contributions obtained from the Morokuma method may differ from the total SCF energies. As it will be shown later, the cases analyzed in this work present a considerable coupling between donation and polarization. However, the use of this methodology permits to identify the leading terms in the protonation of substituted ketones and amides.

Experimental Results

1. X-ray Crystallographic Study. The molecular structures of 1-AdCOMe and $(1\text{-Ad})_2CO$, as determined in this work are shown in Figure 1. The most relevant geometrical parameters are given in Tables 1S and 2S (Supporting Material).

The internal bonding parameters of the adamantyl skeleton in both 1-AdCOMe and $(1\text{-Ad})_2CO$ exhibit no unusual magnitudes and are consistent with the average values obtained for 47 organic structures ($R_{factor} \leq 0.050$ and no metal atoms present) retrieved from the Cambridge Structural Database[32] (October 1996). Some relevant mean values (77 hits), together with the standard deviation of the sample are: D1 = 1.536(9), D2 = 1.533(12), D3 = 1.525(15) Å, A = 110.6(7)°. In the case of 1-AdCOMe, bond distances and angles are similar to those in 1-adamantyl trichloromethyl ketone (CSD refcode:YAKHUN, R = 0.079) except for the shortened O(1)−C(2) bond and reduced O(1)−C(2)−C(10) angle (1.185 Å, 114.5° vs 1.211(3) Å, 119.3(2)° in the present compound) as well as the enlarged C(2)−C(10) bond and widened C(3)−C(2)−C(10) angle (1.575 Å, 124.2° vs 1.505(3) Å and 119.2(2)°). The latter features are actually quite similar to the corresponding values in $(t\text{-Bu})_2CO$ and $(1\text{-Ad})_2CO$. Also, in both cases, the conformations of the four six-membered rings defining the adamantyl framework are almost perfect chairs. Thus, for 1-AdCOMe and $(1\text{-Ad})_2CO$, respectively, the Cremer and Pople parameters[33] are in the ranges $q3$ = 0.612(0) − 0.627(2)/0.604(9) − 0.627(7) Å , $q2$ = 0.004(3) − 0.008(2)/0.009(9) − 0.016(8) Å, $\theta 2$ = 0.4(1) − 0.7(2)/0.8(8) − 1.7(5)° versus $q2$ = 0 Å and $\theta 2$ = 0° for a perfect chair.

2. Gas-Phase Basicities. Table 1 presents the results of proton-transfer equilibria 6 between different carbonyl compounds and a series of standard reference bases. The values of $\delta\Delta G_{H^+}$(g) given in Table 1 are defined as:

$$\delta\Delta G_{H^+}(g) = -RT \ln K_p \qquad (7)$$

All GBs are referred to ammonia. With respect to this compound, GB(B) = $-\Delta\Delta G_{H^+}$(g) for reaction 8:

$$B(g) + NH_4^+(g) \rightarrow BH^+(g) + NH_3(g)\ \Delta\Delta G_{H^+}(g) \qquad (8)$$

$\Delta\Delta G_{H^+}$ (g) is the average of the $\Delta\Delta G$ values obtained through eq 9:

$$\Delta\Delta G_{H^+}(g) = \delta\Delta G_{H^+}(g) + \Delta\Delta G_{H^+}(std) \qquad (9)$$

where $\Delta\Delta G_{H^+}$(std) pertains to reaction 10:

(32) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, J. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187.

(33) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.

$$B_{ref}(g) + NH_4^+(g) \rightleftarrows B_{ref}H^+(g) + NH_3(g) \quad (10)$$

Proton affinities cannot be obtained directly from ICR spectrometry. Entropy terms, however, were evaluated in the SCF calculations. The proton affinities, PA, are collected in Table 2. In the case of large molecules for which ab initio calculated entropies were not available, entropy changes for reaction 10 were computed using the AM1 values. For the purpose of obtaining absolute PAs from our relative PAs, we have used PA(NH_3) = 204.0 kcal mol^{-1} [11] which agrees nicely with the value recently obtained by Szulejko and McMahon[26] (203.5 kcal mol^{-1}) in a careful HPMS study and with the high-level ab initio (G2) result (204.1 kcal/mol) from Smith and Radom.[34]

Proton exchange studies of carboxamides and *N*,*N*-dimethyl carboxamides (particularly the former) meet with difficulties because of the competition between reaction 6 and the formation of the proton-bound dimer of the amide. This effect is moderately important for bulky molecules, but becomes quite significant in the case of propanamide. As shown in Table 1, this entails a larger uncertainty in GB for this compound.

Computational Results

The total energies, the ZPE energies, the total entropy values, the C=O stretching frequencies, and the calculated proton affinities are summarized in Table 3.

Discussion

1. Structures. Few structural studies (particularly in the gas-phase) have been carried out on the molecules studied herein.[35−43] In particular, the experimental information concerning the structures of amides is very scarce. Thus, we have only found gas-phase structural studies for acetamide[44,45] (an important neutron diffraction study in condensed phase is given in ref 46). For other members of the series this information originates in X-ray studies (refs 47−49 and this work). Their structural features most relevant to our present discussion are summarized in Tables 4a and 4b. The labeling of atoms presented in Chart 1 is used throughout.

Table 2. Experimental and Calculated (AM1) Gas Phase Basicities (GB)[a] and Proton Affinities (PA)[a] of Selected Ketones, Carboxamides, and *N*,*N*-Dimethyl Carboxamides

		GB(exp)[b]	PA(exp)[c]	PA(AM1)
	Ketones			
1	$(CH_3)_2CO$	187.4	194.9	192.5
2	$C_2H_5COCH_3$	190.5	198.1	194.9
3	*n*-$C_3H_7COCH_3$	191.4[d]	197.9[e]	195.4
4	*i*-$C_3H_7COCH_3$	192.3	199.8	195.5
5	*t*-$C_4H_9COCH_3$	193.5	201.0	196.8
6	1-$C_{10}H_{15}COCH_3$	198.8[d]	206.0[e]	199.5
7	$(C_2H_5)_2CO$	192.8	200.8	196.2
8	$(n\text{-}C_3H_7)_2CO$	195.1	203.0[e]	196.6
9	$(i\text{-}C_3H_7)_2CO$	196.0	203.7	196.7
10	$(t\text{-}C_4H_9)_2CO$	198.7	206.5	199.6
11	$(1\text{-}C_{10}H_{15})_2CO$	205.8	213.1[e]	203.7
	Carboxamides			
12	CH_3CONH_2	198.4[f]	206.2[f]	205.3
13	$C_2H_5CONH_2$	201.4[d]	209.7	207.1
14	*i*-$C_3H_7CONH_2$	203.1[d]	211.8	209.3
15	*t*-$C_4H_9CONH_2$	204.7[d]	213.4	208.5
16	1-$C_{10}H_{15}CONH_2$	210.1[d]	218.7[e]	210.9
	N,*N*-Dimethylcarboxamides			
17	$CH_3CON(CH_3)_2$	209.3	216.9	211.3
18	$C_2H_5CON(CH_3)_2$	212.2	219.6	212.6
19	*n*-$C_3H_7CON(CH_3)_2$	212.5	219.9[e]	212.1
20	*i*-$C_3H_7CON(CH_3)_2$	212.6[d]	220.2	212.7
21	*t*-$C_4H_9CON(CH_3)_2$	213.7[d]	221.6	214.2
22	1-$C_{10}H_{15}CON(CH_3)_2$	218.6[d]	226.1[e]	216.2

[a] All values in kcal·mol^{-1}. [b] Values from Prof. Taft's laboratory as reported in reference 11. [c] From the experimental GB values and the calculated 6-31G(d) entropy changes. [d] This work. [e] From the experimental GB values and the calculated AM1 entropy changes. [f] From reference 11.

Calculations, notably by Wiberg,[50] Appeloig, Arad, and Rappoport[51] (see also refs 42 and 43) on some of these compounds have already been reported, but structural information on the protonated species is much scarcer.

In the case of neutral ketones, the agreement between our optimized geometries and the experimental ones, when available, is fairly good as shown in Table 4a. Systematically, however, the calculated C=O bond is predicted to be slightly too short, since no correlation effects were included[52] in our geometry optimization procedure. The paucity of experimental data notwithstanding, some general structural features of the carboxamides are well reproduced and rationalized by our calculations. For instance, the $C_4C_1N_3$ angle (see Chart 1) for *N*,*N*-dimethyl amides (∼118° in the case of **17**) is about 2° larger than in primary amides (∼115° for **12**) in good agreement with the experimental evidence (See Table 4b). C−N bond lengths are also found to be slightly longer in the former, again in agreement with experiment.[53]

We shall restrict our discussion to those geometrical parameters which may be directly affected by strain effects; namely the $C_4C_1C_3$ bond angle (See Chart 1) (or alternatively the $C_4C_1N_3$ and $Z_6N_3C_1$ angles for amides) and the tilt of the substituents. As we shall show later,

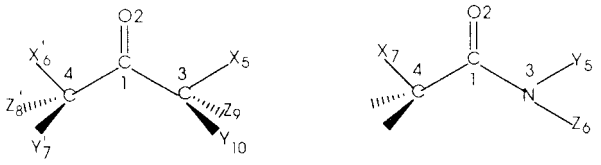
(34) Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1993**, *115*, 4885−4889.
(35) Hildebrandt, R. L.; Andreassen, A. L.; Bauer, S. H. *J. Phys. Chem.* **1970**, *74*, 1586−1592.
(36) Iijima, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3526−3530.
(37) Kato, C.; Konaka, S.; Iijima, T.; Kimura, M. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2148−2158.
(38) Smalen, J. D.; Constain, C. C. *J. Chem. Phys.* **1959**, *31*, 1562−1574.
(39) Nelson, R.; Pierce, L. *J. Mol. Spectrosc.* **1965**, *18*, 344−352.
(40) Abe, M. M.; Kuchitsu, K.; Shimanouchi, T. *J. Mol. Struct.* **1969**, *4*, 245−253.
(41) Sakurai, T.; Ishiyama, M.; Takeuchi, H.; Takeshita, K.; Fukushi, K.; Konaka, S. *J. Mol. Struct.* **1989**, *213*, 245−261.
(42) Takeuchi, H.; Sakurai, T.; Takeshita, K.; Fukushi, K.; Konaka, S. *J. Phys. Chem.* **1990**, *94*, 1793−1799.
(43) Liedle, S.; Oberhammer, H.; Allinger, N.-L. *J. Mol. Struct.* **1994**, *317*, 69−75.
(44) Kojima, T.; Yano, E.; Nakagawa, K.; Tsunekawa, S., *J. Mol. Spectrosc.* **1987**, *122*, 408−416.
(45) (a) Kimura, M.; Aoki, M. *Bull. Chem. Soc. Jpn.* **1953**, *26*, 429−433. (b) Kitano, M.; Kuchitsu, K., *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3048−3051. (c) For an important compilation of structural data for simple amides and Molecular Mechanics calculations on these molecules, see: Schnur, D. M.; Yuh, Y. H.; Dalton, D. R. *J. Org. Chem.* **1989**, *54*, 3779−3785.
(46) Jeffrey, G. A.; Ruble, J. R.; McMillan, R. K.; DeFrees, D. J.; Binkley, J. S.; Pople, J. A. *Acta Crystallogr. B* **1980**, *36*, 2292−2299.
(47) For protonated DMA: Benedetti, L.; Di Blasio, B.; Baine, P. *J. Chem. Soc., Perkin Trans. 2* **1980**, 500−503.
(48) For *N*,*N*-diethylacetamide: Cohen-Addad, C. *Acta Crystallogr. B* **1979**, *35*, 2471−2473.
(49) For *N*,*N*-dimethyladamantanecarboxamide: Thackeray, M. M.; White, J. *Cryst. Struct. Commun.* **1977**, *6*, 499−502.
(50) (a) Wiberg, K. B.; *J. Am. Chem. Soc.* **1986**, *108*, 5817−5822. (b) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035−5041.
(51) Appeloig, Y.; Arad, D.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 9131−9140.
(52) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644−8654.
(53) (a) Chakrabarti, P.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1555−1562. (b) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211−7218.

Table 3. HF and MP2 Total Energies (Hartrees), HF ZPE Energies (kcal/mol), Entropy Values (cal/mol·K), Vibrational Wavenumbers (cm^{-1}), and MP2 Proton Affinities (kcal/mol) for Selected Carbonyl Compounds

compound	HF/6-31G(d)	ZPE	MP2/6-311+G(d,p)	S	ν_{CO}	PA
1	−191.962236	0.08991	−192.653731	70.957	2021.6	191.4
1H$^+$	−192.287839	0.10334	−192.970726	71.880	1765.7	
2	−230.998047	0.12076	−231.849675	79.243	2014.3	194.2
2H$^+$	−231.327243	0.13411	−232.171017	79.585	1750.1	
4	−270.030887	0.15130	−271.046828	83.665	2007.8	195.4
4H$^+$	−270.363158	0.16479	−271.370502	84.610	1740.9	
5	−309.063389	0.18134	−310.246415	88.077	2000.7	197.8
5H$^+$	−309.398921	0.19501	−310.573768	88.811	1722.4	
7	−270.033649	0.15156	−271.045608	86.183	2010.5	195.7
7H$^+$	−270.364967	0.16504	−271.369560	85.268	1740.3	
9	−348.100370	0.21240	−349.441535	96.918	2002.3	199.5
9H$^+$	−348.438480	0.22614	−349.771690	96.922	1725.1	
10	−426.153132	0.27303	−427.831074	104.108	1969.7	201.8
10H$^+$	−426.495050	0.28703	−428.165071	103.861	1683.4	
12	−207.976011	0.07898	−208.783436	71.323	1987.9	204.8
12H$^+$	−208.324628	0.09396	−209.123163	68.445	1674.2	
13	−247.011703	0.10983	−247.903008	77.931	1981.4	206.4
13H$^+$	−247.362345	0.12492	−248.245096	76.183	1672.2	
14	−286.046254	0.14013	−287.101451	85.753	1962.9	208.1
14H$^+$	−286.399880	0.15506	−287.446085	82.608	1672.4	
15	−325.078068	0.17022	−326.299909	89.537	1948.9	210.2
15H$^+$	−325.434928	0.18513	−326.647884	86.229	1669.4	
17	−286.030105	0.14018	−287.077719	84.680	1940.9	215.9
17H$^+$	−286.392273	0.15435	−287.434535	85.199	1665.7	
18	−325.065081	0.17088	−326.273412	90.945	1934.8	217.3
18H$^+$	−325.429267	0.18523	−326.632556	92.011	1657.8[a]	
20	−364.090467	0.20116	−365.470417	98.356	1919.9	219.2
20H$^+$	−364.464643	0.21546	−365.832522	98.803	1654.7[a]	
21	−403.121078	0.23147	−404.662811	101.022	1913.2	219.7
21H$^+$	−403.490017	0.24607	−405.026267	100.575	1668.6[a]	

[a] For these systems, the C=O stretching appears mixed with other normal modes.

Chart 1



some of the geometrical distortions will be reflected in other molecular properties such as the C=O stretching frequencies. From Table 3 it can be seen that for methyl ketones, RCOMe, the angles $C_4C_1C_3$ vary between fairly narrow limits: 116.0−119.2°. A substantial widening of this angle takes place in **10** (124.9° [43]) and **11** (128.2°, this work). They are examples of Dubois's[54] *framework distortion* associated to gem-6 substitution in the C3C(CZ)CC3 families (Z = O, NH, etc.). As indicated earlier, a similar situation appears in trichloromethyl adamantyl ketone: $C_3C_1C_4$ = 124.2° and again in carboxamides, wherein the $C_4C_1N_3$ bond angle increases from 115.1° in **12** to 122° in **21** and **22**. This angle increases by about 6° upon protonation in both ketones and in amides. This is the result of two effects. First, protonation at the carbonyl oxygen implies a significant charge transfer to the bare proton and a hybridization change at the oxygen which is transmitted to the carbon atom. Oxygen is more electronegative than carbon and thus recovers part of this electronic charge by depopulating the C=O bond, which becomes weaker and longer. As a result, the s character of the carbon hybrid which participates in the C=O bond decreases, and by orthogonality, the s character of the other two hybrids as well as the angle between them should increase. Even larger effects are displayed by the $Z_6N_3C_1$ angle in *N*,*N*-dimethyl carboxamides. Thus, in **12** and **17**, it amounts, respectively, to 117.5 (experimental 118.5° [45b]) and 123.4° (calculated, this work) and reaches 128.8°in **22**.[49] These qualitative arguments are confirmed, from a quantitative point of view, by means of a natural bond order analysis (NBO)[55] of these species. As an illustration, we present in Table 5 the corresponding NBO results for acetamide. The second consequence of the charge transfer from the base to the incoming proton is an increase of the net positive charge borne by the substituents, which enhances their mutual repulsion.

For those species which have methyl or t-Bu substituents, the tilt of the substituent, defined as the angle between the C−C bond and the C_3 symmetry axis, is not a straightforward measure of the strain in the system. It undergoes, however, some very substantial changes upon protonation and is highly sensitive to conformational effects. Thus, in **1** and in **10**, the experimental/calculated tilts are respectively 2.5° [36]/0.4° and 1.6° [43]/4.3°. Representative tilt changes upon protonation due to the additional interaction of the substituents with the proton are as follows: in **1H**$^+$ the methyl group closer to the proton increases its tilt up to 1.7°, while the other methyl group decreases it down to 0.2°. Something similar happens when both substituents are bulkier, as in **10H**$^+$. There, one of the tilts increases up to 5.1° while the other decreases to 2.7°. In the case of *solid* **11** the tilt angles for the two adamantyl moieties are different: 1.5° and 8.4°. This likely reflects a crystal-packing effect.

The nonplanarity of the amino group is of particular interest in the case of amides. This problem has been thoughtfully studied by Wong and Wiberg[56] for the particular case of **12**, which exhibits a clear departure

(54) Dubois, J.-E.; Cossé-Barbi, A. *J. Am. Chem. Soc.* **1988**, *110*, 1220−1228.

(55) (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066−4073. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

(56) Wong, M. W.; Wiberg, K. B. *J. Phys. Chem.* **1992**, *96*, 668−671.

Table 4.

A. Experimental Geometrical Parameters for Some Ketones. Bond Distances in Angstroms, Bond Angles in Degrees (calculated values in parentheses)

compound	C_1-O	C_1-C_3	C_1-C_4	$C_3C_1C_4$
$(CH_3)_2CO$	1.210[a,b]	1.507[a,e]	1.507[a,e]	116.0[b]
	1.211[c]	1.515[d]	1.515[d]	116.2[d]
	1.215[d]	1.517[b,c]	1.517[b,c]	116.7[a]
	1.222[e]			117.2[e]
	(1.192)[f]	(1.514)[f]	(1.514)[f]	118.6[c]
	(1.235)[g]	(1.495)[g]	(1.495)[g]	(116.6)[f]
				(115.4)[g]
$C_2H_5COCH_3$	1.219[h]	1.518[h]	1.518[h]	116.1[h]
	(1.192)[f]	(1.518)[f]	(1.515)[f]	(116.6)[f]
	(1.235)[g]	(1.496)[g]	(1.503)[g]	(114.9)[g]
i-$C_3H_7COCH_3$	1.217[i]	1.521[i]	1.529[i]	118.0[i]
	(1.193)[f]	(1.517)[f]	(1.525)[f]	(117.7)[f]
	(1.234)[g]	(1.495)[g]	(1.514)[g]	(115.3)[g]
1-$C_{10}H_{15}COCH_3$	1.211[j]	1.505[j]	1.520[j]	119.2[j]
	(1.236)[g]	(1.496)[g]	(1.518)[g]	(117.1)[g]
(*i*-$C_3H_7)_2CO$	1.215[k]	1.535[k]	1.535[k]	116.6[k]
	(1.194)[f]	(1.525)[f]	(1.525)[f]	(117.5)[f]
	(1.234)[g]	(1.514)[g]	(1.514)[g]	(115.2)[g]
(*t*-$C_4H_9)_2CO$	1.222[l]	1.544[l]	1.544[l]	124.9[l]
	(1.196)[f]	(1.554)[f]	(1.554)[f]	(125.4)[f]
	(1.238)[g]	(1.529)[g]	(1.429)[g]	(123.4)[g]
(1-$C_{10}H_{15})_2CO$	1.229[j]	1.515[j]	1.520[j]	128.0[j]
	(1.240)[g]	(1.528)[g]	(1.528)[g]	(124.5)[g]

B. Experimental Geometrical Parameters for Some Carboxamide and *N,N*-dimethylcarboxamides. Bond Distances in Å,Bond Angles in Degrees. (Calculated values in parentheses)

compound	C_1-O	C_1-N	C_1-C_4	C_4C_1N
CH_3CONH_2	1.21[a]	1.36[a]	1.519[b]	113.0[a]
	1.220[b]	1.380[b]	1.53[a]	115.1[b]
	(1.197)[c]	(1.358)[c]	(1.514)[c]	(115.2)[c]
	(1.248)[d]	(1.375)[d]	(1.508)[d]	(118.2)[d]
$CH_3CON(CH_3)_2$	1.228[e]	1.322[e]	1.520[e]	118.7[e]
	(1.202)[c]	(1.363)[c]	(1.517)[c]	(117.9)[c]
	(1.248)[d]	(1.390)[d]	(1.508)[d]	(118.5)[d]
1-$C_{10}H_{15}CON(CH_3)_2$	1.223[f]	1.35[f]	1.55[f]	122.1[f]
	(1.250)[d]	(1.395)[d]	(1.533)[d]	(123.1)[d]

[a] Reference 35. [b] Reference 36. [c] Reference 37. [d] Reference 38. [e] Reference 39. [f] HF/6-31G(d) calculated values. This work. [g] AM1 calculated values. This work. [h] Reference 40. [i] Reference 41. [j] This work. [k] Reference 42. [l] Reference 43. [m] Reference 45a. [n] Reference 45b. [o] HF/6-31G(d) calculated values. This work. [p] AM1 calculated values. This work. [q] Reference 53a. [r] Reference 49.

Table 5. Percentage of s Character of the Bonding Hybrid Orbitals of Acetamide and Its Protonated Form

bond	neutral	protonated
C_1-O_2	32.7−44.5	27.8−38.6
C_1-N_3	31.2−38.6	33.2−39.7
C_1-C_4	35.8−26.5	38.9−24.8

from planarity. This work also shows that the structural results obtained at the HF/6-31G(d) level do not change significantly at higher levels of accuracy. This allows us to have some confidence on the predictions of our results regarding the planarity of the amino group in more complicated amides. Two facts clearly emerge from this study: (i) the departure from planarity decreases considerably when the size of the alkyl substituent increases. Thus, when the substituent is isopropyl or *tert*-butyl, the NH_2 group is predicted to be practically planar. A similar effect, but considerably attenuated, is observed for *N,N*-dimethyl amides. For **17**, the pyramidalization of the amino group is very similar to that found in **12**. When the substituent is a *tert*-butyl group, the amino group is only slightly pyramidal. *(ii) In all cases,the amino group becomes completely planar upon protonation, thus favoring the conjugation of the nitrogen lone pair with the C═O linkage, which became electron deficient following charge transfer to the proton.* It is interesting that even in the solid state and in the presence of strong hydrogen bonding interactions the protonated dimethylcarbamoyl group in **17** departs from strict planarity by only 3°.[47] This is confirmed by the fact that protonation implies simultaneously a sizable shortening of the C−N bond. *Thus, steric strain in these compounds is not able to significantly hinder resonance stabilization in protonated carboxamides and N,N-dimethyl carboxamides.*

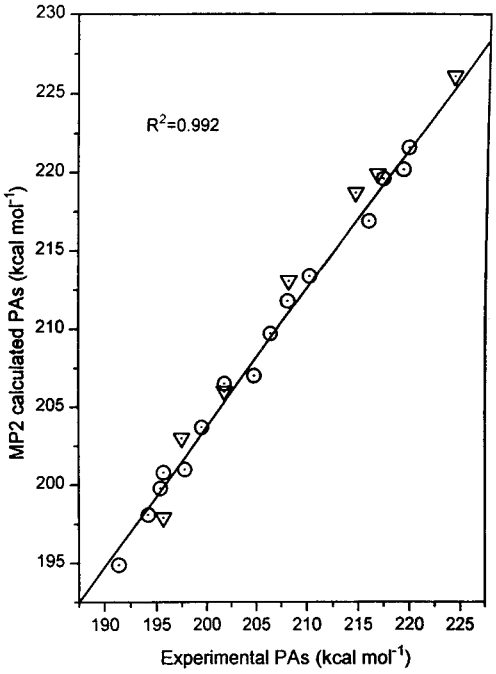


Figure 2. MP2 calculated vs experimental proton affinities of selected ketones, carboxamides, and *N,N*-dimethyl carboxamides. (Values identified with triangles corresponding to PA values calculated from the correlation between AM1 and MP2 calculations).

2. Proton Affinities. There is an excellent linear relationship between experimental and calculated (MP2/6-311+G(d,p)//6-31G(d)) proton affinities (Figure 2). Its slope (1.09) is close to unity, and only the PA of **12** deviates from the line by more than 1.5 kcal/mol (the experimental proton affinity of acetamide was taken from the literature[11]).

When the AM1-calculated proton affinities are plotted against the experimental values, ketones and carboxamides follow linear correlations of similar slope but quite different intercepts. Also, as shown in Table 2, the AM1 results underestimate absolute PAs. This notwithstanding, this method seems to be a good tool to estimate relative proton affinities of very large carbonyl bases, provided they belong to an homologous series of compounds.

In Table 6 we present the results of the CSOV analysis[31a−c] of representative ketones, carboxamides, and *N,N*-dimethyl carboxamides. The dependence of the CSOV results on the order of analysis may be partially due to a BSSE. However, inasmuch as oxygen and proton share similar spatial distributions in the MO's, it shows that polarization and charge transfer are coupled, a fact which cannot be taken into account by using frozen orbital formalisms.[31d] Furthermore, in all cases the polarization term is always clearly dominant and quali-

Table 6. CSOV Energy Contributions (eV) for the Protonation of Ketones, Carboxamides and *N,N*-Dimethyl Carboxamides

		run 1[a]		run 2[b]	
R_1	R_2	charge transfer	polarization	charge transfer	polarization
CH_3	CH_3	2.870	4.156	1.141	5.885
CH_3	$C(CH_3)_3$	2.845	4.405	1.166	5.967
NH_2	CH_3	2.875	4.095	1.137	5.833
NH_2	$C(CH_3)_3$	2.883	4.330	1.157	6.056
$N(CH_3)_2$	CH_3	2.947	4.140	1.124	5.963
$N(CH_3)_2$	$C(CH_3)_3$	2.831	4.637	1.169	6.298

[a] Polarization of the neutral molecule is evaluated prior to charge transfer to the proton. [b] The order of steps is reversed with respect to run 1, i.e., charge donation from the neutral molecule to the proton is evaluated prior to polarization.

tatively reflects the ranking of polarizabilities of the substituents, as it is always larger for *tert*-butyl- than for methyl-substituted derivatives. It is interesting to note that when the Taft−Topsom model,[14] which considers substituent effects classified according to their origin in field, resonance, and polarizability effects, was applied to a large series of carbonyl [14] and thiocarbonyl[57] compounds, the polarizability contributions were found to be often dominant, accounting in some specific cases for as much as 80% of the differential proton affinity change. It is also relevant that *there is no definite trend indicating any significant reduction of either polarizability or charge-transfer contributions with a simultaneous increase in the size of the substituents and this irrespective of the order of the decomposition steps.* A significant steric inhibition of resonance would appear as a significant decrease of the charge-transfer contribution with an increase in the size of the substituent.

3. CO Stretching Frequencies. Table 3 shows that, for the three series of compounds, the calculated harmonic CO stretching frequencies slightly decrease on going from methyl- to *tert*-butyl- and then on to 1-adamantyl-substituted compounds, in good agreement with the experimental evidence when available.[58] In the case of ketones a much larger decrease is found in the cases of **10** and **11**. This effect *is not* a linear function of the number of methyl substituents at the α carbon, as it has been conclusively shown by Dubois and co-workers using a set of 32 ketones.[58e] Our results show that this is essentially a consequence of the existence of a significant strain when *both* substituents are *tert*-butyl or 1-adamantyl groups. As we mentioned above, in these cases the $C_3C_1C_4$ angles considerably widens to avoid the repulsion between these substituents. This implies a sizable hybridization change at the carbonyl carbon atom (C_1) which affects the C=O stretching frequency.

Figure 3 is a plot of the computed (HF/6-31G(d,p)) harmonic stretching frequencies of acetone (scaled by the factor 0.8602[59]) against the CC(O)C angle. The available experimental frequencies for ketones ranging from cyclobutanone (c-C_3H_6C=O) to **11** are also plotted. These frequencies are known to have two components, respectively, kinematic and potential (electronic) in origin.[60] This plot shows that the latter plays a leading role and is largely determined by the CC(O)C angle.

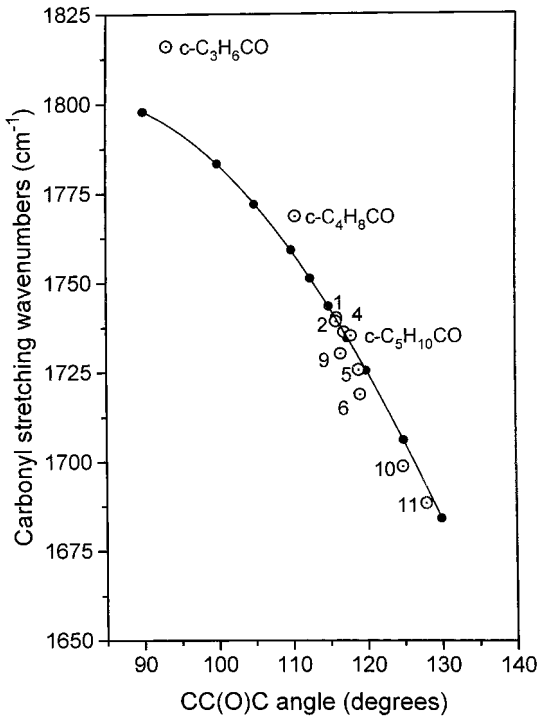


Figure 3. C=O stretching wavenumbers for ketones vs CC(O)C angle in dimethyl ketone. Solid circles: calculated (HF/6-31G(d,p)) values multiplied by the factor 0.8602 (see text). Open circles: experimental values.

Something similar can be concluded regarding the carboxamides, since there is an extremely good linear relationship between the C=O stretching frequencies of acetamide and those of the dimethyl ketone, when the bond angle centered at the carbonyl atom changes from 90° to 130°.

Upon protonation there is a considerable red shifting of the C=O stretching band, since, as we mentioned above, there is a significant depopulation of the C=O linkage. The strain effect on the C=O stretching frequencies is also apparent for the corresponding protonated species (see Table 3), but slightly larger. Actually, on going from **1** to **10** and then on to **11**, the experimental CO stretching frequency decreases 40.5 (calculated, 52 cm^{-1}) and 49.4 cm^{-1}, respectively. The computed difference for $\mathbf{1H}^+$ and $\mathbf{7H}^+$ being 82 cm^{-1} (It is to be hoped that techniques currently available for the study of the vibrational spectra of gaseous ions[61] will confirm these predictions). This seems to indicate, as we shall confirm in forthcoming sections, that strain effects are slightly larger in protonated than in neutral species.

4. Strain Energetics. The effects of internal strain in neutral and protonated ketones were quantitatively

(57) Abboud, J.-L. M.; Mó, O.; de Paz J. L. G.; Yáñez, M.; Esseffar, M.; Bouab, W.; El-Mouhtadi, M.; Mohklisse, R.; Ballesteros, E.; Herreros, M.; Homan, H.; López-Mardomingo, C.; Notario, R. *J. Am. Chem. Soc.* **1993**, *115*, 12468−12476.

(58) Regarding structural effects on the C=O stretching frequencies of ketones, see the following: (a) For classical examples of cyclic ketones, Ingraham, L. L. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley: New York, 1956; Ch. 11, pp 479−522. (b) Dubois, J. E.; Massat, A. *C. R. Acad. Sci. (Paris),* **1967,** *265B,* 757−759. (c) Morgan, K. J.; Unwin, N. *J. Chem. Soc. (B)* **1967**, 1336−1340. (d) Dubois, J. E.; Massat, A. *J. Chem. Soc., Chem. Commun.* **1968,** 778−779. (e) Dubois, J.-E.; Massat, A.; Guillaume, Ph. *J. Mol. Struct.* **1969**, *4*, 403−418. (f) Guonan, S.; Xun, C.; Daouyan, D. *J. Mol. Struct.* **1988**, *175*, 359−364.

(59) This is the ratio of the experimental to the computed (HF/6-31G(d,p)) C=O stretching frequency of gaseous acetone.

(60) Galabov, B.; Suzuki, S.; Orville-Thomas, W. J. *Chem. Phys. Lett.* **1980**, *73*, 561−564.

(61) Schaefer, H. F., III. In *Ion and Cluster Ion Spectroscopy and Structure*; Maier, J. P., Ed., Elsevier: Amsterdam, 1989; chapter 4, pp 109−129.

Table 7. Enthalpies (kcal/mol) for Reaction 1. Values in Parentheses Correspond to the Reactions Involving the Corresponding Protonated Species (reaction 2)

R	AM1	HF/6-31G(d)	MP2/6-311+G (d,p)//6-31G(d)	experimental
CH_3	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
C_2H_5	0.0 (1.1)	0.1 (1.1)	0.0 (1.2)	0.7 ± 0.4 (1.2 ± 0.6)
n-C_3H_7	0.0 (1.5)	–	–	0.5 ± 0.4 (−1.6 ± 0.6)
i-C_3H_7	0.2 (2.0)	−0.7 (−0.1)	−1.2 (−0.9)	−0.9 ± 0.4 (0.1 ± 0.7)
t-C_4H_9	5.1 (6.5)	7.3 (9.6)	3.5 (5.8)	4.5 ± 0.5 (5.1 ± 0.7)
1-$C_{10}H_{15}$	5.4 (8.1)	–	–	2.8 ± 1.7 (6.8 ± 1.8)

Table 8. Enthalpies (kcal/mol) for Reaction 11. Values in Parentheses Correspond to the Reactions Involving the Corresponding Protonated Species (reaction 12)

R	AM1	HF/6-31G(d)	MP2/6-311+G(d,p)//6-31G(d)	experimental
CH_3	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
C_2H_5	0.5 (−0.1)	0.1 (−1.2)	0.0 (−1.3)	−0.3 ± 0.4 (0.0 ± 0.6)
n-C_3H_7	−0.2 (−1.1)	–	–	−0.3 ± 0.4 (–)
i-C_3H_7	0.1 (1.1)	1.0 (0.1)	0.6 (−0.1)	−0.3 ± 0.4 (0.4 ± 0.6)
t-C_4H_9	0.8 (−0.3)	0.6 (−0.2)	0.0 (−0.9)	0.2 ± 0.5 (1.3 ± 0.7)
1-$C_{10}H_{15}$	0.8 (−0.5)	–	–	−0.2 ± 1.0 (1.2 ± 1.1)

Table 9. Enthalpies (kcal/mol) for Reaction 13. Values in Parentheses Correspond to the Reactions Involving the Corresponding Protonated Species (reaction 14)

R	AM1	HF/6-31G(d)	MP2/6-311+G(d,p)//6-31G(d)	experimental[a]
CH_3	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
C_2H_5	−0.6 (−1.7)	−0.4 (−1.5)	−0.0 (−1.5)	0.1 ± 0.5 (−0.4 ± 0.7)
n-C_3H_7	−0.3 (2.4)	–	–	0.2 ± 0.6 (0.2 ± 0.8)
i-C_3H_7	−0.7 (−2.3)	−5.2 (−1.7)	−0.2 (−1.0)	– (–)
t-C_4H_9	−3.5 (−4.9)	−6.5 (−8.4)	−4.9 (−7.1)	−3.7 ± 0.7 (−5.1 ± 0.8)
1-$C_{10}H_{15}$	−4.1 (−6.2)	–	–	−5.5 ± 1.1 (−7.4 ± 1.2)

[a] Using experimental $\Delta_f H°_m$ values for neutral species from refs 16a−e.

defined by means of the isodesmic reactions 1 and 2. In this model, strain effects are thus referred to the methyl ketones.

In the cases of carboxamides and *N*,*N*-dimethyl carboxamides, we followed our previous approach[16a−c] and Liebman's pioneering treatment[62] and used again methyl ketones (and their protonated forms) as reference compounds, reactions 11−14: For carboxamides,

$$RCONH_2 + CH_3COCH_3 \rightarrow CH_3CONH_2 + RCOCH_3 \quad (11)$$

$$RC(OH^+)NH_2 + CH_3C(OH^+)CH_3 \rightarrow CH_3C(OH^+)NH_2 + RC(OH^+)CH_3 \quad (12)$$

For *N*,*N*-dimethyl carboxamides,

$$RCON(CH_3)_2 + CH_3COCH_3 \rightarrow CH_3CON(CH_3)_2 + RCOCH_3 \quad (13)$$

$$RC(OH^+)N(CH_3)_2 + CH_3C(OH^+)CH_3 \rightarrow CH_3C(OH^+)N(CH_3)_2 + RC(OH^+)CH_3 \quad (14)$$

These reactions are "operational definitions of strain", in the spirit of Schleyer's studies.[12b]

The heats of formation of some of the neutral species considered were reported by us elsewhere.[16a−d] Others were taken from the literature.[16e] Heats of formation of the corresponding protonated species were determined by combining the heats of formation of the neutrals and their proton affinities (as indicated in the Introduction). The values of the enthalpies of reactions 1 and 2 and 11−14 have been summarized in Tables 7, 8, and 9, respectively.

Reaction 1, Table 7, is nearly thermoneutral for methyl, ethyl, and isopropyl substituents, but endothermal when the substituents are *t*-Bu and 1-Ad. These thermodynamic results clearly reflect the onset of framework distortion (structural effect) and substantial red-shifting of the C=O stretching band, *all the effects becoming significant simultaneously*. (Notice that Table 7 seems to suggest that the strain in **11** is slightly smaller than that in **10**. Most likely this reflects the substantial experimental uncertainties on $\Delta H°_1$ associated to these molecules.

A comparison of the values presented in Tables 8 and 9 clearly shows that the presence of a voluminous *N*,*N*-dimethyl group in *N*,*N*-dimethyl carboxamides produces a sizable increase in strain effects. Actually, Table 8 shows that in all cases, reactions 11 and12 are nearly thermoneutral, which indicates that the size of the interactions between the substituents in methyl ketones are practically equal to those found in primary amides. The situation is quite different for *N*,*N*-dimethyl amides (Table 9). For the latter, reactions 13 and 14 are only thermoneutral for methyl and ethyl substituents, but exothermic when the substituent is *t*-Bu and 1-Ad, indicating enhanced strain effects in *N*,*N*-dimethyl carboxamides with respect to the corresponding methyl ketones and primary carboxamides.

From Tables 7−9 *it is also evident that these effects are more important in the protonated species.* This is also associated to larger spectral shifts (ν_{CO}). Protonation brings about a significant charge redistribution within the molecule. As shown in ref 18a, charge transfer to the incoming proton results in a charge density depletion at the C=O bond which is transmitted to the carbonyl carbon and through it to the substituent. Hence, in the protonated species the net positive charge at the substituent (particularly the hydrogen atoms) is greater than in the neutral compound and, as a consequence, an enhancement of the repulsive interactions between them

(62) Greenberg, A.; Chin, Y.-Y.; Johnson, J. L.; Liebman, J. F. *Struct. Chem.* **1991**, *2*, 117−131.

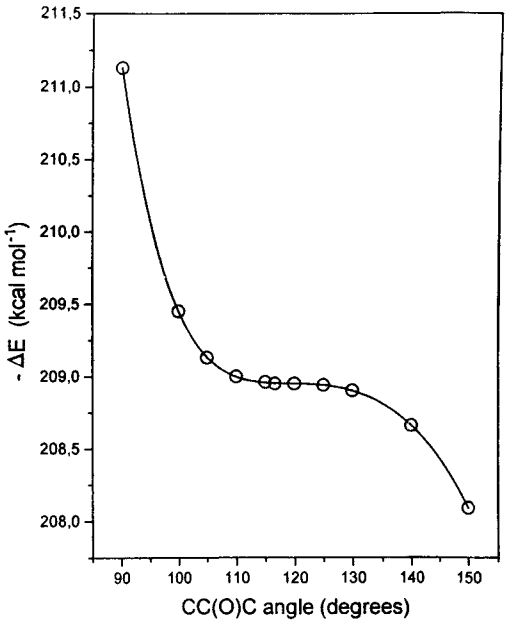


Figure 4. HF/6-31G(d,p) total energy differences between neutral and protonated acetone vs CC(O)C angle.

occurs. In fact, two opposing effects are operative: (i) the C−C bonds originating at the carbonyl group become shorter, following the effective increase of the electronegativity of this group upon protonation. This leads to an increased repulsion and, (ii) the CC(O)C angle widens, and this counterbalances the first effect. Inspection of Tables 7−9 shows that steric effects associated to *N*,*N*-dimethylamino groups are very close to those induced by *tert*-butyl groups. Also, in view of the planarity of carbamoyl and *N*,*N*-dimethylcarbamoyl groups in the corresponding protonated amides, it follows that these effects are not likely to involve a significant inhibition of resonance. Finally, we notice the fair agreement between the experimental reaction enthalpies and those calculated at the MP2/6-311+G(d,p) level.

Last, we address the problem of the possible influence of the strain on the intrinsic basicities of the carbonyl compounds. For this purpose, we have calculated the energy difference between neutral and protonated acetone as a function of the CC(O)C angle. Calculations were performed at the 6-31G(d,p) level with full optimization of geometries (only the value of the CC(O)C angle was imposed) using Spartan[30] and it was systematically assumed that the angle opened 5.4° upon protonation (this is the value pertaining to the protonation of unconstrained acetone). The results are presented in Figure 4.

It can be seen that this energy difference changes appreciably for angles between 90° and 100° but remains practically constant for angles in the 105−130° range. Inasmuch as the CC(O)C angles for the species (both neutral and protonated) studied in this work are within these limits, we may consider that strain effects do not alter in any significant way the intrinsic basicity of carbonyl compounds. In other words, the much larger basicity of **10** and **11** with respect to acetone essentially reflects the balance between the positive charge stabilizing effect of the large polarizabilities of *t*-Bu and 1-Ad and their sizable intramolecular repulsions.

Conclusions

1. The quantitative agreement between the experimental and calculated changes in thermodynamic state functions is excellent.
2. Relative to methyl ketones (neutral and protonated), sizable strain effects appear only in the case of ketones R_1COR_2 wherein R_1 and R_2 are tertiary carbons. They are clearly associated to a distortion of the molecular framework.
3. Methyl and amino groups in ketones and carboxamides (both neutral and protonated) lead to essentially the same strain effects.
4. The *N*,*N*-dimethylamino group in neutral and protonated carboxamides leads to strain effects very similar to those produced by a *tert*-butyl group in neutral and protonated ketones.
5. Both the carbamoyl and dimethylcarbamoyl groups in protonated carboxamides are planar: steric inhibition of resonance in these species is thus very small or nil.
6. Strain effects on carbonyl stretching frequencies of ketones and carboxamides, both neutral and protonated, are linearly related and have a common origin: the changes in the hybridization of the carbonyl carbon.
7. Over the range 105° < C−C(O)−C < 130°, the calculated PA of Me_2CO is essentially independent of the angle. Thus, in agreement with the overall experimental and theoretical evidence, structural effects on the intrinsic basicity of acyclic ketones are mostly determined by the competition between polarizability (stabilizing) and steric (destabilizing) contributions of the substituents.

Acknowledgment. This work was supported by grants PB 93-0289-C02 and PB-93-0142-C03-01 from the Spanish D.G.I.C.Y.T. Work by H.H. was supported by the Moroccan Ministry of Education and C.S.I.C.

Supporting Information Available: X-ray data (bond distances, bond angles, torsion angles, and potential hydrogen bonds) (Å,°) for 1-AdCOMe and $(1\text{-Ad})_2CO$ (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971330D