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Solution and Gas-Phase Acidities of *all-trans* (*all-E*) Retinoic Acid: An Experimental and Computational Study

José-Luis M. Abboud,*[a] Ilmar A. Koppel,*[b] Einar Uggerud,*[c] Ivo Leito,*[b] Ivar Koppel,*[d] Osamu Sekiguchi,[c] Karl Kaupmees,[b] Jaan Saame,[b] Karl Kütt,[b] and Masaaki Mishima*[a]

Abstract: Retinoic acid is of fundamental biological importance. Its acidity was determined in the gas phase and in acetonitrile solution by means of mass spectrometry and UV/Vis spectrophotometry, respectively. The intrinsic acidity is slightly higher than that of benzoic acid. In solution, the situation is opposite. The experimental systems were described theoretically applying quantum chemical methods (wave function theory and density functional theory). This allowed the determination of the molecular structure of the acid and its conjugate base, both in vacuo and in solution, and for computational estimates of its acidity in both phases.

Introduction

All-trans (*All-E*) retinoic acid, (**I**, Ret—CO₂H)[1–3] is central to biology.[4] It is structurally related to retinol (**II**)[5,6] and retinal (**III**),[7–9] both of which are fundamental for the mechanism of vision in humans and other species.[10] **I** plays on its own a very general and fundamental role in biological processes. This originates in the fact that it acts by binding to the *all-trans* retinoic acid receptor (RAR). *All-trans* retinoic acid receptors mediate transcription of different sets of genes controlling differentiation of a variety of cell types. Thus, the target genes regulated depend upon the target cells. The ability of *all-trans* retinoic acid to regulate the expression of several hundred genes through binding to nuclear transcription factors is believed to mediate most of these processes,[11–15] including those of the fundamental Hox genes.[16] These properties confer to **I** activity as anticancer drug[17–21a,b] while being endowed with potential teratogenic and toxic properties.[22,23]

The anionic form of **I** bound to proteins can exist in a variety of conformeric forms, as demonstrated in a carefully conducted computational quantum chemistry study.[11] A set of 66 conformers were identified and their geometries in the gas phase were optimized at high levels of theory. The numbering of atoms in Scheme 1 is the same as in that study.[11]
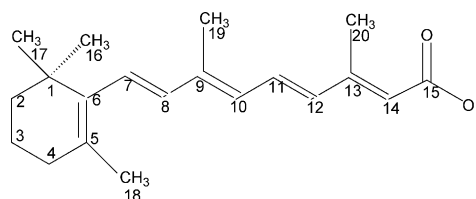
Scheme 1. *All-trans* (*all-E*) retinoic acid.

Herein, we report the experimental determination of the acidity of **I** in the gas phase and in MeCN solution.[24–27] This study seems in order because the simple determination of the aqueous pK_a of this compound is by no means trivial owing to the low water solubility of (**I**) and the fact that micelles start to form already in the μM range of concentration. As the concentration decreases, so does the apparent pK_a. According to Noy,[28a] the lowest pK_a observed was about 6. His estimated limiting value was about 5. The experimental aqueous pK_a of benzoic acid, a useful reference, is 4.20.[28b] Interestingly, the pK_a of this compound in acetonitrile is 21.51.[28c] The results are also analyzed computationally.

[a] Prof. Dr. J.-L. M. Abboud, Prof. Dr. M. Mishima
Institute for Materials Chemistry and Engineering
Kyushu University, 6-10-1, Hakozaki, Higashi-ku
Fukuoka 812-8581 (Japan)
Fax: (+81) 92-642-2715
E-mail: abboud@ms.ifoc.kyushu-u.ac.jp
       mishima@ms.ifoc.kyushu-u.ac.jp

[b] Prof. Dr. I. A. Koppel, Prof. Dr. I. Leito, Dr. K. Kaupmees, J. Saame, K. Kütt
University of Tartu, Institute of Chemistry
Ravila 14a, 50411 Tartu (Estonia)
Fax: (+372) 7-375264
E-mail: ilmar@chem.ut.ee
       ivo.leito@ut.ee

[c] Prof. Dr. E. Uggerud, O. Sekiguchi
Mass Spectrometric Laboratory and
Center for Theoretical and Computational Chemistry (CTCC)
Department of Chemistry, University of Oslo, P.O.B. 1033
Blindern, 0315 Oslo (Norway)
Fax: (+47) 22855441
E-mail: einar.uggerud@kjemi.uio.no

[d] Dr. I. Koppel
Institute of Computer Sciences, University of Tartu
Liivi 2, 50409 Tartu (Estonia)
Fax: (+372) 7-375468
E-mail: Ivar.Koppel@ut.ee

Results

Experimental acidity of I in acetonitrile

UV/Vis spectrophotometric titration was used to determine the pK_a value of retinoic acid (RA) in acetonitrile. The relative measurement method used in this work is similar to the one used previously.[24–27] Every measurement consisted of UV/Vis spectrophotometric titration of a mixture of RA and a reference acid with known pK_a value using non-absorbing acidic and basic titrants. The titration was conducted using a UV/Vis spectrometer, where the different proportions of both the neutral and anionic forms of the substances could be monitored. Separate titrations were also made with both RA and the reference acid to obtain the neutral and anionic spectra for the pure compounds. From the titration data, a difference in the acidities of the observed acids, represented as ΔpK_a, the relative acidity of the compounds, was found. The reliability of the results was increased by measuring RA against three different reference acids with known pK_a values in acetonitrile.[26]

It is worth noting that all of the substances used in the measurements have different UV/Vis spectra for their respective neutral and anionic forms and that RA also displays an isosbestic point (a wavelength where both the anionic and the neutral forms have an identical molar absorptivity). The sharpness of isosbestic points serves as the indicator of the quality of the results. Existence of the isosbestic points is also useful for the calculations,[26] as isosbestic points enable the ionization ratios of two compounds to be obtained simultaneously in the same solution (in all spectra, in a set of spectra obtained in one titration) using only spectral data (that is, the concentrations of the compounds are not needed).

Combining the obtained ΔpK_a values from the measurements with the known pK_a values of the reference acids, the pK_a value of RA could be calculated. The final value was represented as the average of the three measurements. In each of the measurements, the relative acidity was determined as the average of at least 5 ΔpK_a values, wherein each value represents a separate spectrophotometric titration of the mixture of acids.
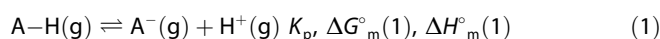
For comparison purposes we have determined the pK_a value of sorbic acid (2,4-hexadienoicacid), a smaller unsaturated carboxylic acid, $H_3CCH=CHCH=CHCO_2H$, $C_6H_8O_2$. This compound can also exist under two conformations A and B. The results are summarized in Table 1.

Table 1. Results of UV/Vis spectrophotometric titration experiments in MeCN solution and assigned pK_a values for *all-trans* (*all-E*) retinoic acid and sorbic acid.

Acid (A)	Reference acid (R_a)	pK_a (R_a)[a]	ΔpK_a	Assigned pK_a(A)	Average pK_a(A)
retinoic:					
	$(4\text{-}CH_3\text{-}C_6F_4)(C_6F_5)CHCN$	21.94	−0.84[b]	22.78	
	$(4\text{-}CH_3\text{-}C_6F_4)_2CHCN$	22.80	0.03[b]	22.77	22.77 ± 0.20
	9-COOMe-fluorene	23.53	0.76[b]	22.77	
sorbic:					
	2-nitrophenol	22.85	−0.10	22.95	
	$(4\text{-}Cl\text{-}C_6F_4)NH(C_6F_5)$	23.21	0.27	22.94	22.95 ± 0.20
	9-COOMe-fluorene	23.53	0.54	22.99	

[a] Ref. [26]. [b] ΔpK_a = pK_a(reference acid) − pK_a(retinoic acid). [c] ΔpK_a = pK_a(reference acid) − pK_a(sorbic acid).

Experimental acidity of I in the gas phase

Considering the ionization of an acid A–H in the gas phase according to reaction (1):

$$A-H(g) \rightleftharpoons A^-(g) + H^+(g) \quad K_p, \Delta G^\circ_m(1), \Delta H^\circ_m(1) \tag{1}$$

$\Delta G^\circ_m(1)$ is the gas-phase acidity of A–H and $\Delta H^\circ_m(1)$ is the proton affinity of A^-, respectively GA(AH) and PA(A^-).

The low volatility of **I** at temperatures of up to 50–60 °C prompted us to apply Cooks kinetic method,[29–34] which was already used for the determination of the acidities of other carboxylic acids.[35] It involves the collision-induced decomposition (CID) of $(Ret-CO_2\cdots H\cdots O_2C-R_{ref})^-$. Here, Ret stands for the retinyl group (Scheme 2). $R_{ref}-CO_2H$ are reference carboxylic acids
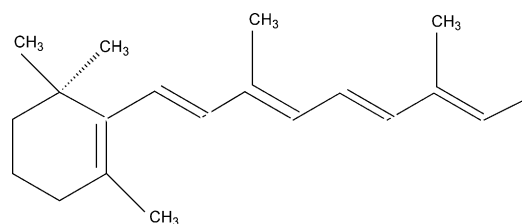
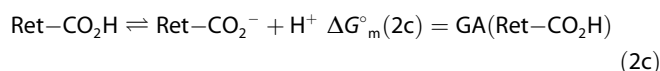**Scheme 2.** *All-trans* retinyl group (Ret).

of known GAs. These ionic adducts undergo reactions (2a) and (2b):

$$Ret-CO_2H + R_{ref}-CO_2^- \tag{2a}$$

$$Ret-CO_2^- + R_{ref}-CO_2H \tag{2b}$$

$$(Ret-CO_2\cdots H\cdots O_2C-R_{ref})$$
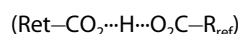
The ratios of the ion intensities (Int), Int(Ret–CO_2^-)/Int(R_{ref}–CO_2^-) for different reference acids are linked to the formal equilibrium (2c):

$$Ret-CO_2H \rightleftharpoons Ret-CO_2^- + H^+ \quad \Delta G^\circ_m(2c) = GA(Ret-CO_2H) \tag{2c}$$

1:1 solutions of Ret–CO_2H and a reference acid, R_{ref}–CO_2H, were ionized in the electrospray ion source section of a QTOF mass spectrometer, leading to the formation of adducts (Ret–$CO_2\cdots H\cdots O_2C$–$R_{ref})^-$. Such adducts were mass-selected and brought to collide with argon in the intermediate hexapole

collision cell with collision energy in the range $E_{lab} = 6$–40 eV. The signal intensities of the $^-O_2C-R_{ref}$ and Ret$-CO_2^-$ fragment ions so formed were determined as a function of the collision energy.

The quantitative treatment of the experimental data closely follows Armentrout's treatment.[36a] Table 2 displays the refer-

Table 2. Experimental thermodynamic data for the reference acids.[a]

Acid (R—CO₂H)	GA(R—CO₂H)[b]	PA(R—CO₂⁻)[b]	PA(R—CO₂⁻)—PAavg[c]
pivalic	1413.5	1442.5	20.2
phenylacetic	1399.0	1428.0	5.7
m-toluic	1395.5	1426.5	4.2
benzoic	1393.3	1423.0	0.7
4-F-benzoic	1381.0	1410.0	−12.0
4-Cl-benzoic	1374.0	1404.0	−18.3
average	1392.7 ± 8.4	1422.3 ± 10.1	0.0

[a] All values in kJ mol⁻¹. [b] Average of the values given in Ref. [37]. [c] PAavg is the average of the PA(R—CO₂⁻) values.

ence acids used, including the PA values of their respective anions. The acids were selected to cover a suitable PA range in such a way that the average value, PA_{avg}, is close to PA(Ret—CO₂⁻). This situation allows a substantial simplification of the treatment.[36a] Provided single collision conditions, this allows for a rigorous determination of the uncertainty limits of $\Delta G^\circ_m(1)$ and $\Delta H^\circ_m(1)$ for Ret—CO₂H. At the collision gas pressure applied herein, the results are to some degree affected by multiple collisions, which inevitably leads to some error, as previously shown by a systematic analysis.[36b] It is difficult to assess this probably small error quantitatively, and the process relative proton acidity and gas phase acidity by interpolation will be discussed in the following:

The data are analyzed in two steps[36a] and follow the Wesdemiotis–Fenselau approaches[38–41] wherein reaction (2) is treated as a reversible process taking place at an "effective temperature" T_{eff}.

First we define ρ as the ratio of ion intensities (Int):

$$\rho = Int(Ret-CO_2^-)/Int(R_{ref}-CO_2^-)$$

For a given collision energy over the selected range, there is an approximately linear relationship between $\ln(\rho)$ and PA(R—CO₂⁻)—PA_{avg}. This holds for a limited range of collision energies. We observed experimentally that the common range for all reference acids is 0.75–2.25 eV as energies at the center of mass, E_{cm}, defined by Equation (3):

$$E_{cm} = E_{lab} \times m_{Ar}/[M(Ret-CO_2 \cdots H \cdots O_2C-R_{ref})^- + m_{Ar}] \quad (3)$$

where m_{Ar} and $[M(Ret-CO_2\cdots H\cdots O_2C-R_{ref})^-]$ correspond to the atomic mass of argon and the molecular mass of the adduct, respectively. This is portrayed in Figure 1.

Each of these lines is characterized by a slope y' and an intercept m_1 (reported values in Table S1 of the Supporting Information). In the model we follow, these magnitudes are defined in E quations (4) and (5):
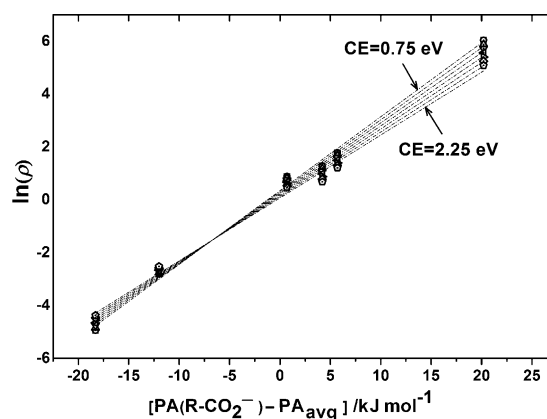

Figure 1. Experimental plot of $\ln(\rho)$ vs. PA(R—CO₂⁻)—PA_{avg} for the six reference acids (their PA values are given in Table 2) under seven evenly spaced collision energies.

$$m_1 = -1/RT_{eff} \quad (4)$$

$$y' = [PA(Ret-CO_2^-)-PA_{avg}]/RT_{eff} \quad (5)$$

A plot of y' versus $1/RT_{eff}$ is linear and provides the optimized value of PA(Ret—CO₂⁻)—PA_{avg} as the slope and $-\Delta S/R$ as the intercept. ΔS is the average relative entropy of dissociation. Because of the complexity of these molecules and the rather small absolute value of ΔS, we prefer not to attempt a discussion of its value.

From the linear relationship shown in Figure 2 we obtain at the 95 % confidence level:

$$PA(Ret-CO_2^-)-PA_{avg} = -6.7 \pm 1.0 \text{ kJ mol}^{-1};$$
$$-\Delta S/R = -1.52 \pm 0.26$$

Combining these results with PA_{avg} and the average dissociation entropy, 99.6 J mol⁻¹ K⁻¹, together with the average uncertainties indicated by the NIST archive[37] for the reference acids, respectively 10.1 and 8.4 kJ mol⁻¹ for PA and GA, we obtain:

$$PA(Ret-CO_2^-) = 1416 \pm 11 \text{ kJ mol}^{-1}$$
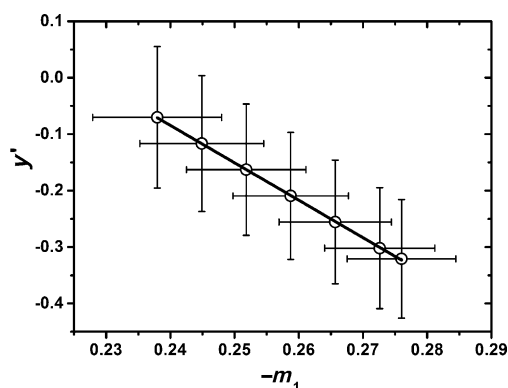
$$GA(Ret-CO_2H) = 1381.8 \pm 8.5 \text{ kJ mol}^{-1}$$


Figure 2. Intercepts (y') vs. slopes ($-m_1$) of the lines portrayed in Figure 1 (see text for details). Segments are one standard error.

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The final values of PA and GA obtained from Figure 1 correspond closely to the region where the various lines cross (even though it is not a single intersection point.) A careful examination of the 21 possible intersections shows that they are very close. As a consequence, this leads to Figure 2 looking as though the points all line up exactly on one line. Recently[36b] the "othogonal distance regression method" (ORD) was developed for the treatment of the experimental data. It would lead to a single intersection point in Figure 1 and a perfect correlation in Figure 2.

Computational Studies

The hydrogen bonded adducts $(Ret-COO\cdots H\cdots OOC-R_{ref})^-$ were studied in the gas phase applying the compound G3MP2 method,[42] which is known to reproduce experimental PA values well.[42, 43] In view of our experimental results, we included both $Ret-CO_2H$ and $C_6H_5-CO_2H$ in this part of the study, as well as sorbic acid, $H_3C-CH=CH-CH=CHCO_2H$, an unsaturated carboxylic acid of smaller size.

Protonation of the retinoate ion, that is, the ion obtained by deprotonation of **I** (Scheme 3), can take place at either one of the oxygen atoms A and B. B-protonation leads to structure **I** of retinoic acid, **I**(B). Protonation at oxygen A leads to structure **I**(A), represented in Scheme 4.
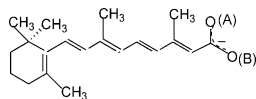
Scheme 3. Structure of the retinoate anion.
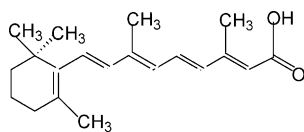
Scheme 4. Structure **I**(A).

Thermodynamic results: Gas-phase acidities

Table 3 summarizes a comparison of the experimental and computed acidities in the gas phase. Some further comments about the experimental values are in order.

The computed GA values of **I**(A) and **I**(B) differ by 6.7 kJ mol^{-1}; this follows from the difference in the thermodynamic stabilities of the neutrals, **I**(A) and **I**(B). We have also calculated this difference by the B3LYP/6-311++G** and found a similar value. Under conditions of thermodynamic equilibrium, the ratio of the partial pressures of these species, $P_{I(B)}/P_{I(A)}$ would then amount to about 15.0. Now, we consider collisional activation of the isobaric ions $[Ret(A)-CO_2\cdots H\cdots O_2C-R_{ref}]^-$ and $[Ret(B)-CO_2\cdots H\cdots O_2C-R_{ref}]^-$, which are both likely to be formed as a mixture. They correspond to structures involving the most stable conformer of the retinoate anion (Scheme 3).[11] According to the high-level systematic study,[11] this structure is at least 15 kJ mol^{-1} more stable than all other possible conformers. Collisional activation is essentially a non-equilibrium process and in a naïve interpretation we could expect that

Table 3. Gas-phase acidities: Experimental and computational results.[a]				
Compound	Experimental PA(Anion)	GA(Acid)	G3MP2 PA(Anion)	GA(Acid)
$C_6H_5CO_2H$	1423.0 ± 8.4	1393.6 ± 8.4	1425.2	1395.9
$C_3H_7CO_2H$	1450.3 ± 8.4	1420.0 ± 8.4	1449.7	1417.2
$C_5H_7CO_2H$ (A)			1441.7	1409.3
$C_5H_7CO_2H$ (B)			1421.2	1389.7
$C_5H_7CO_2H$ (Blend)			1420.8	1389.3
Ret(A)$-CO_2H$ (B)			1418.2	1386.4
Ret(B)$-CO_2H$			1425.7	1392.9
Ret$-CO_2H$ (Blend)	1416 ± 11	1385.0 ± 8.5	1419.0	1387.1
[a] All values in kJ mol^{-1}.				

Ret(A)$-CO_2^-$ would originate from the decomposition of the former while Ret(B)$-CO_2^-$ is obtained in the decomposition of the latter. In other words, the relative abundances of these two ions is then determined by the relative stabilities of the adducts. We have not examined all the six reference acids for this possibility, but as shown in Figure 1, benzoic acid seems an excellent candidate for a comparison. Because of the size of the systems, we have studied both adducts using B3LYP/6-311++G(d,p):

$$[Ret(B)-CO_2\cdots H\cdots O_2C-C_6H_5]^- \rightleftharpoons$$
$$[Ret(A)-CO_2\cdots H\cdots O_2C-C_6H_5]^-\Delta G^\circ(6) \quad (6)$$
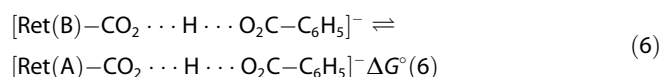
We obtained $\Delta G^\circ(6)=-5.1$ kJ mol^{-1} and the equilibrium constant $K_p(6)$ equals 7.7. From the above, it follows that the experimental PA and GA values obtained by the kinetic method pertain to a mixture or blend of two different species, and it is heavily weighted in favor of Ret(A)$-CO_2H$. The experimental and computational data pertaining to the gas phase study are summarized in Table 3. In connection with the discussion we also report the experimental and computed PA and GA values for butyric and sorbic acids. For the latter, two conformers A and B also exist.

From the above we see that the model leads to very consistent results. Of course, some caveats are in order because the CID process is a kinetic and not a thermodynamic process.

Thermodynamic results: Solution acidities

The results are summarized in Table 4, where our results for sorbic acid are also presented. It is important to note that the experimental pK_a values in MeCN are quite different from those in aqueous solution.

The solution pK_a values were calculated by means of the COSMO-RS[45] method using the two step procedure with Turbomole version 6.5[47] and COSMOthermX version C30 with parametrization 1401.[48] The geometry optimization were performed at DFT-bp-TZVP level and in the statistical thermodynamics step the standard COSMOtherm tool for MeCN pK_a calculations was used. COSMO-RS has been previously used in a number of cases.[45c, 46, 49]

↖↖ **These are not the final page numbers!**

Table 4. Acidities in MeCN solution: Experimental and computational results.

Compound	Experimental pK_a	COSMO-RS[45] pK_a
$C_3H_7CO_2H$	22.70	27.70
$C_5H_7CO_2H$ (A)		27.13
$C_5H_7CO_2H$ (B)		27.68
Blend	22.95	27.51
$C_6H_5CO_2H$	21.51	24.83
Ret(A)—CO_2H		27.03
Ret(B)—CO_2H		28.28
Blend	22.77	28.31

Discussion

Consider reactions (7a) to (7c):

$$Ret-CO_2H \ (blend) + C_6H_5-CO_2^- \rightleftharpoons$$
$$Ret-CO_2^- + C_6H_5-CO_2H \quad \Delta G^\circ_m(7a) \tag{7a}$$

$$Ret-CO_2H \ (blend) + C_3H_7-CO_2^- \rightleftharpoons$$
$$Ret-CO_2^- + C_3H_7-CO_2H \quad \Delta G^\circ_m(7b) \tag{7b}$$

$$Ret-CO_2H \ (blend) + C_5H_7-CO_2^- \rightleftharpoons$$
$$Ret-CO_2^- + C_5H_7-CO_2H(Blend) \quad \Delta G^\circ_m(7c) \tag{7c}$$
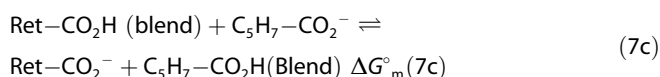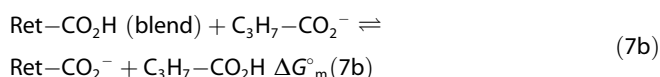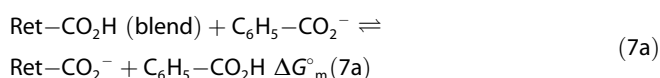
The results given above lead to $\Delta G^\circ_m(7a)$ to $\Delta G^\circ_m(7c)$. $\Delta G^\circ m(7a)$ and $\Delta G^\circ m(7b)$ values originate in direct comparisons; $\Delta G^\circ_m(7c)$ in the gas phase is purely computational (Table 5).

The agreement between the experimental and computed values in the gas phase is excellent. In solution, the agreement is not as good, but this is not unexpected as it has been previously shown that in case of carboxylic acids COSMO-RS tends to (mainly over)estimate the pK_a values in MeCN with errors up to several pK_a units.[45c,49] Another reason might be the unsuitability of benzoic acid for the isodesmic reaction in the solution. The unfolding of the conjugated system along with the methyl substituents at the C9 and C13 in the retinyl group might bring different solvation effects compared to the compact cyclic conjugated system in the benzoic acid. It can be argued that a carboxylic acid with long unfolded chain might be a better choice for the isodesmic reaction partner in the solution. If butyric acid is considered as a reference acid for reaction (7), the experimental and computed ΔG°_m values would be 0.4 and 3.5 kJ mol^{-1}, respectively. In the case of sorbic acid, the ΔG°_m values are −1.3 and 4.5 kJ mol^{-1}. This indicates con-

Table 5. Experimental and computational values of $\Delta G^\circ_m(7a)-\Delta G^\circ_m(7c)$ in the gas phase and in solution.[a]

Medium	$\Delta G^\circ_m(7a)$		$\Delta G^\circ_m(7b)$		$\Delta G^\circ_m(7c)$	
	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
Gas phase	−8.6	−8.8	−35.0	−30.1		−2.2
MeCN	7.2	3.5	0.4	3.5	−1.3	4.6

[a] All values in kJ mol^{-1}.

siderable improvement of the agreement between computational and experimental results.

Conclusion

We have determined experimentally the acidity of (**I**) in the gas phase (by the kinetic method) and in solution in MeCN. The experimental study was followed by a computational analysis. Both studies were in good agreement as they showed that both in the gas phase and in solution two structures are relevant. In the gas-phase experiments, under the conditions of collision activation, the less abundant but slightly more acidic one determines the observed acidity. In the case of the solution studies the agreement between experimental and computed acidity is not as satisfactory.

Experimental Section

Most chemicals used in the gas-phase studies were Aldrich products of the highest purity available. Their identity was confirmed by mass spectrometry. The acetonitrile used for the determination of the solution pK_a was from Romil, Super purity Far-UV Solvent, > 99.9 %.

The measurements for the solution studies were conducted in an MBraun Unilab glovebox so as to avoid the influence of traces of water[27] or oxygen on the results. As Ret—CO_2H is somewhat unstable, it was stored at −20 °C in a cold well located inside a glovebox. To be able to conduct spectrophotometric measurements inside the glovebox, an external cuvette compartment located inside the glovebox was used. Two fiber optic cables were used to connect it with the spectrophotometer, which was located outside of the box. The solvent, acetonitrile, was dried with molecular sieves (3 Å) for at least 24h prior to use. Our previous experience has shown that such a method yields a solvent with a water concentration under 0.001 %.[24]

Gas-phase experiments were performed in a mass spectrometer with QHT (quadrupole/hexapole, time-of-flight) geometry (QTOF 2, Micromass/Waters, Manchester, U.K.)[44] The experimental setup consists of an electrospray ion source working at atmospheric pressure. After having entered the high vacuum section of the instrument, ions are focused into the quadrupole mass filter. Experiments are carried out by setting the quadrupole either in the broad-band mode, effectively allowing all ions to pass, whereupon a mass spectrum is recorded by means of the time-of-flight analyzer or in the narrow-band mode, in which the quadrupole voltages are set to transmit only ions with the relevant *m/z* ratio. This is carried out at a sufficiently high mass resolution to avoid passage of ions with *m/z* ± 1 Th. The ions thus selected are then accelerated/decelerated to a variable energy in the range $E_{lab} = 8$–40 eV before entering a collision cell (path length 16 cm). The latter includes a hexapole ion guide. In this region, the ions collide with argon (nominal pressure of 5×10^{-4} mbar). After leaving the collision cell, the ions are accelerated to a few electron-volts and then transferred into the time-of-flight (TOF) region, which is kept under high vacuum (2×10^{-7} mbar). The TOF is of the reflectron type, and the ion beam is extracted and accelerated to 7.0 keV in a direction orthogonal to the ion optical axis of the QH assembly by applying a high voltage pulse to a set of acceleration electrodes. The duty cycle of the TOF is fixed to allow all ions in a wide mass range to arrive before sending off the next burst of ions and the ion count is adjusted to allow for a sufficiently wide linear dynamic range.

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The mass resolving power of the TOF analyzer was set to $m/\Delta m = 5000$ (fwhm).

In the experiments, a 1:1 mixture of **I** and the reference acid (10^{-5} M solution) with ca. 10% of $BuNH_2$ in a 1:1 mixture of MeOH and MeCN was injected at a rate of 10 µL min^{-1}).

Acknowledgements

[1] IUPAC name: (2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid.

[2] Molecular structure: P. Karrer, R. Morf, K. Schöpp, *Helv. Chim. Acta* **1931**, *14*, 1431–1436.

[3] Crystal structure: K. Kühnel, N. NKe, M. J. Cryle, S.G. Sligar, M. A. Schuler, I. Schlichting, *Biochemistry* **2008**, *47*, 6552–6559.

[4] The number of publications on **I** between January and November 2014 amount to ca. 800, mostly involving biological studies. Data from CAS Scifinder.

[5] IUPAC name:(2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol.

[6] Molecular structure: P. Karrer, R. Morf, K. Schöpp, *Helv. Chim. Acta* **1931**, *14*, 1036–1040.

[7] IUPAC name: (2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)-nona-2,4,6,8-tetraenal.

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The acidity of retinoic acid in the gas phase and in acetonitrile solution was determined by means of mass spectrometry and UV/Vis spectrophotometry. The intrinsic acidity is slightly higher than that of benzoic acid; in solution, the situation is opposite. The experimental systems were described theoretically with quantum chemical methods.
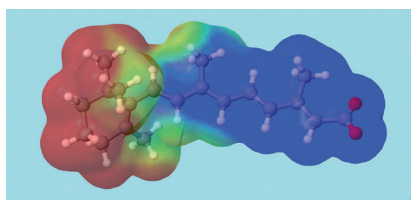
Acidity

J.-L. M. Abboud,* I. A. Koppel,*
E. Uggerud,* I. Leito,* I. Koppel,*
O. Sekiguchi, K. Kaupmees, J. Saame,
K. Kütt, M. Mishima*

■■ – ■■

Solution and Gas-Phase Acidities of *all-trans* (*all-E*) Retinoic Acid: An Experimental and Computational Study

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